Doctoral Dissertation

Silyl Borane-mediated or Mechanochemical Promoted C–F Bond Activation of Fluorinated Compounds

(シリルボランまたはメカノケミカル促進による C-F 結合の活性化を基盤とする分子変換の開発)

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Preface

Through the centuries, fluorinated compounds have become indispensable yet controversial chemicals in both industrial and our daily life. Ever Since Polytetrafluoroethylene (PTFE) was accidently discovered by Roy J. Plunkett in 1938, the use of fluorinated compounds gained significant momentum with the development of technologies related to polymers, refrigerants, and pharmaceuticals. There are mainly two reasons for fluorinated compounds exerting such great influence. Firstly, because of the unique physiochemical properties of fluorine atoms, introducing fluorine atoms into molecules would boost their lipophilicity, metabolic stability, and bioactivity. Secondly, the C-F bond is the strongest bond of carbon atom can ever form, which makes fluorinated compounds chemically stable. However, With the explosive prevalent of fluorinated compounds, problems have happened. It was found that fluorinated compounds, particularly those containing per- or polyfluoroalkyl substances (PFAS), can pose threats to the environment and human health. Many fluorinated compounds are extremely persistent in the environment, meaning they do not readily break down, which is partly because of the strength of C-F bond. This persistence can lead to their accumulation in soil, water, and organisms over time, furtherly causes a series of problems, such as bioaccumulation, potential carcinogenicity, and environmental contamination.

Amid the escalating concerns surrounding the hazardous nature of fluorinated compounds, the imperative need for urgent and critical research on their degradation has become apparent. Within this realm, my primary focus centers on the C-F bond activation of aryl fluorides, particularly targeting unactivated aryl fluoride compounds. Despite notable advancements made in recent years in this area, persistent challenges remain, specifically in broadening the reactivity scope to encompass electron-deficient substrates and monocyclic fluoroarenes. Hence, we have introduced a pioneering protocol for C-F bond activation, employing a synergistic combination of silyl boronate reagents and a base, representing a significant step forward in addressing these challenges.

In Chapter 1, noteworthy advancements were showcased in activating unactivated fluoroarenes through exceptional methodologies. Various bond formation reactions including C-C, C-B, C-N, C-O, C-Si, and C-P bonds were exemplified, elucidating specific reaction mechanisms. Furthermore, a concise summary and prospects stemming from these accomplishments in this field are provided.

In Chapter 2, the realization of defluorosilylation in aryl fluorides to access aryl silanes was demonstrated under transition-metal-free conditions, employing an inert C–F bond activation. This process was meticulously described, showcasing the effectiveness of silylboronates and KOtBu in mediating the defluorosilylation, which proceeded seamlessly at ambient temperature, yielding a diverse array of aryl silanes in commendable yields. While a comparative experiment underscored the higher efficiency of the Ni catalyst in facilitating this transformation, the transition-metal-free protocol bears distinct advantages from a green chemistry standpoint.

In Chapter 3, we elucidated an effective silylboronate-mediated cross-coupling reaction between aryl fluorides and arylalkanes, all achieved under transition-metal-free conditions at ambient temperature. The synergistic interplay of silylboronate and KOtBu assumes paramount importance in orchestrating a radical process, culminating in the cleavage of both C–F and C–H bonds within the respective coupling precursors, ultimately yielding the coveted cross-coupling product. This versatile cross-coupling protocol finds wide-ranging applicability across a diverse spectrum of aryl fluorides, each bearing a C(sp2)–F bond. Furthermore, this methodology seamlessly extends its reach to encompass various coupling partners endowed with a C(sp3)–H bond, including diarylmethanes, diarylethanes, and monoarylalkanes. Noteworthy is the facile access to a multitude of di- and triarylalkanes, some bearing tertiary or quaternary carbon centers, all obtained in yields ranging from moderate to high. We assert that this developed silylboronate-mediated cross-coupling

methodology constitutes a valuable and substantive contribution to the burgeoning field of C–F and C–H activation chemistry.

In Chapter 4, we unveiled a sophisticated silylboronate-mediated protocol for the selective defluorinative cross-coupling of organic fluorides with secondary amines, executed through a transition-metal-free approach. The harmonious interplay of silylboronate and potassium tert-butoxide facilitates the cross-coupling of C–F and N–H bonds at ambient temperature, circumventing the formidable energy barriers associated with thermally induced S_N2 or S_N1 amination processes. A key distinction of this transformation lies in its exceptional selectivity, wherein the C–F bond of the organic fluoride is activated by silylboronate, leaving potentially cleavable C–O, C–Cl, heteroaryl C–H, or C–N bonds, as well as CF3 groups, unaffected. This innovative method enables the efficient one-step synthesis of tertiary amines, bearing aromatic, heteroaromatic, and/or aliphatic groups, by judiciously employing electronically and sterically diverse organic fluorides in conjunction with N-alkylanilines or secondary amines. Notably, the protocol extends its utility to the late-stage synthesis of potential drug candidates, encompassing their deuterium-labeled analogs.

In chapter 5, we described a silyl-boronate-mediated cross-coupling strategy that directly combines unreactive aryl fluorides with acetonitrile. The α-arylation of nitriles is a central pathway for the synthesis of α-aryl nitriles and is an essential scaffold in pharmaceutical research. Although numerous methods such as radical nucleophilic aromatic substitution ($S_{RN}1$), aryne reactions, nucleophilic aromatic substitution (S_NAr), and transition metal catalysis exist, they often suffer from narrow substrate compatibility and struggle with inert aryl halides coupled with acetonitrile. This protocol performed under ambient conditions, eliminates the need for transition-metal catalysts or photoirradiation, and provides α-aryl nitriles in commendable yields. This transformative method demonstrates unparalleled versatility, accommodating a wide range of aryl fluorides and even unreactive alkyl nitriles, ensuring selective monoarylation, and avoiding diarylation byproducts.

In chapter 6, we developed solvent-free mechanochemical deoxyfluorination of carboxylic acids to acyl fluorides mediated by 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA) using a ball mill. This method facilitated high product yields in shorter reaction times, even for sterically challenged carboxylic acids. We also realized mechanochemical coupling of acyl fluorides and amines, as well as the TFEDMA-mediated direct mechanochemical coupling reaction of carboxylic acids with amines via a sequential one-pot deoxyfluorination/coupling pathway. Furthermore, this protocol has been expanded to peptide synthesis. The efficiency of the protocol, in terms of speed, its solvent-free characteristics, and its favorable E-factor, aligns well with the requirements of current environmental policies.

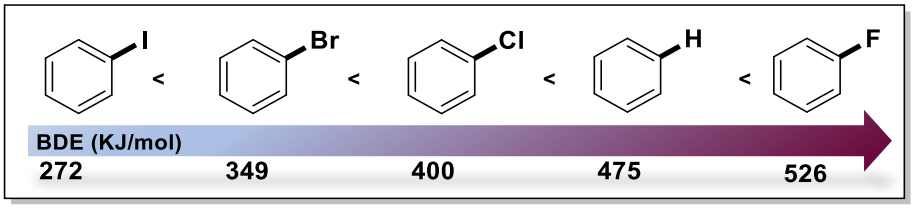
Chapter 1. Introduction

1.1 Introduction of C-F bond

The activation of carbon-fluorine (C-F) bonds in aryl fluoride compounds stands at the forefront of contemporary chemical research, representing a pivotal advancement in the field of organofluorine chemistry. The importance of C-F bond activation lies in its potential to unlock a wealth of synthetic opportunities. Aryl fluorides are ubiquitous in pharmaceuticals, agrochemicals, and materials science, owing to the prevalence of fluorine in bioactive molecules and advanced materials.[1] However, their unreactive C-F bonds have traditionally hindered facile functionalization. The strong electronegativity of fluorine is responsible for the bond strength, as it polarizes the C-F bond, resulting in a strong electrostatic attraction between $C^{\delta+}$ and $F^{\delta-}$, rendering it notoriously inert and resistant to conventional reactivity.[2] This inherent inertness has posed a significant challenge for chemists seeking to functionalize aryl fluoride substrates. By devising strategies to activate and manipulate these bonds, chemists can access a vast array of fluorinated compounds with tailored properties and functionalities.

1.2 C-C bond formation reactions via unactivated C(Aryl)-F bond activation

Transition metal-catalyzed C-C bond formation reactions are useful tools for wide fields of chemistry. Cross coupling reactions via selective functionalization of Ar-X bonds have witnessed a significant development in modern organic synthesis. Compared to Aryl halides (Cl, Br, I), the functionalization of the Ar-F bond in transition metal-catalyzed reactions has received comparatively less attention. The robust nature of the C-F bond was historically viewed as a hindrance to the oxidative addition step in these reactions due to its elevated bond dissociation energy (BDE),[3] which surpasses that of all other aryl halides and aryl-H (Scheme 1.1).



Scheme 1.1 Comparison of BDE of Ar-X

Nonetheless, in 1973, Kumada and colleagues[4] presented a groundbreaking advancement in the field of

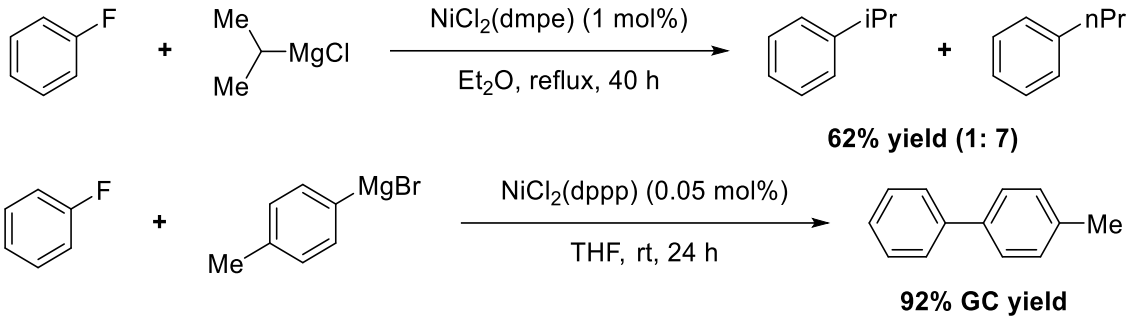
[1] (a) J. Wang, M. Sμnchez-Roselló, J. L. AceÇa, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432-2506; (b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320-330; (c) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, 101467–110519. (d) Kirsch P. Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, 2nd ed. Weinheim: Wiley-VCH, 2013; (e) M. Inoue, Y. Sumii, N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, *ACS Omega* **2020**, *5*, 10633−10640.

[2] (a) Uneyama K. Organofluorine Chemistry. Oxford: Blackwell, 2006; (b) D. O'Hagan, Understanding Organofluorine Chemistry. An Introduction to the C−F Bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319.

[3] (a) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, Activation of Carbon-Fluorine Bonds by Metal Complexes, *Chem. Rev.* **1994**, *94*, 373-431. (b) S. Murai, Activation of Unreactive Bonds and Organic Synthesis, Ed.; Springer-Verlag: Berlin, Heidelberg, **1999**.

[4] Y. Kiso, K. Tamao, M. Kumada, Effects of the nature of halides on the alkyl group isomerization in the nickel-catalyzed cross-coupling of secondary alkyl Grignard reagents with organic halides, *J. Organomet. Chem.* **1973**, *50*, C12-C14.

chemical synthesis: the utilization of nickel-catalyzed cross-coupling reactions involving Grignard reagents and aryl halides. Their seminal work not only established the viability of employing nickel complexes to mediate cross-coupling reactions with aryl fluorides (Scheme 1.2, top), but also laid the foundation for subsequent developments in this area. Although the reaction conditions were not rigorously optimized at the time, they later reported nickel and palladium-catalyzed cross-coupling reactions of aryl fluorides with Grignard reagents,[5] spurred by a series of reports detailing transition metal-catalyzed cross-coupling reactions involving various activated aryl fluorides.[6] The indispensability of nickel catalysts in conjunction with Grignard reagents for effecting C-F bond transformations is underscored in Scheme 1.2 (bottom). Notably, it is worth mentioning that palladium catalysts also exhibit efficacy in this context, demonstrating superior selectivity particularly in cases involving di- or tri-fluorobenzene substrates.



Scheme 1.2 Ni-Catalyzed cross-coupling reaction involving Grignard reagents and aryl fluorides

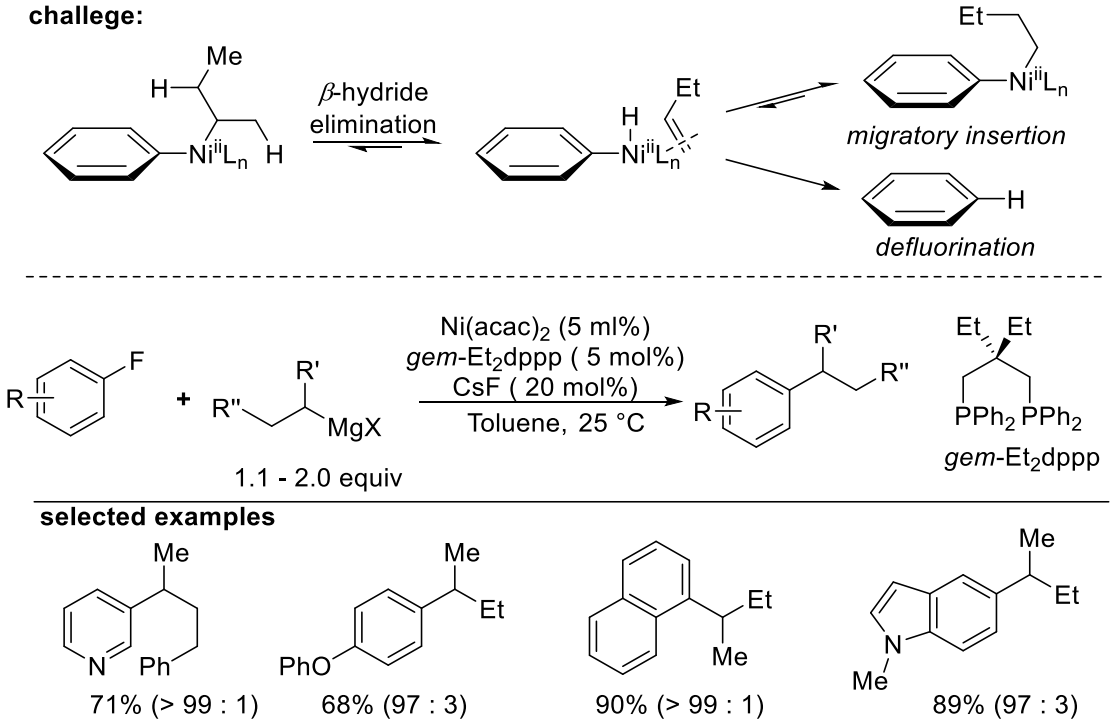
Since Kumada's initial report of significant isomerization upon the reaction of *i*PrMgCl with fluorobenzene, the endeavor to effectuate C(sp2)-C(sp3) bond formation via C-F bond activation has endured as a formidable challenge in the realm of catalysis. This is due to the delicate balance between the relative rates of β-hydride elimination and reductive elimination from the pivotal intermediate formed post-transmetallation, leading to the potential emergence of two degenerate products through unproductive pathways, ultimately diminishing both yield and selectivity. However, in the year 2018, Cornella and colleagues[7] introduced a catalytic paradigm predicated on an innovative nickel system, adept at mitigating some of the aforementioned limitations. This groundbreaking protocol facilitates the coupling of unprejudiced secondary alkylmagnesium halides with inert aryl fluorides under exceedingly mild reaction conditions, thereby minimizing undesirable isomerization. This investigation unveiled a universal Thorpe-Ingold effect embedded within the ligand framework, endowing a heightened level of selectivity for the secondary carbon center in the C(sp2)-C(sp3) coupling event. Noteworthy attributes of this protocol encompass its mild reaction conditions and its adaptability towards both electron-deficient and electron-rich aryl fluorides. Furthermore, it extends its versatility to encompass a diverse array of heterocycles, enabling coupling without succumbing to over-alkylation at the electrophilic sites

[5] Nickel- and Palladium-Catalyzed Cross-Coupling Reaction of Polyfluorinated Arenes and Alkenes with Grignard Reagents, T. Saeki, Y. Takashima, K. Tamao, *Synlett* **2005**, *11*, 1771-1774.

[6] (a) M. Aizenberg, D. Milstein, Catalytic Activation of Carbon-Fluorine Bonds by a Soluble Transition Metal Complex, science, **1994**, *265*, 359-361; (b) M. Aizenberg, D. Milstein, Homogeneous Metal-Catalyzed Hydrogenolysis of C−F Bonds, *J. Am. Chem. Soc.* **1995**, *117*, 8674-8675; (c) G. Cahiez, F. Lepifre, P. Ramiandrasoa, Manganese-Catalyzed Substitution of Activated Aryl Halides (X=Cl, Br and F) and Aryl Ethers by Organomagnesium Reagents, *Synthesis* **1999**, *12*, 2138-2144; (d) R. Wilhelm, D. A. Widdowson, Palladium Catalysed Cross-coupling of (fluoroarene)tricarbonylchromium(0) complexes, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3808-3814. (e) T. Barun, R. N. Perutz, Routes to Fluorinated Organic Derivatives by Nickel Mediated C–F Activation of Heteroaromatics *Chem. Commun.* **2002**, 2749-2757. (f) Y. M. Kim, S. Yu, Palladium(0)-Catalyzed Amination, Stille Coupling, and Suzuki Coupling of Electron-Deficient Aryl Fluorides *J. Am. Chem. Soc.* **2003**, *125*, 1696-1697. (g) S. bahmanyar, B. C. Borer, Y. M. Kim, D. M. Kurtz, S. Yu, Proximity Effects in the Palladium-Catalyzed Substitution of Aryl Fluorides, *Org. Lett.* **2005**, *7*, 1011- 1014.

[7] M. J. O'Neill, T. Riesebeck, J. Cornella, Thorpe-Ingold Effect in Branch-Selective Alkylation of Unactivated Aryl fluorides, *Angew. Chem. Int. Ed.* **2018**, *57*, 9103–9107.

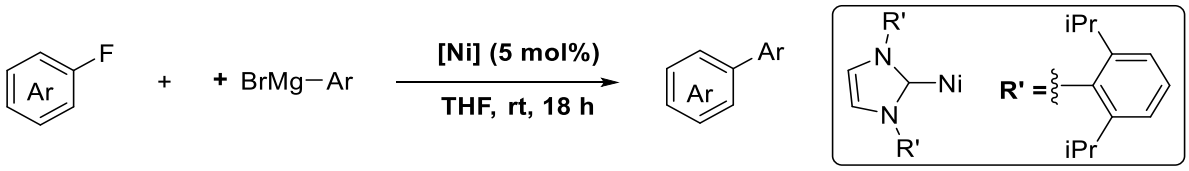
(Scheme 1.3).



Scheme 1.3 Branch-Selective Alkylation of Unactivated Aryl Fluorides

Furthermore, the Ackermann research group has documented a cognate investigation, wherein the utilization of a secondary phosphine oxide (SPO)-nickel catalyst facilitated an exquisitely branch-selective activation of unactivated fluoroarenes. This selectivity manifested notably in the context of formidable couplings with primary and secondary alkyl Grignard reagents.[8]

In the year 2001, Herrmann[9] and colleagues achieved a pioneering milestone in the realm of chemical synthesis by devising a discriminating C(sp2)-C(sp2) cross-coupling reaction involving inert aryl fluorides and Grignard reagents, all conducted at ambient temperature. This transformative advance was made possible through the utilization of a remarkably potent *N*-heterocyclic carbene Ni catalyst. Their observations suggest the plausible involvement of either a radical or polar pathway in the mechanistic underpinnings of this reaction (Scheme 1.4).

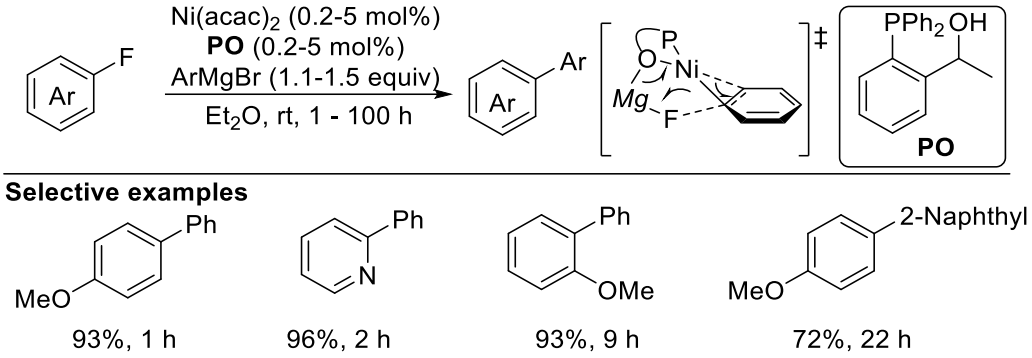


Scheme 1.4 catalytic C(sp2)−C(sp2) cross-coupling via selective C-F bond activation

[8] V. Müller, D. Ghorai, L. Capdevila, A. M. Messinis, X. Ribas, L. Ackermann, C–F Activation for C(sp2)–C(sp3) Cross-Coupling by a Secondary Phosphine Oxide (SPO)-Nickel Complex, *Org. Lett.* **2020**, *22*, 7034–7040.

[9] V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, Catalytic C−C Bond Formation through Selective Activation of C−F Bonds, *Angew. Chem. Int. Ed.* **2001**, *40*, 3387-3389.

Furtherly, Nakamura and his collaborators[10] made a significant contribution to the field by elucidating the remarkable impact of hydroxyphosphine ligands (denoted as PO ligands) in expediting nickel-catalyzed cross-coupling reactions involving inert aryl fluorides and Grignard reagents. This catalytic paradigm, predicated on the synergistic interplay of nickel, PO ligands, and Grignard reagents, bestows the remarkable ability to activate otherwise recalcitrant aryl fluorides, yielding the desired products in yields ranging from good to excellent. The crux of this transformation lies in the activation of aryl fluorides through the formation of a nickel phosphine/magnesium alkoxide bimetallic species, orchestrated by the concerted action of the nucleophilic nickel center and the Lewis acidic magnesium moiety. Notably, this protocol also extends its compatibility to encompass aryl chlorides and phenol phosphates as viable substrates, thereby broadening the scope of its synthetic utility (Scheme 1.5).

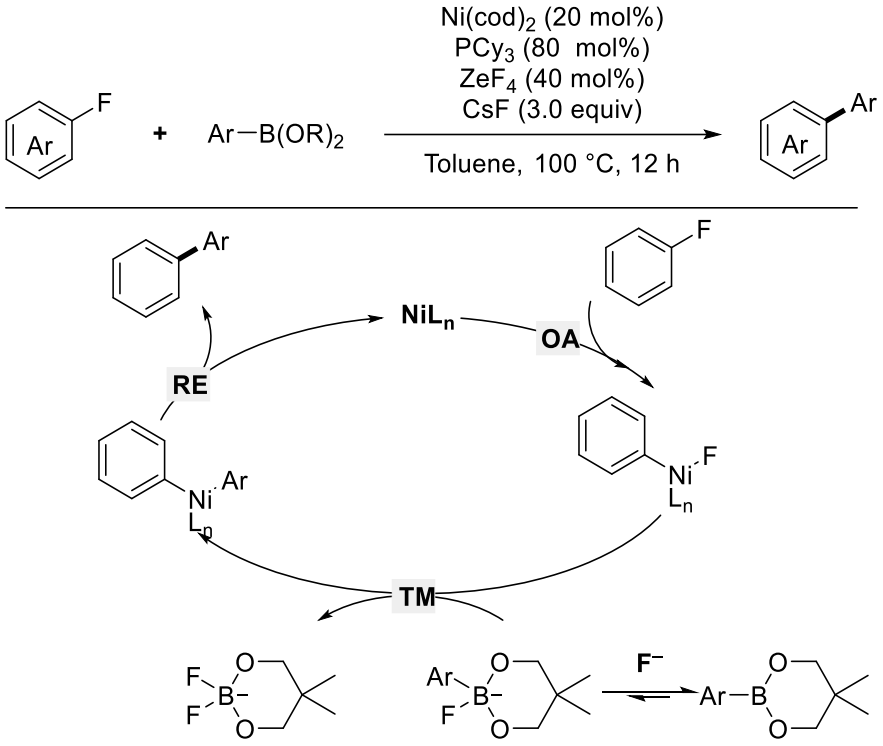


Scheme 1.5 Hydroxyphosphine Ligand-promoted catalytic C-F bond activation

Owing to the diminished Lewis acidity exhibited by boronic acids, effecting fluoride elimination during the oxidative addition and/or transmetallation stages proves to be a formidable task, rendering the Suzuki-Miyaura reaction of aryl fluorides a notable challenge. However, in the year 2011, Chatani and colleagues[11] made a notable breakthrough with the introduction of a nickel-catalyzed Suzuki-Miyaura reaction involving aryl fluorides and aryl boronic esters. In this transformative process, they strategically incorporated a fluoride cocatalyst, namely ZrF_4, which served as a pivotal facilitator. This cocatalyst, deemed to function as a Lewis acid, played a crucial role in expediting the elimination of the fluorine atom within the oxidative addition and/or transmetalation processes, thereby enabling the successful execution of the Suzuki-Miyaura reaction with aryl fluorides (Scheme 1.6).

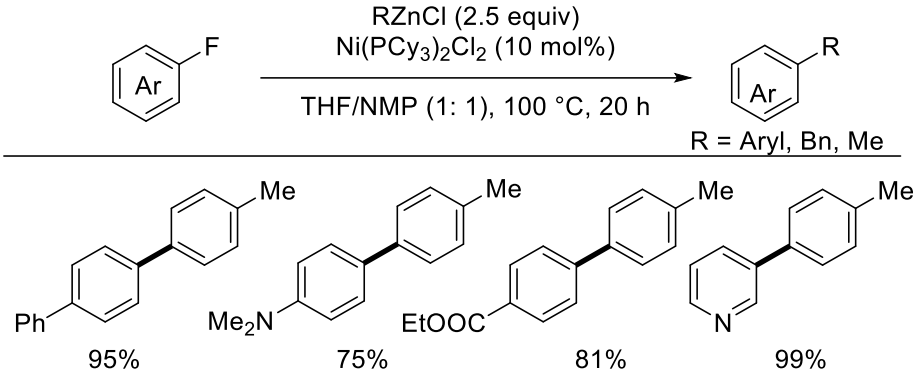
[10] N. Yoshikai, H. Matsuda, E. Nakamura, Hydroxyphosphine Ligand for Nickel-Catalyzed Cross-Coupling through Nickel/Magnesium Bimetallic Cooperation, *J. Am. Chem. Soc.* **2009**, *131*, 9590–9599.

[11] M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, Nickel-Catalyzed Suzuki–Miyaura Reaction of Aryl Fluorides, *J. Am. Chem. Soc.* **2011**, *133*, 19505–19511.



Scheme 1.6 Nickel-Catalyzed Suzuki-Miyaura Reaction of Aryl Fluorides

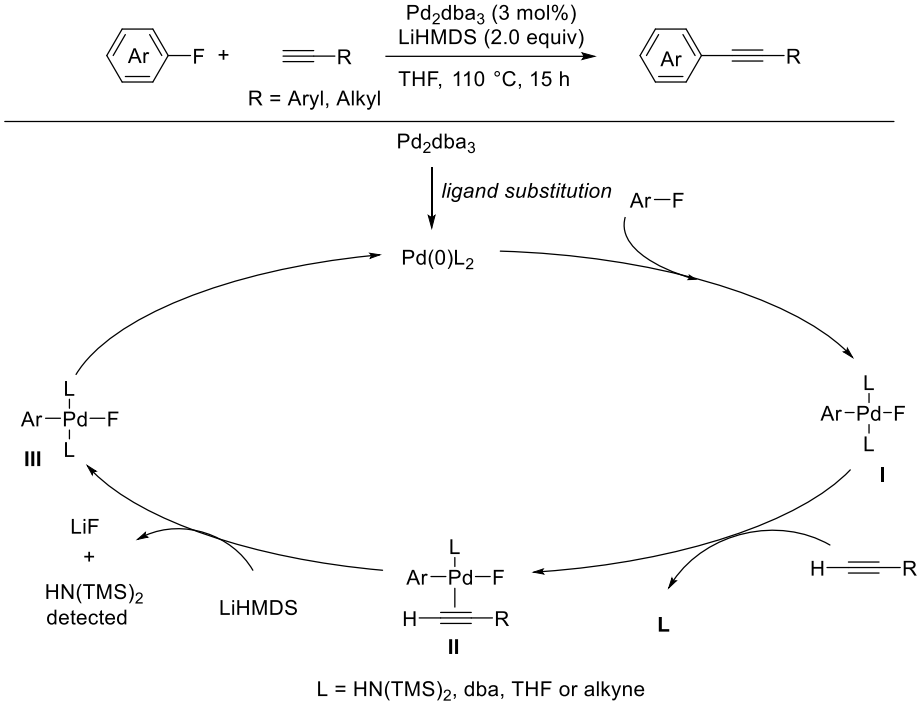
Moreover, in the year 2014, Wang and collaborators[12] unveiled a notable achievement with the introduction of a nickel-catalyzed cross-coupling reaction involving aryl fluorides and organozinc reagents, wherein the effectiveness of $Ni(PCy_3)_2Cl_2$ as a catalyst was unequivocally established. This innovative methodology exhibits remarkable versatility, accommodating both activated and unactivated aryl fluorides with equal efficiency. Furthermore, it was demonstrated that a diverse array of aryl zinc reagents, encompassing both electron-rich and electron-deficient variants, serve as compatible nucleophiles within this transformative protocol (Scheme 1.7).



Scheme 1.7 Ni-Catalyzed Cross-coupling of Aryl Fluorides and Organozinc Reagents

[12] F. Zhu, Z. Wang, Nickel-Catalyzed Cross-Coupling of Aryl Fluorides and Organozinc Reagents, *J. Org. Chem.* **2014**, *79*, 4285–4292.

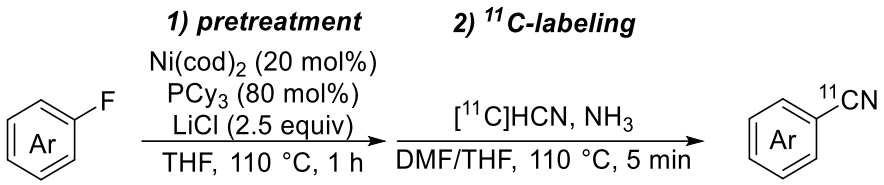
In 2019, Cao and colleagues[13] unveiled a remarkably efficient palladium catalyzed Sonogashira coupling methodology. This innovative approach enabled the coupling of unactivated aryl fluorides with terminal alkynes, and its orchestration involved the presence of lithium hexamethyldisilazide (LiHMDS). This C(sp2)-C(sp) cross-coupling protocol demonstrated a broad spectrum of functional group compatibility, extending its applicability to both electron-rich and electron-poor fluoroarenes. The mechanistic intricacies underlying this transformative process are characterized by the oxidative addition of the C-F bond in the fluoroarene at the catalytically active $Pd(0)L_n$ species, leading to the formation of the $ArPd(II)L_nF$ complex. Subsequent coordination with the alkyne generates intermediate II. The deprotonation of intermediate II, facilitated by LiHMDS, yields complex III, culminating in the final product through process of reductive elimination. Additionally, the authors underscored the nuanced role of LiHMDS, positing its dual functionality as both a base and a ligand in this intricate catalytic cycle (Scheme 1.8).



Scheme 1.8 Pd-Catalyzed Sonogashira Cross-coupling of Aryl fluorides and Terminal Alkynes

In 2023, Hosoya[14] and his collaborators elucidated a nickel-catalyzed ^{11}C-cyanoation strategy through the activation of C-F bonds (Scheme 1.9). This protocol unfolds across two phases: an initial pretreatment phase, wherein the generation of the aryl(chloro)nickel(II) intermediate is achieved via the strategic cleavage of the C-F bond. It is noteworthy that LiCl emerges as a pivotal factor, exerting a discernible influence on the oxidative addition step, thereby shaping the efficiency of the overall process. The subsequent phase involves a temporally restricted ^{11}C-radiolabeling step employing [^{11}C]hydrogen cyanide. The outcome of this intricate orchestration is the seamless and efficient synthesis of a diverse array of [^{11}C]aryl nitriles, derived from their corresponding aryl fluorides. This nuanced approach not only reflects a significant advancement in radiochemical methodologies but also underscores the versatility of C-F bond activation in enabling expedient access to radiolabeled aryl nitriles.

[13] J. He, K. Yang, J. Zhao, S. Cao, LiHMDS-Promoted Palladium-Catalyzed Sonogashira Cross-Coupling of Aryl Fluorides with Terminal Alkynes, *Org. Lett.* **2019**, *21*, 9714–9718.
[14] Z. Zhang, T. Niwa, K. Watanabe, T. Hosoya, ^{11}C-Cyanation of Aryl Fluorides via Nickel and Lithium Chloride-Mediated C-F bond activation, *Angew. Chem. Int. Ed.* **2023**, *62*, e202302956

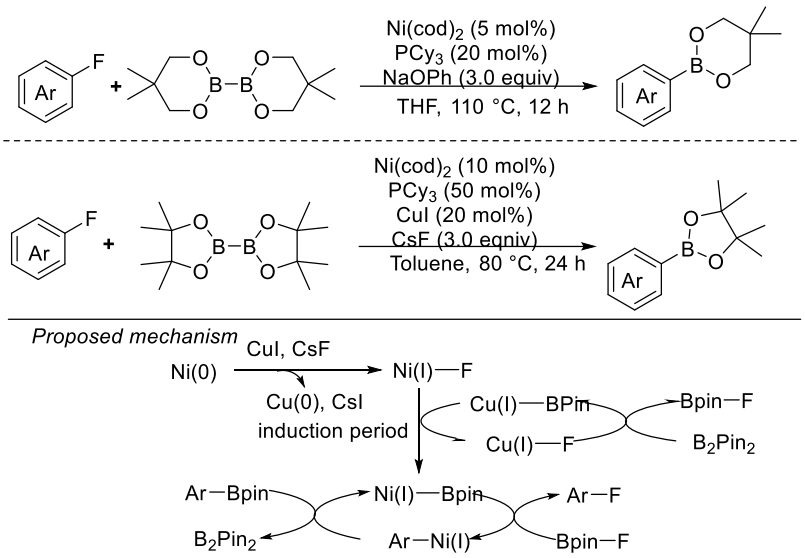


Scheme 1.9 ^{11}C-Cyanation of Aryl Fluorides via Nickel and Lithium Chloride-Mediated C-F bond activation

1.3 C-B bond formation reactions

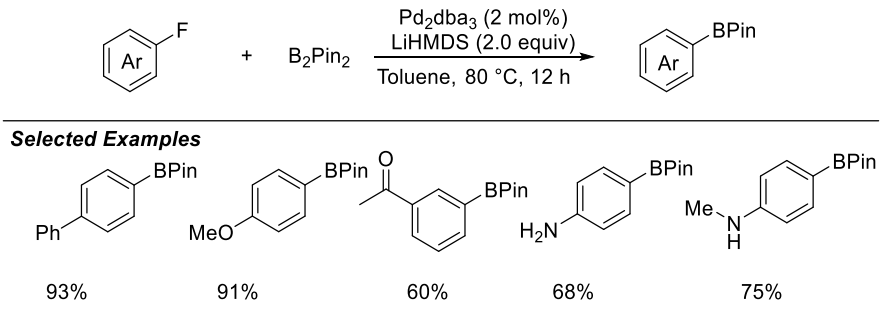
Prompted by the pioneering research of Kumada[4], the predominant focus within catalytic C-F bond activation has hitherto revolved around C-C bond formation. Meanwhile, the exploration of C-heteroatom bond formation has languished, remaining confined primarily to nucleophilic aromatic substitution techniques, specifically involving activated fluoroarenes[15] or perfluorinated aryls[16]. These characteristics collectively foster the notion that effecting the direct C-F bond activation of unactivated fluoroarenes may constitute a formidable yet exceedingly gratifying endeavor in the realm of C-heteroatom bond formation. A seminal contribution by Nozaki[17] in 2008 elucidated that stoichiometric and precisely defined boryllithium reagents possess the capacity to catalyze a C-B bond-forming event through the cleavage of the C-F bond in fluorobenzene. Subsequently, in 2015, Martin[18] and colleagues unveiled an unconventional Ni-catalyzed C-F bond cleavage/C-B bond formation in monofluoroarenes (Scheme 1.10 top). Their proposed reaction mechanism entails a conventional Ni(0)-Ni(II) catalytic cycle. This protocol not only distinguishes itself through its expansive applicability to unactivated fluorides, without compromising efficacy and scalability, but also emerges as a potent alternative to other borylation methodologies relying on more reactive carbon−halide (Cl, Br, I) bonds. Notably, the absence of borylation reactivity with B_2Pin_2 underscores the imperative of a nuanced balance of steric effects on the boron reagent for the C-B bond-forming reaction. In the same year, the Hosoya[19] group disclosed a parallel defluoroborylation of fluoroarenes facilitated by a Ni/Cu dual catalytic system (Scheme 1.10 bottom). Herein, B_2Pin_2 was employed to engage with various unactivated fluoroarenes, yielding the desired products with consistently commendable yields. The pivotal role of the Cu catalyst in effecting this transformation cannot be overstated; in its absence, no borylation product was observed, aligning with Martin's findings. Drawing from their experimental outcomes, they posited an unorthodox Ni(I) mechanism wherein the Cu catalyst assumes a dual role: firstly, effecting the oxidation of the Ni(0) complex via one-electron oxidation, and secondly, activating B_2Pin_2 to engender a borylcopper complex. Subsequent to this development, the research group disclosed a copper-catalyzed *ipso*-borylation of fluoroarenes[20]. The orchestration of this reaction unfolds through an $S_{RN}1$ mechanism, characterized by a singular electron-transfer (SET) process. This methodology, distinguished by its expansive substrate scope and commendable scalability, surpasses antecedent reports in its efficacy. It is of particular note that the application of this protocol extends to the efficient achievement of double and triple borylations, exemplifying a notable advancement that augments the synthetic utility of this catalytic approach.

[15] F. Terrier, Ed. In Modern Nucleophilic Aromatic Substitution; Wiley-VCH: Weinheim, Germany, **2013**.
[16] J. Weaver, S. Senaweera, C–F activation and functionalization of perfluoro- and polyfluoroarenes, *Tetrahedron* **2014**, *70*, 7413-7428.
[17] Y. Segawa, Y. Suzuki, M. Yamashita, K. Nozaki, Chemistry of Boryllithium: Synthesis, Structure, and Reactivity, *J. Am. Chem. Soc.* **2008**, *130*, 16069–16079.
[18] X. Liu, J. Echavarren, C. Zarate, R. Martin, Ni-Catalyzed Borylation of Aryl Fluorides via C–F Cleavage, *J. Am. Chem. Soc.* **2015**, *137*, 12470–12473.
[19] T. Niwa, H. Ochiai, Y. Watanabe, T. Hosoya, Ni/Cu-Catalyzed Defluoroborylation of Fluoroarenes for Diverse C–F Bond Functionalizations, *J. Am. Chem. Soc.* **2015**, *137*, 14313–14318.
[20] T. Niwa, H. Ochiai, T. Hosoya, Copper-Catalyzed *ipso*-Borylation of Fluoroarenes, *ACS Catal.* **2017**, *7*, 4535–4541.



Scheme 1.10 Ni-catalyzed Defluoroborylation of Fluoroanrenes

In the year 2018, the Cao[21] research group unveiled a groundbreaking and highly efficacious synthetic methodology, whereby arylboronic acid pinacol esters were synthesized through a palladium-catalyzed borylation of fluoroarenes utilizing B_2Pin_2, all within the ambient presence of lithium hexamethyldisilazide (LiHMDS). This innovative reaction not only operates with diminished catalyst loadings but also exhibits remarkable compatibility with a diverse array of functional groups (Scheme 1.11). Notably, the incorporation of an iron catalyst proves efficacious within this protocol as well. However, it merits emphasis that this alternative approach is restricted to biaryl fluorides, as fluoroarenes lacking a π-conjugated system manifest suboptimal reactivity in this context.

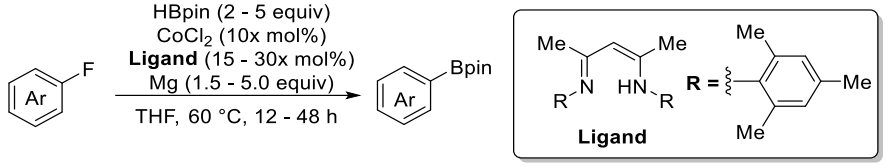


Scheme 1.11 LiHMDS-Promoted Pd-Catalyzed *ipso*-Defluoroborylation

Subsequent to the seminal demonstration by Holland[22] in 2011, illustrating the capacity of a low-valent cobalt complex to activate the recalcitrant C-F bond, the Kim[23] research group has achieved a noteworthy milestone in effecting the C-F bond borylation of aryl fluorides through the strategic implementation of a

[21] X. Zhao, M. Wu, Y. Liu, S. Cao, LiHMDS-Promoted Palladium or Iron-Catalyzed *ipso*-Defluoroborylation of Aryl Fluorides, *Org. Lett.* **2018**, *20*, 5564–5568.
[22] (a) T. R. Dugan, X. Sun, E. V. Rybak-Akimova, O. Olatunji-Ojo, T. R. Cundari, P. L. Holland, A Masked Two-Coordinate Cobalt(I) Complex That Activates C–F Bonds, *J. Am. Chem. Soc.* **2011**, *133*, 12418–12421. (b) T. R. Dugan, J. M. Goldberg, W. W. Brennessel, P. L. Holland, Low-Coordinate Cobalt Fluoride Complexes: Synthesis, Reactions, and Production from C–F Activation Reactions, *Organometallics* **2012**, *31*, 1349–1360.
[23] S. Lim, D. Song, S. Jeon, Y. Kim, H. Kim, S. Lee, H. Cho, B. C. Lee, S. E. Kim, K. Kim, E. Lee, Cobalt-Catalyzed C–F Bond Borylation of Aryl Fluorides, *Org. Lett.* **2018**, *20*, 7249–7252.

cobalt catalyst in tandem with pinacolborane (HBPin) (Scheme 1.12). This innovative methodology facilitates the direct functionalization of fluoroarenes, showcasing a pronounced predilection for the selective borylation of C-F bonds vis-à-vis C-H bonds. Although the intricate mechanism governing this transformative process remains the subject of ongoing investigation, it is noteworthy that magnesium, while serving as a reductant, concurrently exhibits the generation of Grignard reagent during the course of the reaction, thereby introducing a layer of complexity to the overall reaction pathway.



Scheme 1.12 Co-Catalyzed Defluoroborylation with HBpin

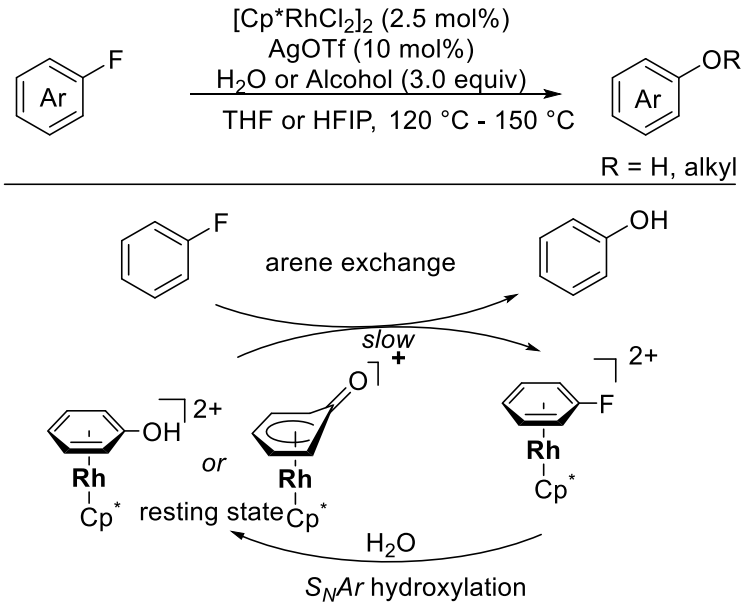
1.4 C-O bond formation reactions

The alkoxylation of aryl fluorides, affording the synthesis of aryl alkyl ethers, presents a formidable challenge within the realm of chemical synthesis. Established methodologies such as the Ullmann, Buchwald-Hartwig, and Chan-Evans-Lam coupling reactions have proven reliable in accessing aryl ethers[24]. However, the applicability of these methods to aryl fluorides, with the exception of activated derivatives, remains limited for the establishment of aryl C-O bonds. In a pivotal advancement dating back to 1988, Shteingarts[25] and collaborators introduced a transformative approach involving rhodium(III)-catalyzed defluoroetherification of fluoroarenes with alcohols. This groundbreaking method demonstrated efficacy with both primary and secondary alcohols, resulting in the generation of the corresponding aryl ethers. Regrettably, tertiary alcohols proved recalcitrant to this transformative process. In the subsequent year 2021, Shi[26] and colleagues further expanded the repertoire of accessible methodologies by unveiling a rhodium(III)-catalyzed S_NAr protocol for the synthesis of phenols and phenyl alkyl ethers utilizing unactivated aryl fluorides (Scheme 1.13). The elucidation of their catalytic cycle revealed a tandem mechanism comprising arene exchange and nucleophilic aromatic substitution on η^6-fluoroarene complexes. Noteworthy is the meticulous comparison of the condensed local electrophilicity indices between 4-nitrofluorobenzene and $[Cp^*Ru^{II}]^+$ activated fluorobenzene, which unveiled the activating effect of the doubly cationic Cp^*Rh^{III} species in the S_NAr reaction. This effect, characterized by a reduction in electron density at the carbon adjacent to the fluorine, underscores the intricacies of the catalytic landscape in the pursuit of aryl C-O bond formation from unactivated aryl fluorides.

[24] (a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, C−C, C−O, C−N Bond Formation on sp2 Carbon by Pd(II)-Catalyzed Reactions Involving Oxidant Agents, Chem. Rev. 2007, 107, 11, 5318–5365; (b) X. Shen, C. N. Neumann, C. Kleinlein, N. W. Goldberg, T. Ritter, Alkyl Aryl Ether Bond Formation with PhenoFluor, *Angew. Chem. Int. Ed.* **2015**, *54*, 5662–5665; (c) S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang, Selected Copper-Based Reactions for C−N, C−O, C−S, and C−C Bond Formation, *Angew. Chem. Int. Ed.* **2017**, *56*, 16136–16179.

[25] L. I. Goryunov, V. V. Litvak, V. D. Shteingarts, Arene complexes of transition metals in reactions with nucleophilic reagents. XVII. Nucleophilic substitution of the fluorine atom by alkoxy groups, catalyzed by the (/eta/-benzene)(/eta/-ethyltetramethylcyclopentadienyl)rhodium(III) dication, in the reaction of fluoroarenes with alcohols, *J. Org. Chem. USSR (Engl.Transl.); (UnitedStates)* **1988**, *24*, 401−405.

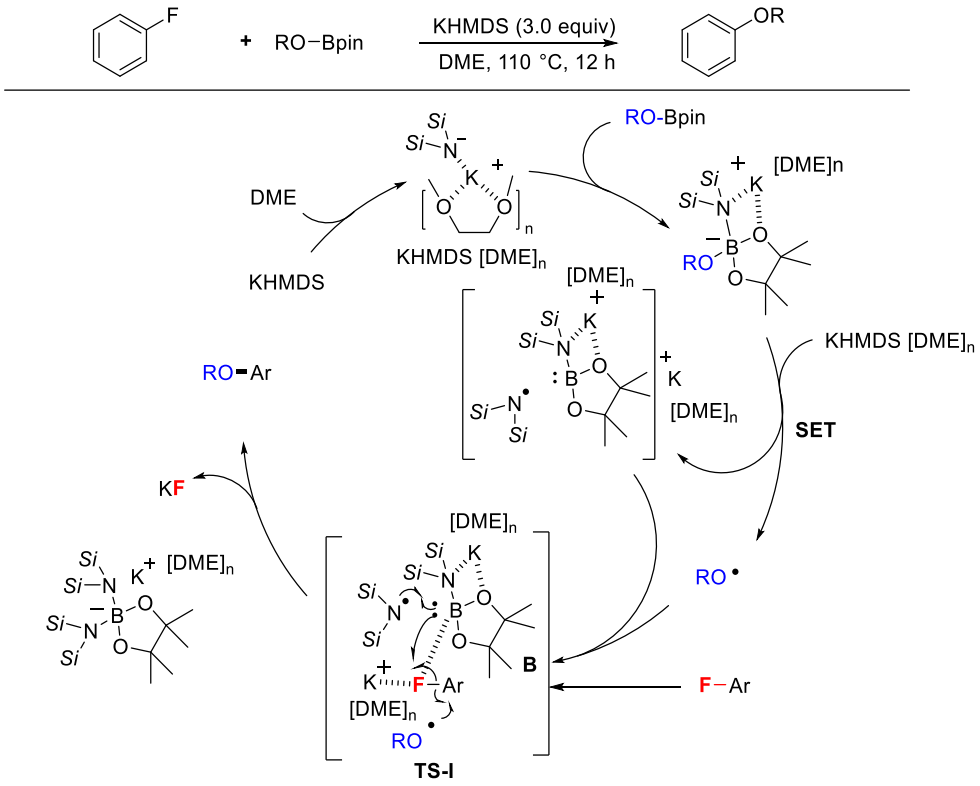
[26] Q. Kang, Y. Lin, Y. Li, L. Xu, K. Li, H. Shi, Catalytic S_NAr Hydroxylation and Alkoxylation of Aryl Fluorides, *Angew. Chem. Int. Ed.* **2021**, *60*, 20391–20399.



Scheme 1.13 Rh-Catalyzed S_NAr Hydroxylation and Alkoxylation of Aryl Fluorides

In 2022, the Shibata [27] research group unveiled a sophisticated potassium-base-mediated defluoroetherification methodology, orchestrating the transformation of (hetero)aryl fluorides through judicious interaction with alkoxyboronic acid pinacol esters (Scheme 1.14), all conducted under conditions devoid of transition metal catalysis. This protocol, distinguished by its efficiency and safety, confers a broad array of aryl ethers in elevated yields, eschewing the need for metallic catalysts or specialized ligands while selectively forging Csp2−O bonds through the incisive cleavage of Csp2−F bonds. Mechanistically, the orchestration of this reaction unfolds through a single electron transfer (SET) process catalyzed by potassium hexamethyldisilazide (KHMDS), resulting in the generation of an alkoxyl radical (RO•). Subsequently, this radical entity engages in an attack upon the benzene ring of the aryl fluoride, an activation achieved through collaboration with the K cation and boron atom in preceding steps, culminating in the synthesis of the respective aryl ethers.

[27] J. Zhou, B. Jiang, Z. Zhao, N. Shibata, Etherification of Fluoroarenes with Alkoxyboronic Acid Pinacol Esters via C−F Bond Cleavage, *Org. Lett.* **2022**, *24*, 5084–5089.



Scheme 1.14 Etherification of Fluoroarenes with Alkoxyboronic Acid Pinacol Esters

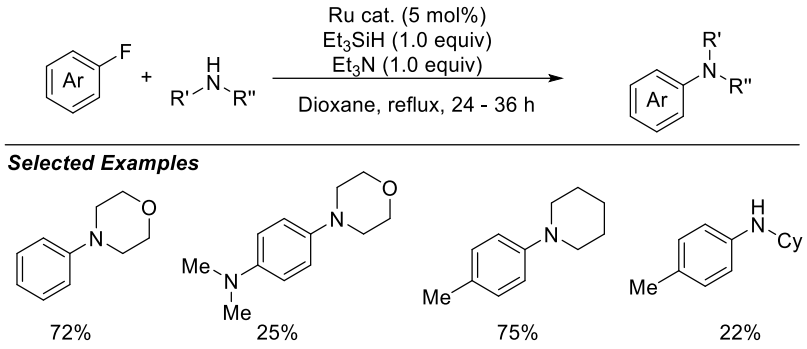
1.5 C-N bond formation reactions

The synthesis of C-N bonds through the interaction between haloarenes and amines stands as a pivotal facet within the realm of organic synthesis. Nonetheless, the inherent reluctance of C-F bonds poses a challenge, rendering unactivated fluoroarene substrates incompatible with transition metal-catalyzed reactions or nucleophilic aromatic substitution involving external nucleophiles. Traditionally, the access to aminated products via the S_NAr process necessitated the use of activated fluoroarenes exclusively. It wasn't until the 1980s that discoveries emerged, enabling the amination of unactivated fluoroarenes with amines via the S_NAr process employing stoichiometric amount of transition metals[28]. However, the limited applicability of these methods stems from the requirement for stoichiometric transition metal usage. Addressing this limitation, Shibata[29] and colleagues pioneered the catalytic S_NAr reaction of unactivated fluoroarenes with amines through Ru η^6-arene complexes. While this reaction exhibited commendable reactivity with cyclic amines, acyclic counterparts yielded lower yields, and less nucleophilic substrates, such as *N*-methyl aniline, failed to yield any product, underscoring the pivotal role of heightened nucleophilicity in achieving

[28] (a) J. P. Gilday, D. A. Widdowson, Flourine directed lithiation in tricarbonylarenechromium(0) complexes: The regiospecific synthesis of polysubstituted arenes, *Tetrahedron Lett.*, **1986**, *27*, 5525-5528; (b) F. Hong, S. Lo, M. Liou, L. Chou, C. Lin, Nucleophilic substitution reactions of (η^6-fluorotoluene)$Cr(CO)_3$ and (η^6-fluoroanisole)$Cr(CO)_3$ toward phenylacetylide, fluorenyl, indolinyl and carbazolinyl lithium: crystal structures of tricarbonyl[η^6-(1,2-diphenylethynyl)benzene]chromium and tricarbonyl[η^6-(1,4-fluorenyl)toluene]chromium, *J. Organomet. Chem.* **1996**, *516*, 123-131; (c) C. Baldoli, S. Maiorana, E. Licandro, L. Casiraghi, G. Zinzalla, P. Seneci, E. D. Magistris, A. Paio, C. Marchioro, Polymer-Supported Haloarene Chromium Dicarbonyl Isonitrile Complexes: A Study of Their Synthesis and Reactivity, *J. Comb. Chem.* **2003**, *5*, 809–813; (d) K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takamoto, H. Matsuzaka, M. Uemura, Stereoselective Synthesis of Both Enantiomers of N-Aryl Indoles with Axially Chiral N−C Bonds, *J. Org. Chem.* **2007**, *72*, 3394–3402.

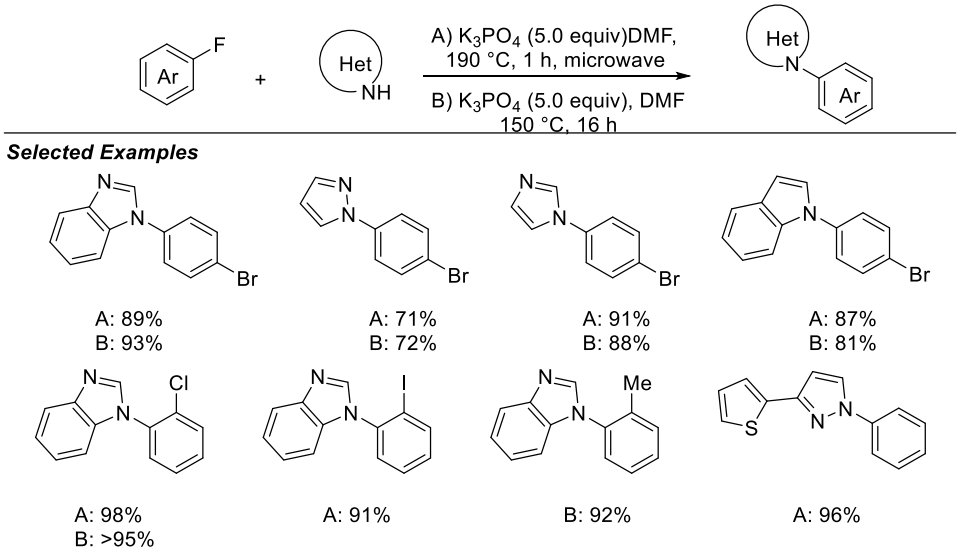
[29] M. Otsuka, K. Endo, T. Shibata, Catalytic S_NAr reaction of non-activated fluoroarenes with amines *via* Ru η^6-arene complexes, *Chem. Commun.* **2010**, *46*, 336–338.

optimal yields. The successful synthesis of proposed Ru η^6-arene complexes strongly supports the inference that this S_NAr reaction proceeds via such intermediates.



Scheme 1.15 S_NAr Reaction of Fluoroarenes with Amines via Ru η^6-arene Complexes

In 2012, the Fairlie[30] group made a notable advancement by unveiling a catalyst-free method for effectuating C-N bond formation through the activation of C-F bonds using azole and indole derivatives (Scheme 1.16). Contrary to conventional wisdom suggesting the unsuitability of unactivated fluoroarenes for S_NAr reactions, the authors discovered that, contingent upon the selection of both base and solvent, the reaction exhibited remarkable expediency under conditions involving elevated reaction temperatures and/or microwave irradiation.

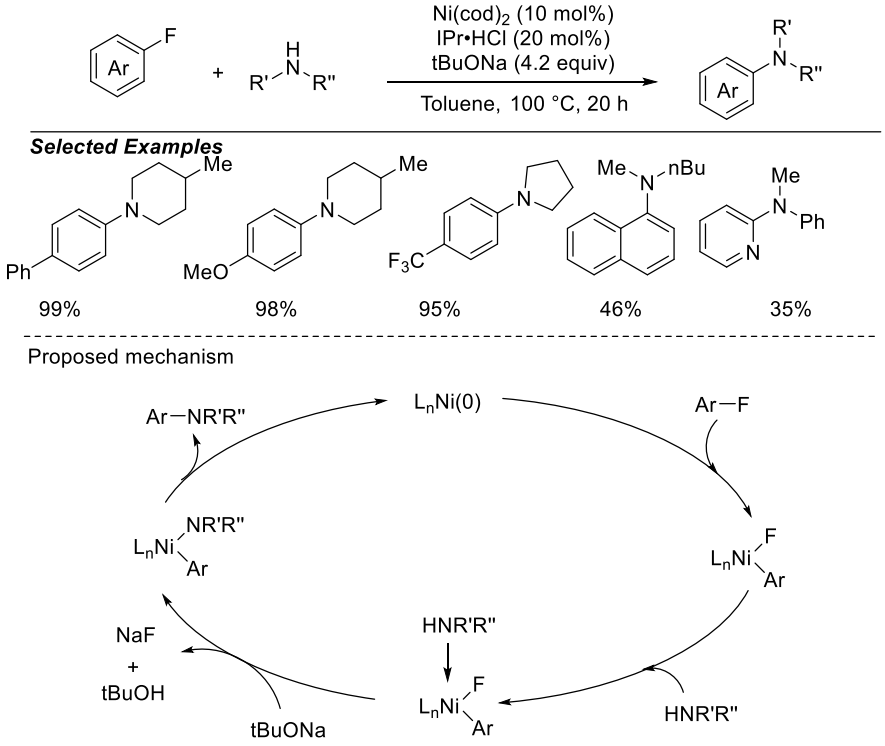


Scheme 1.16 Catalyst-Free N-Arylation Using Unactivated Fluoroarenes

In 2013, Wang[31] and collaborators orchestrated a sophisticated union by employing a combination of a Ni catalyst and a NHC ligand, yielding a robust coupling between unactivated fluoroarenes and secondary amines

[30] F. Diness, D. P. Fairlie, Catalyst-Free N-Arylation Using Unactivated Fluorobenzenes, *Angew. Chem. Int. Ed.* **2012**, *51*, 8012 – 8016.
[31] F. Zhou, Z. Wang, Nickel-Catalyzed Coupling of Fluoroarenes and Amines, *Adv. Synth. Catal.* **2013**, *355*, 3694–3702.

in the presence of sodium tert-butoxide (tBuONa) (Scheme 1.17). This transformative reaction boasts an expansive substrate scope, demonstrating compatibility with diverse functional groups and heteroaryls. Mechanistically elucidated, this process follows a classical Ni(0)/Ni(II) pathway. Initially, the potent electron-donating nature of the carbene ligand facilitates the oxidative addition of the fluoroarene to Ni(0). As per their observations, aryl amido nickel species feature prominently in the subsequent phase of the catalytic cycle. Ultimately, the steric bulk attributed to the carbene arising from the NHC ligand appears instrumental in expediting the carbon-nitrogen bond formation, culminating in the yield of the final product through reductive elimination. The inability to procure secondary aryl amines through the utilization of primary amines within this protocol prompted the Sawamura[32] group in 2018 to devise a Ni-catalyzed cross-coupling reaction between fluoroarenes and primary amines, employing bidentate phosphine ligands. This methodology exclusively yielded secondary amines, thereby supplementing and advancing the findings established by Wang's earlier work.

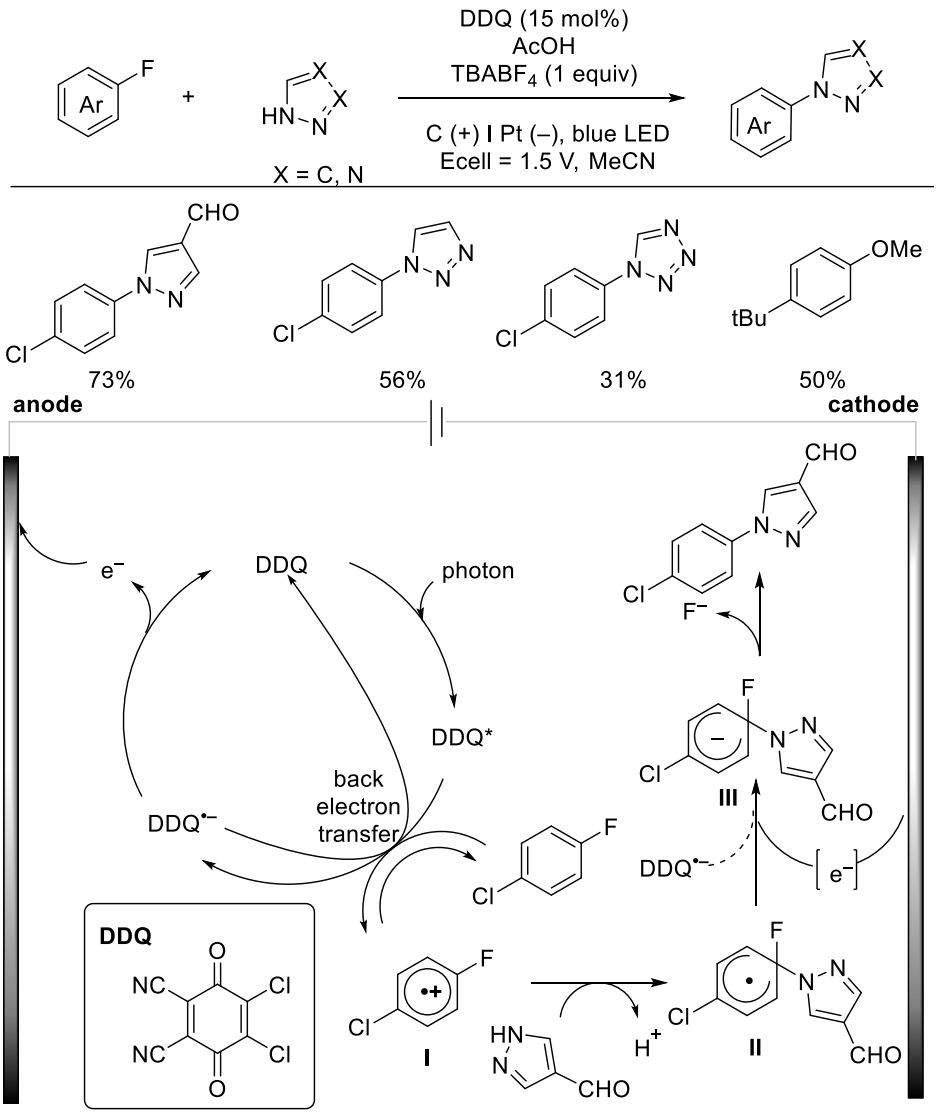


Schem1.17 Ni-Catalyzed Coupling of Fluoroarenes and Amines

In 2019, Lambert[33] and colleagues unveiled a pioneering electrophotocatalytic S_NAr reaction, heralding a breakthrough in effectuating C-N bond formation utilizing unactivated fluoroarenes under ambient conditions devoid of strong base involvement. The benign reaction milieu of this method delineates its remarkable substrate tolerance; not confined to pyrazole, it also accommodates alcohols—an aspect contributing to its versatility. It is essential to underscore that fluoroarenes possessing electron-neutral characteristics exhibit greater favorability in this reaction. Mechanistically, this process commences with the photoexcitation of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), giving rise to an excited state species possessing the capacity to oxidize fluoroarenes. Subsequent nucleophilic attack by pyrazole with the resulting radical cation **I**

[32] T. Harada, Y. Ueda, T. Iwai, M. Sawamura, Nickel-catalyzed amination of aryl fluorides with primary amines, *Chem. Commun*. **2018**, *54*, 1718—1721.
[33] H. Huang, T. H. Lambert, Electrophotocatalytic S_NAr Reactions of Unactivated Aryl Fluorides at Ambient Temperature and Without Base, *Angew. Chem. Int. Ed*. **2020**, *59*, 658–662.

generates radical **II**. The envisaged transformation of **II** via a one-electron reduction to produce an anion **III**, facilitating the expulsion of the fluoride leaving group and subsequent product formation, was initially postulated. However, owing to the limited reductive capacity of the DDQ radical anion, the closure of the catalytic cycle through an electron transfer from DDQ radical anion to **II** seems unattainable. Instead, the reduction of **II** and the reoxidation of DDQ radical anion likely necessitate electrochemical mediation to ensure the completion of the cycle.

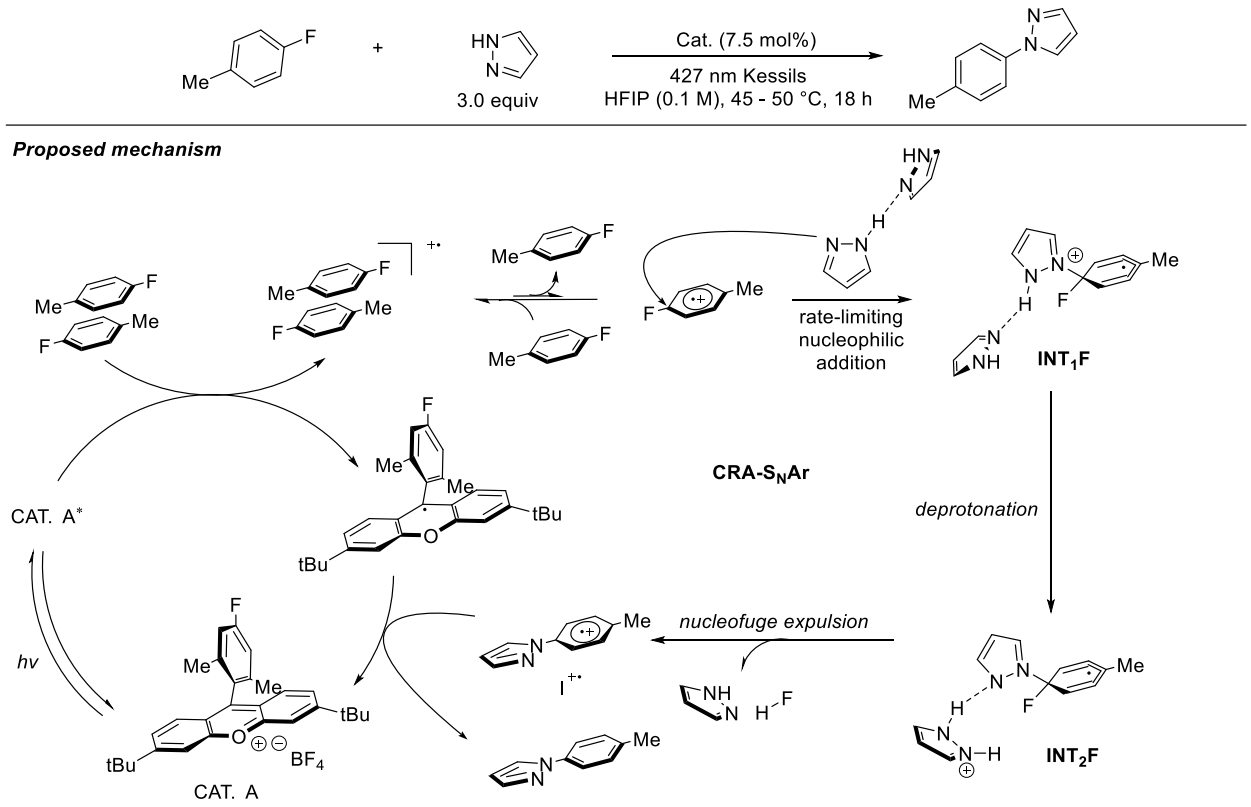


Scheme 1.18 Electrophotocatalytic S_NAr Reactions of Unactivated fluoroarenes

In the year 2020, Nicewicz[34] introduced an innovative organic photoredox-catalyzed nucleophilic aromatic substitution method tailored for unactivated fluoroarenes, accommodating a diverse array of nucleophilic classes, ranging from azoles to amines and carboxylic acids (Scheme 1.19). Notably, both electron-rich and electron-neutral fluoroarenes manifest suitability within this framework. Initially posited as a cation radical

[34] V. A. Pistritto, M. E. Schutzbach-Horton, D. A. Nicewicz, Nucleophilic Aromatic Substitution of Unactivated Fluoroarenes Enabled by Organic Photoredox Catalysis, *J. Am. Chem. Soc.* **2020**, *142*, 17187−17194.

accelerated nucleophilic aromatic substitution (CRA-S_NAr)[35] pathway, subsequent kinetic experimentation diverged from this hypothesis, revealing the existence of fluoroarenes in solution as ground state dimers facilitated by a slipped-stacking arrangement between two fluoroarene molecules. Consequent revisions in the proposed reaction mechanism, informed by Density Functional Theory (DFT) calculations, elucidated that fluoroarenes in solution exist as dimers undergoing single-electron transfer with the photocatalyst. which engenders the generation of an arene cation radical dimer, capable of dissociating to unveil a liberated arene cation radical. This intermediate is prone to interception by pyrazole, forming **INT_1F**, while a second equivalent of pyrazole engages in hydrogen bonding with the active nucleophile, based on the second-order kinetics observed. The subsequent addition step, irreversible and deemed rate-limiting, prompts rapid, barrier-free deprotonation of **INT_1F**, yielding **INT_2F** and pyrazolium. Fluoride, as a nucleofuge, is expelled from **INT_2F**, facilitated by the intervention of pyrazolium. This process leads to the concomitant creation of hydrofluoric acid alongside pyrazole, culminating in the generation of the $\mathbf{I}^{\cdot+}$ radical cation intermediate. Ultimately, the reduction of the $\mathbf{I}^{\cdot+}$ radical cation effectuates the production of the observed substitution product, concurrently restoring the catalyst to its functional state[36].



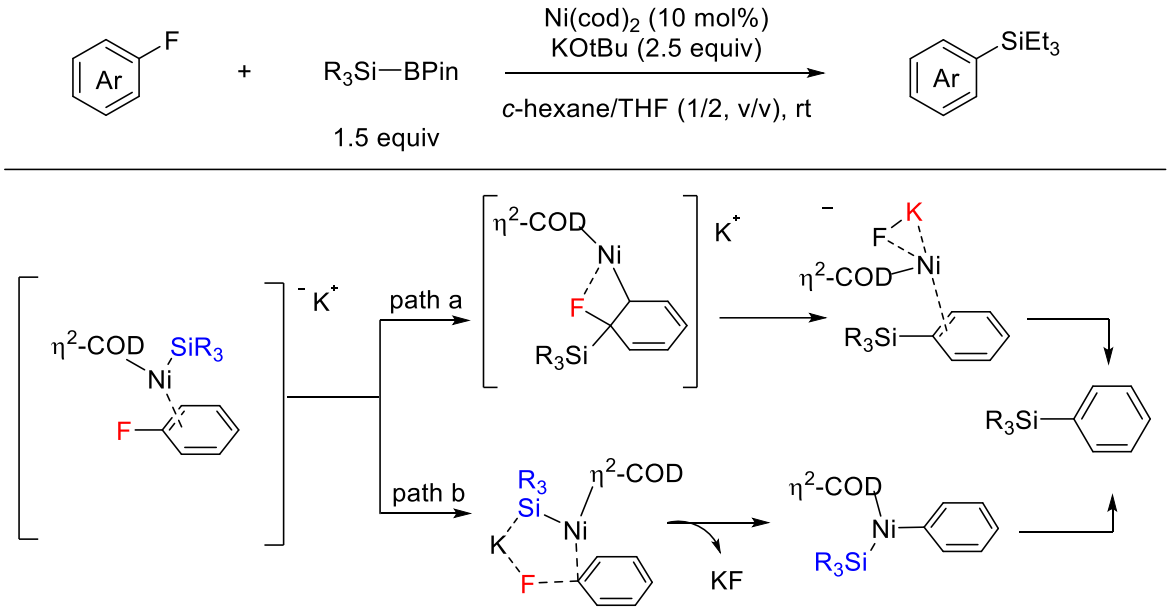
Scheme 1.19 Photoredox catalysis enabled S_NAr reaction of unactivated fluorroarenes

[35] (a) N. E. S. Tay, D. A. Nicewicz, Cation Radical Accelerated Nucleophilic Aromatic Substitution *via* Organic Photoredox Catalysis, *J. Am. Chem. Soc.* **2017**, *139*, 16100–16104; (b) N. Holmberg, D. A. Nicewicz, Arene Cyanation *via* Cation-Radical Accelerated-Nucleophilic Aromatic Substitution, *Org. Lett.* **2019**, *21*, 7114–7118; (c) N. J. Venditto, D. A. Nicewicz, Cation Radical-Accelerated Nucleophilic Aromatic Substitution for Amination of Alkoxyarenes, *Org. Lett.* **2020**, *22*, 4817–4822; (d) N. E. S. Tay, W. Chen, A. Levens, V. A. Pistritto, Z. Huang, Z. Wu, Z. Li, D. A. Nicewicz, ^{19}F- and ^{18}F-arene deoxyfluorination via organic photoredox-catalysed polarity-reversed nucleophilic aromatic substitution, *Nat. Catal.* **2020**, *3*, 734-742.

[36] V. A. Pistritto, S. Liu, D. A. Nicewicz, Mechanistic Investigations into Amination of Unactivated Arenes via Cation Radical Accelerated Nucleophilic Aromatic Substitution, *J. Am. Chem. Soc.* **2022**, *144*, 15118–15131.

1.6 C-Si Bond Formation Reactions

Organosilicon compounds have garnered extensive utilization in catalysis and a multifarious array of reactions, serving as both substrates and reagents. In the year 2018, the Shibata[37] group disclosed a pioneering Ni-catalyzed defluorosilylation reaction, marking the inaugural utilization of a silyl boronated reagent in conjunction with tBuOK. This groundbreaking approach exhibited notable compatibility with both electron-neutral and electron-rich fluoroarenes. The intricate mechanistic pathway hinges upon the generation of an active nickel complex, wherein the subsequent steps diverge contingent upon the nature of the substrates involved. In the case of π-extended aromatic rings, the reaction embarks upon an internal nucleophilic aromatic substitution pathway, attributing this behavior to the η^2 coordination with nickel while retaining aromaticity. Conversely, simpler fluoroarenes are more inclined toward a non-classical oxidative addition pathway, navigated through a five-centered transition state, culminating in C-F bond cleavage. Subsequent to this milestone, the following year witnessed the Martin[38] group unveiling a parallel transformation devoid of transition metals. This alternative approach operates through a concerted S_NAr process, representing a noteworthy departure from the metal-catalyzed paradigm.



Scheme 1.20 Ni-catalyzed defluorosilylation of unactivated fluoroarenes

Subsequent to these seminal discoveries, a succession of defluorosilylation reactions concerning fluoroarenes has been documented by several researchers[39]. Despite the diverse repertoire of nucleophilic silyl sources like $PhMe_2SiBpin$ and $PhMe_2SiLi$ utilized to effectuate this transformation, these reactions have exhibited a proclivity towards electron-rich and electron-neutral fluoroarenes. However, it is noteworthy that these

[37] B. Cui, S. Jia, E. Tokunaga, N. Shibata, Defluorosilylation of fluoroarenes and fluoroalkanes, *Nat. Commun.* **2018**, *9*, 4393-4400.

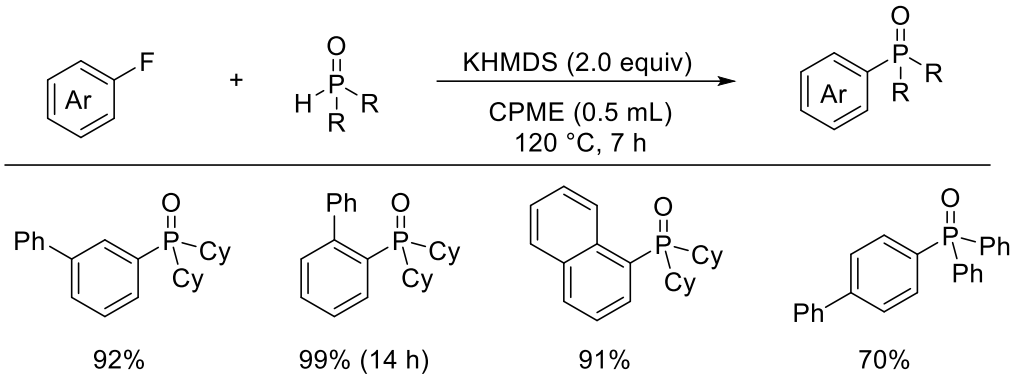
[38] X. Liu, C. Zarate, R. Martin, Base-Mediated Defluorosilylation of C(sp2)−F and C(sp3)−F Bonds, *Angew. Chem. Int. Ed.* **2019**, *58*, 2064–2068.

[39] (a) S. Mallick, P. Xu, E. Würthwein, A. Studer, Silyldefluorination of Fluoroarenes by Concerted Nucleophilic Aromatic Substitution, *Angew. Chem. Int. Ed.* **2019**, *58*, 283–287; (b) K. Kojima, Y. Nagashima, C. Wang, M. Uchiyama, *In Situ* Generation of Silyl Anion Species through Si−B Bond Activation for the Concerted Nucleophilic Aromatic Substitution of Fluoroarenes, *ChemPlusChem* **2019**, *84*, 277–280; (c) S. Lim, H. Cho, J. Jeong, M. Jang, H. Kim, S. H. Cho, E. Lee, Cobalt-Catalyzed Defluorosilylation of Aryl Fluorides via Grignard Reagent Formation, *Org. Lett.* **2020**, *22*, 7387–7392; (d) M. Sun, M. Tao, L. Zhao, W. Li, Z. Liu, C. He, Z. Feng, Iron-catalyzed C–F bond silylation and borylation of fluoroarenes, *Org. Chem. Front.* **2021**, *8*, 5322-5327.

advancements did not yield substantial enhancements beyond the antecedent methodologies previously established. Further development and refinement of a more extensive and inclusive methodology remains imperative to adequately address the multifaceted aspects of the subject matter at hand.

1.7 C-P Bond Formation Reactions

In the year 2021, the Sawamura[40] group pioneered a novel base-induced phosphinylation technique targeting unactivated fluoroarenes (Scheme 1.21). Quantum chemical computations have delineated this reaction as reliant on nucleophile sensitivity, elucidating a mechanism that amalgamates both concerted and stepwise S_NAr processes. This mechanistic peculiarity proves intriguing as conventional wisdom dictates S_NAr reactions to be predominantly governed by the electronic properties of aryl electrophiles, rather than nucleophiles. Despite demonstrating compatibility with both electron-rich and electron-deficient fluoroarenes, it's crucial to underscore that electron-rich substrates chiefly represent π-extended architectures, whereas monocyclic fluoroarenes exhibited negligible reactivity within this transformation.

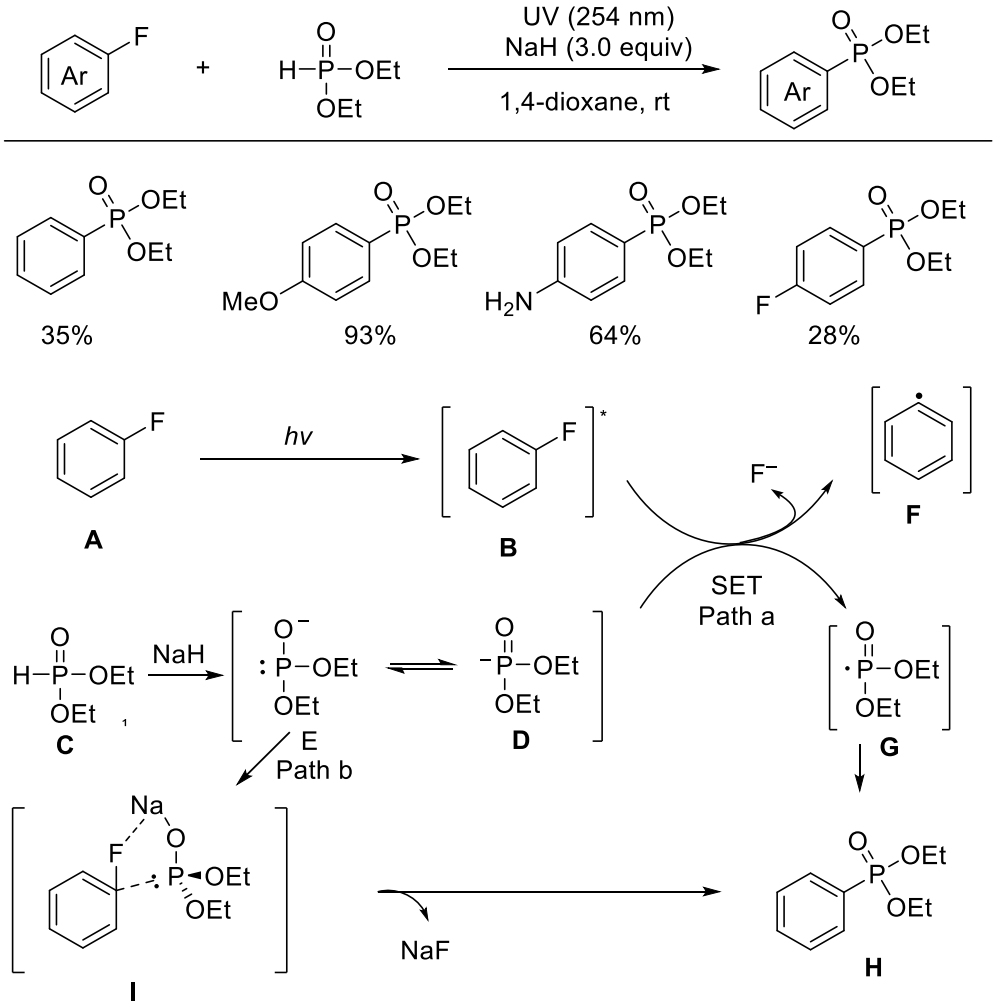


Scheme 1.21 Phosphinylation of unactivated fluoroarenes via concerted and stepwise S_NAr pathway

In that same year, Li[41] and colleagues unveiled a photoinduced phosphonation method targeting unactivated fluoroarenes, adeptly navigating a Single Electron Transfer (SET) process sans any reliance on external photosensitizers or transition metals (Scheme 1.22). This innovative approach partially mitigated the limitations observed in the aforementioned reaction; monocyclic fluoroarenes demonstrated successful transformation into the corresponding products, yielding moderate to commendable yields. Complementary to the experimental investigations on the mechanism, a proposed photoinduced SET pathway emerged from the studies. Under ultraviolet (UV) irradiation, Fluorobenzene A undergoes an ascent to an excited state B, fostering its reaction with diethyl phosphite anion D—formed from ethyl phosphite under profoundly basic conditions. This interaction begets the generation of aryl radical F and diethyl phosphite radical G via intermolecular single electron transfer (path a), concomitant with the release of fluoride anion. Subsequently, these two radicals engage in a coupling event, culminating in the formation of the targeted product. An alternate pathway, albeit viable, involves the interaction of diethyl phosphite (III) anion E with the excited state of fluorobenzene B through an intermolecular six-membered ring (path b), resulting in the expulsion of sodium fluoride and ultimately leading to product formation. Subsequently, two years later, the Zhou[42] group divulged a Ni-catalyzed phosphorylation technique targeting fluoroarenes, showcasing compatibility with both electron-

[40] Z. You, K. Higashida, T. Iwai, M. Sawamura, Phosphinylation of Non-activated Aryl Fluorides through Nucleophilic Aromatic Substitution at the Boundary of Concerted and Stepwise Mechanisms, *Angew. Chem. Int. Ed.* **2021**, *60*, 5778–5782.
[41] Q. Dou, Y. Lang, H. Zeng, C. Li, Photoinduced transition-metal and external photosensitizer free phosphonation of unactivated C(sp2)–F bond via SET process under mild conditions, *Fundamental Research* **2021**, *1*, 742–746.
[42] J. Yang, L. Fan, C. Chen, M. Wang, B. Sun, S. Wang, H. Zhong, Y. Zhou, Ni-catalyzed C–F activation to construct C–P bond with P–P(O) and P(O)OR mediation, *Org. Biomol. Chem.* **2023**, *21*, 494–498.

rich and electron-deficient monocyclic fluoroarenes—a facet ascribed to the catalytic prowess of nickel. Notably, the Ni-catalyst played a dual role, not only catalyzing the formation of P(III)-P(V)=O intermediates with the aid of a base and fluoroarenes but also facilitating the activation of otherwise inert unactivated fluoroarenes in the reaction process.



Scheme 1.22 Photoinduced phosphonation of unactivated fluoroarenes via SET process

1.8 Conclusion

The exploration of C-F bond activations in unactivated aryl fluorides has been a captivating endeavor, redefining the landscape of modern organic synthesis. The relentless pursuit to surmount the intrinsic inertness of C-F bonds has led to pioneering methodologies, unveiling the potential for diverse chemical bond transformations. The evolution of transition metal-catalyzed reactions has stood out as a cornerstone in this domain, showcasing innovative strategies to breach the perceived inertness of aryl fluorides. Catalysts such as nickel, cobalt, and ruthenium have enabled a spectrum of pathways, from electrophilic aromatic substitution to radical-based mechanisms, thereby broadening access to functionalized aryl fluoride derivatives. Mechanistic insights gained from these reactions have deepened our understanding of the intricate interplay between catalysts and substrates. The revelation of diverse pathways, including SET processes, nucleophile-dependent mechanisms, and S_NAr processes, has underscored the versatility inherent in C-F bond activation reactions, fostering novel avenues for innovation.

1.9 Perspective

Despite remarkable progress, challenges persist, particularly in extending the reactivity scope to encompass electron-deficient substrates and monocyclic fluoroarenes. Bridging this gap demands the exploration of novel catalytic systems and ligands, along with a deeper comprehension of reaction mechanisms. Looking forward, the trajectory of C-F bond activation in unactivated aryl fluorides holds immense promise. Further advancements in catalytic systems, coupled with computational and experimental synergy, will expand our arsenal of efficient and selective methodologies. Bridging academia-industry collaborations will facilitate the translation of fundamental discoveries into practical applications, powering advancements in pharmaceuticals, agrochemicals, and materials science. Moreover, the pursuit of sustainable, cost-effective, and highly selective strategies for C-F bond activation remains a pivotal focus, shaping the forefront of chemical innovation. Continued exploration in this field will not only unlock new synthetic possibilities but also catalyze transformative advancements across various industries in the years ahead.

Chapter 2. Silylboronate-mediated Defluorosilylation of Aryl Fluorides with or without Ni-catalyst

Introduction

Organosilicon compounds represent a fascinating and pivotal class of chemicals that have garnered immense attention and utility across various scientific disciplines and industries. The impact of organosilicon compounds spans multiple sectors, including but not limited to organic synthesis[43], materials science[44], and pharmaceuticals[45]. The scarcity of naturally-occurring organosilicon compounds coupled with their pivotal significance across diverse domains within the realm of chemistry has prompted the pursuit of synthetic methodologies aimed at forging carbon–silicon bonds.[46]

Aryl silanes, an integral subset within the realm of organosilicon compounds, play an indispensable and pivotal role in the domain of organic synthesis. The synthesis of these compounds typically involves the reaction between aryl Grignard or aryl lithium compounds with chlorosilanes.[47] The exploration of transition-metal-catalyzed silylation has predominantly focused on aryl halides (Cl, Br, I).[48] Nonetheless, the utilization of fluoroarenes for silylation remained uncharted territory due to the inherent inertness of the C-F bond. However, in 2018, our research group pioneered a groundbreaking Ni-catalyzed defluorosilylation methodology that effectively harnessed fluoroarenes under mild reaction conditions.[37] Since then, several strategies have emerged aiming to achieve similar transformations sans the involvement of transition metals.[38,39] In 2021, our research further delved into the realm of catalyst-free carbosilylation, targeting alkenes by leveraging $R_3SiBPin$ in conjunction with organic fluorides, encompassing both aryl and alkyl derivatives, thereby enabling selective C–F bond activation.[49] Although a slightly enhanced substrate scope was observed

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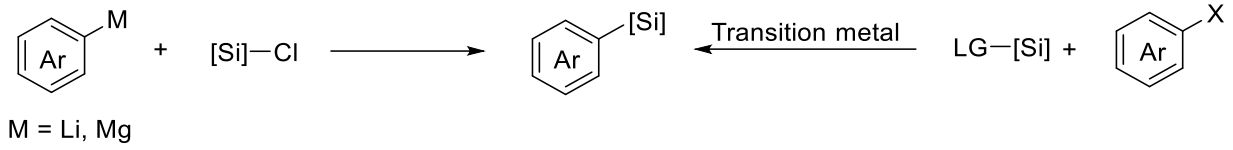
when employing Ni-catalysis, the discernible impact of the Ni-catalyst was not overwhelmingly significant. This observation posits that the indispensability of Ni-catalysis for these transformations is less definitive, as the reaction conditions vary notably in terms of bases, solvents, and reaction durations, complicating a definitive assessment of the Ni-effect. Consequently, we embarked on a meticulous re-evaluation of our initial 2018 defluorosilylation methodology, employing identical conditions involving $R_3SiBPin$ in the presence or absence of Ni-catalyst and KOtBu. This reinvestigation culminated in the elucidation of refined and catalyst-free conditions for effectuating the silylboronate-mediated defluorosilylation of aryl fluorides. An array of aryl fluorides featuring diverse aromatic ring substitutions were proficiently transformed into their corresponding aryl silanes utilizing $R_3SiBPin$ (2.0 equiv) alongside KOtBu (3.0 equiv) in a mixed solvent system (*c*-hex/THF = 1/2) at ambient temperature. Additionally, the protocol exhibited proficiency in the synthesis of heteroaromatic silanes from heteroaromatic fluorides. While the yields attained under catalyst-free conditions were comparatively lower than those under Ni-catalysis, the transition-metal-free approach inherently embodies the principles of green chemistry, positing its advantage in sustainable synthetic methodologies.

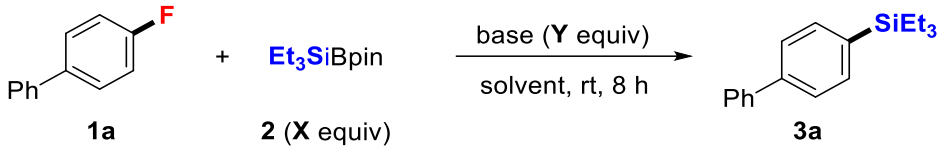


Scheme 2. 2 Conventional Synthetic methodology for preparation of aryl silanes

Optimization of Reaction Conditions

To initiate the optimization process, the 4-fluorobiphenyl (**1a**) and silylboronate $Et_3SiBpin$ (**2**) were meticulously chosen as the model substrates to examine the defluorosilylation reaction. Leveraging our earlier documented conditions for the Ni-catalyzed defluorinative silylation of aryl fluorides **1** [utilizing $Et_3SiBpin$ (1.5 equiv), KOtBu (2.5 equiv), and 10 mol% $Ni(cod)_2$ in a solvent mixture of cyclohexane (*c*-hex) and THF (1/2, v/v) at ambient temperature], we embarked on the reaction involving **1a** and **2** under the aforementioned conditions, albeit in the absence of the Ni-catalyst. All optimization were meticulously conducted on 0.1 mmol scale of **1a**. The anticipated biphenyl-4-yl-triethylsilane (**3aa**) materialized, albeit in a 65% ^1H NMR yield after an 8-hour interval (entry 1, Table 1). As a comparison with Uchiyama's reaction conditions[12b] (NaOtBu, THF), substituting KOtBu with NaOtBu led to a 58% yield of **3a** (entry 2). However, alternative bases like LiOtBu or KOMe exhibited inertness, failing to trigger the reaction (entries 3 and 4). Attempting Martin's conditions[12a] (LiHMDS, DME) with our solvent system (*c*-hex/THF = 1/2, v/v) resulted in no discernible reaction (entry 5). Intriguingly, the utilization of KHMDS facilitated the defluorosilylation reaction, yielding **3a** in 27% yield (entry 6). Further exploration involving individual solvents such as *c*-hex, THF, or diglyme highlighted the superiority of the mixed solvent system, *c*-hex/THF (entry 1), over others (entries 7-9). Optimization of **2** and KOtBu quantities revealed that 2.0 equiv of **2** and 3.0 equiv of KOtBu were optimal, affording **3a** in a 74% yield (56% isolated yield; entry 11). To reaffirm the significance of $Ni(cod)_2$, the reaction was conducted under these optimized conditions (entry 11) but reintroducing Ni catalyst. The defluorosilylation reaction exhibited enhanced efficiency with $Ni(cod)_2$ under the optimal conditions, providing **3a** in an 83% yield (65% isolated yield; entry 12). These comparative analyses substantiate the pivotal role of $Ni(cod)_2$ in accelerating this defluorinative transformation, while emphasizing the greener prospects offered by the transition-metal-free variant (entry 11).

Table 2.1 Optimization of defluorosilylation reaction conditions



Entry	X	Base (Y)	Solvent	Yield of 3a[a]
1	1.5	KOtBu (2.5)	*c*-hex/THF (1/2)	65%
2	1.5	NaOtBu (2.5)	*c*-hex/THF (1/2)	58%
3	1.5	LiOtBu (2.5)	*c*-hex/THF (1/2)	N.R.
4	1.5	KOMe (2.5)	*c*-hex/THF (1/2)	N.R.
5	1.5	LiHMDS (2.5)	*c*-hex/THF (1/2)	N.R.
6	1.5	KHMDS (2.5)	*c*-hex/THF (1/2)	27%
7	1.5	KOtBu (2.5)	*c*-hex	45%
8	1.5	KOtBu (2.5)	THF	62%
9	1.5	KOtBu (2.5)	diglyme	45%
10	1.5	KOtBu (3.0)	*c*-hex/THF (1/2)	60%
11	2.0	KOtBu (3.0)	*c*-hex/THF (1/2)	74% (56%)[c]
12[b]	2.0	KOtBu (3.0)	*c*-hex/THF (1/2)	83% (65%)[c]

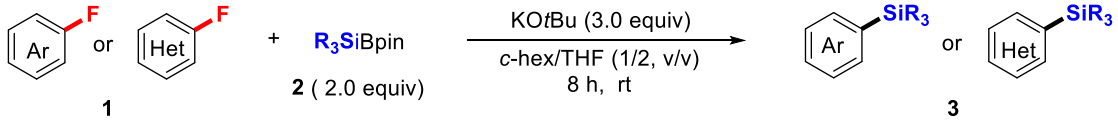
[a]Unless otherwise noted, the reaction was carried out using **1a** (0.1 mmol), $Et_3SiBpin$ (**2**), and a base in solvent (0.6 mL, *v/v*) at rt for 8 h; yields were determined by ^1H NMR and ^{19}F NMR analysis of the crude reaction mixture using 3-fluoropyridine as the internal standard. [b]10 mol% $Ni(cod)_2$ was added. [c]Isolated yield is shown in parentheses.

Substrate Scope

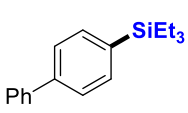
With the optimal reaction conditions (entry 11, Table 2.1), our subsequent investigation delved into exploring the viability of a transition-metal-free defluorosilylation reaction (Table 2.2). Executed on a 0.2 mmol scale of **1**, this exploration encompassed a series of aromatic fluorides under catalyst-free conditions. Impressively, our endeavors yielded favorable outcomes, converting a diverse array of fluoroarenes **1** into their corresponding defluorosilylation products **3** with commendable efficiency. Noteworthy was the versatility observed, demonstrating the feasibility of substitutions at various positions (*o*-, *m*-, or *p*-) within the aromatic moiety of **1**, offering the corresponding products **3** (**3a**: 59%; **3b**: 51%; **3c**: 26%; **3d**: 40%; **3e**: 55%) in yields ranging from acceptable to commendable (26%−59%) under catalyst-free conditions. Repeating the identical substrate scope in the presence of $Ni(cod)_2$ (entry 12, Table 2.1) substantially improved the yield of products **3a**–**3e** (**3a**: 86%; **3b**: 82%; **3c**: 74%; **3d**: 70%; **3e**: 79%). Evidently, these discernible differences underscore the efficiency imparted by $Ni(cod)_2$. For comprehensive elucidation, previous outcomes involving $Ni(cod)_2$ are referenced in Table 1, reaffirming the advantageous role played by the Ni catalyst. Additionally, fluoroarenes 1f–1h bearing electron-rich substitutions exhibited favorable tolerance within this defluorosilylation reaction, albeit in moderate yield (**3f**: 46%; **3g**: 45%; **3h**: 39%). Encouragingly, the synthesis of several substituted aryl silanes (**3i**–**3n**) was obtained under identical conditions, accommodating a diverse array of functional groups such as OMe (**1j**), OMOM (**1k**), OPh (**1l**), NMe_2 (**1m**), and 1*H*-pyrrole (**1n**) with moderate success. Furthermore, the successful transformation of nitrogen-containing hetero-aromatic fluorides **1o**–**1q** into their corresponding silanes **3** was notable. Notably, 5-fluoro-2-phenylpyridine (**1o**) and 1*H*-indole derivatives (**1p** and **1q**), featuring active C–H bonds, underwent the selective defluorosilylation process to furnish the desired products (**3o**: 43%; **3p**: 37%; **3q**: 42%) seamlessly. Remarkably, even 1,2-difluorobenzene (**1r**) demonstrated efficient mono-silylation, culminating in a commendable yield (**3r**: 62%). Furthermore, exploration involving alternative silyl boronates such as $PhMe_2SiBpin$ (**2b**) and $tBuMe_2SiBPin$ (**2c**) instead of **2a** yielded the

corresponding silylated products **3a'** and **3a''** in 36% and 51% yield, respectively. Across the series of explored cases, the Ni catalyst-based protocol[37] consistently demonstrated substantial yield advantages within this defluorosilylation reaction.

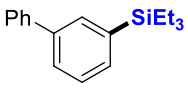
Table 2.2 Substrate scope of the defluorosilylation strategies[a]



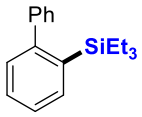
1 **3**



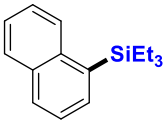
3a: 59%
with [Ni]: 86%
with [Ni]: 71%[b]



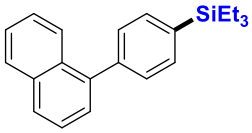
3b: 51%
with [Ni]: 82%
with [Ni]: 76%[b]



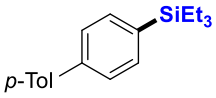
3c: 26%
with [Ni]: 74%
with [Ni]: 69%[b]



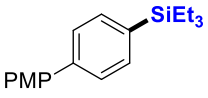
3d: 40%[c]
with [Ni]: 70%
with [Ni]: 61%[b]



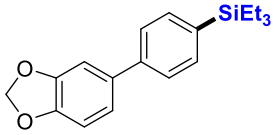
3e: 55%
with [Ni]: 79%



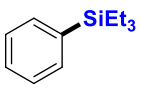
3f: 46%
with [Ni]: 84%[b]



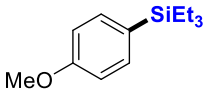
3g: 45%
with [Ni]: 63%[b]



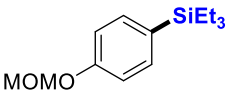
3h: 39%
with [Ni]: 51%[b]



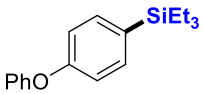
3i: 48%[c]
with [Ni]: 75%[b]



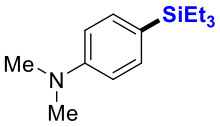
3j: 32%[c]
with [Ni]: 70%[b]



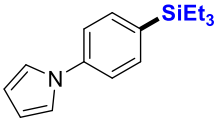
3k: 25%
with [Ni]: 58%[b]



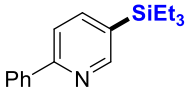
3l: 41%
with [Ni]: 65%[b]



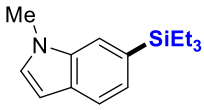
3m: 41%
with [Ni]: 77%[b]



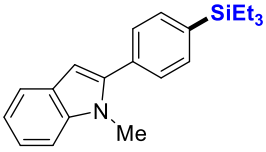
3n: 46%
with [Ni]: 62%[b]



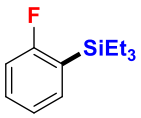
3o: 43%
with [Ni]: 76%



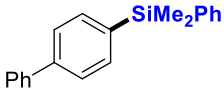
3p: 37%
with [Ni]: 71%[b]



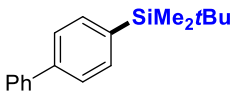
3q: 42%
with [Ni]: 67%[b]



3r: 62%[c]
with [Ni]: 70%[b]



3a': 36%
with [Ni]: 55%[b]



3a'': 51%
with [Ni]: 78%

[a]Unless otherwise noted, the reaction was carried using **1** (0.2 mmol), **2** (2.0 equiv), and KO*t*Bu (3.0 equiv) without or with $Ni(cod)_2$ (10 mol%) in *c*-hex/THF (1.2 mL, 1/2, *v/v*) at rt for 8 h. Isolated yields are shown. [b]The yields shown are previously reported data by using reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv), $Ni(cod)_2$ (10 mol%), KO*t*Bu (2.5 equiv), *c*-hex/THF (0.8 mL, 1/2, *v/v*), rt, 2–12 h. [c]0.4 mmol **1** was used. PMP: *p*-methoxyphenyl. MOM: methoxymethyl.

Mechanistically Study

Drawing from our precedent work encompassing the defluorosilylation of alkyl fluorides **1** employing

$R_3SiBPin$ **2**, mediated by a potassium base[37], as well as the notable contributions elucidating the defluorosilylation of aryl fluorides facilitated by a lithium base (Martin)[38] and a sodium base (Uchiyama)[39b], the anticipated mechanism unfolds through the nucleophilic interception of the silyl anion, culminating in a concerted S_NAr process. We extrapolate insights from our prior endeavors and Uchiyama's DFT calculations.[39b] Initially, the reaction initiates with the interaction between $R_3SiBPin$ **2** and tBuOK, culminating in the generation of a potassium silyl anion species denoted as **C**, intricately coordinated with tBuO-BPin via intermediates A and B.[37,49,50] Following this intricate coordination, species **C** engages the aryl fluoride **1**, leading to the formation of intermediate **I**. Notably, a concerted S_NAr reaction ensues, featuring the boron center of tBuO-BPin encountering another tBuOK via transition state **II**, orchestrating the critical C–F bond cleavage while furnishing the coveted aryl silanes **3**. Simultaneously, this transformation yields KF and **D**, corroborated by the generation of $K^+[tBuO_2BPin]^-$ (Figure 2.1).

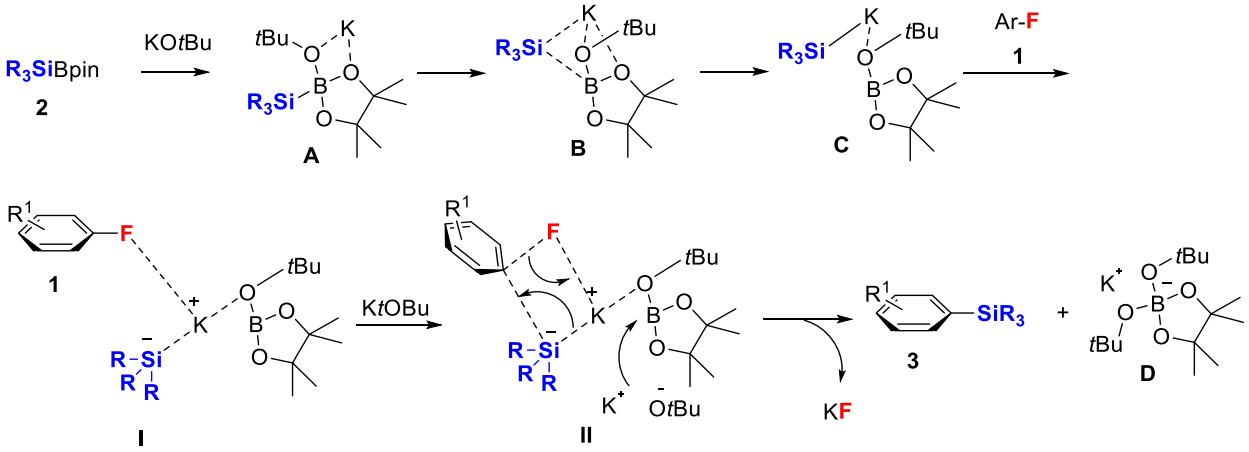


Figure 2.1 Proposed Reaction Mechanism

Conclusion

In summary, our study delineates a viable transition-metal-free avenue in the synthesis of aryl silanes **3** via the defluorosilylation process targeting aryl fluorides **1**, employing silylboronates $R_3SiBPin$ **2** in conjunction with KOtBu. Moreover, juxtaposing our recent findings with a precedent employing Ni-catalyzed defluorosilylation of fluoroarenes, our assessment underscores the viability of effectuating the transformation of aryl fluorides into their respective aryl silanes, bypassing the reliance on $Ni(cod)_2$. Nonetheless, it is noteworthy that the achieved yields under this transition-metal-free protocol, while feasible, trend relatively lower compared to the robust yields attained via the Ni-catalyzed protocol, a consequence attributable to distinctive reaction mechanisms. Our ongoing endeavors are directed towards the broadened extension and refinement of this methodology, aiming to expand its applicability and enhance its efficiency in synthesizing aryl silanes.

[50] P. Jain, S. Pal, V. Avasare, $Ni(COD)_2$-Catalyzed *ipso*-Silylation of 2-Methoxynaphthalene: A Density Functional Theory Study, *Organometallics* **2018**, *37*, 1141–1149.

Chapter 3. Synthesis of triarylmethanes by silyl radical-mediated cross-coupling of aryl fluorides and arylmethanes

Introduction

Benzylic motifs incorporating a C(sp3)–H bond ($ArCHR_2$) constitute a prevalent structural feature in numerous bioactive compounds[51], with approximately a quarter of the 200 top-selling pharmaceuticals exhibiting these motifs.[52] Hence, the strategic functionalization of these benzylic C–H bonds to establish new C–C[53], C–N[54], and C–O[55] bonds represents a logical and consequential avenue for advancing the diversification of drug candidates. Notably, triarylmethanes ($ArCHAr_2$) and diarylalkanes (Ar_2CHR) stand as highly sought-after structural frameworks for the functionalization of benzylic C–H bonds, owing to their widespread presence in pharmaceuticals[56], functional materials[57], and sensing systems.[58] Several emblematic triarylmethanes and diarylalkanes compounds have exhibited promising pharmacological attributes in treating conditions such as viral infections, bacterial infections, breast cancer, and diabetes (Fig. 3.1).

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[52] (a) N. A. Mcgrath, M. Brichacek, J. T. Njardarson, Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives, *J. Chem. Edu.*, **2010**, *87*, 1348–1349; (b) W. Xu, W. Wang, T. Liu, J. Xie, C. Zhu, Late-Stage Trifluoromethylthiolation of Benzylic C-H Bonds, *Nat. Commun.* **2019**, *10*, 4867–4874.

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[57] (a) D. F. Duxbury, The Photochemistry and Photophysics of Triphenylmethane Dyes in Solid and Liquid Media, *Chem. Rev.* **1993**, *93*, 381–433; (b) M. S. Shchepinov, V. A. Korshun, Recent Applications of Bifunctional Trityl Groups, *Chem. Soc. Rev.* **2003**, *32*, 170–180.

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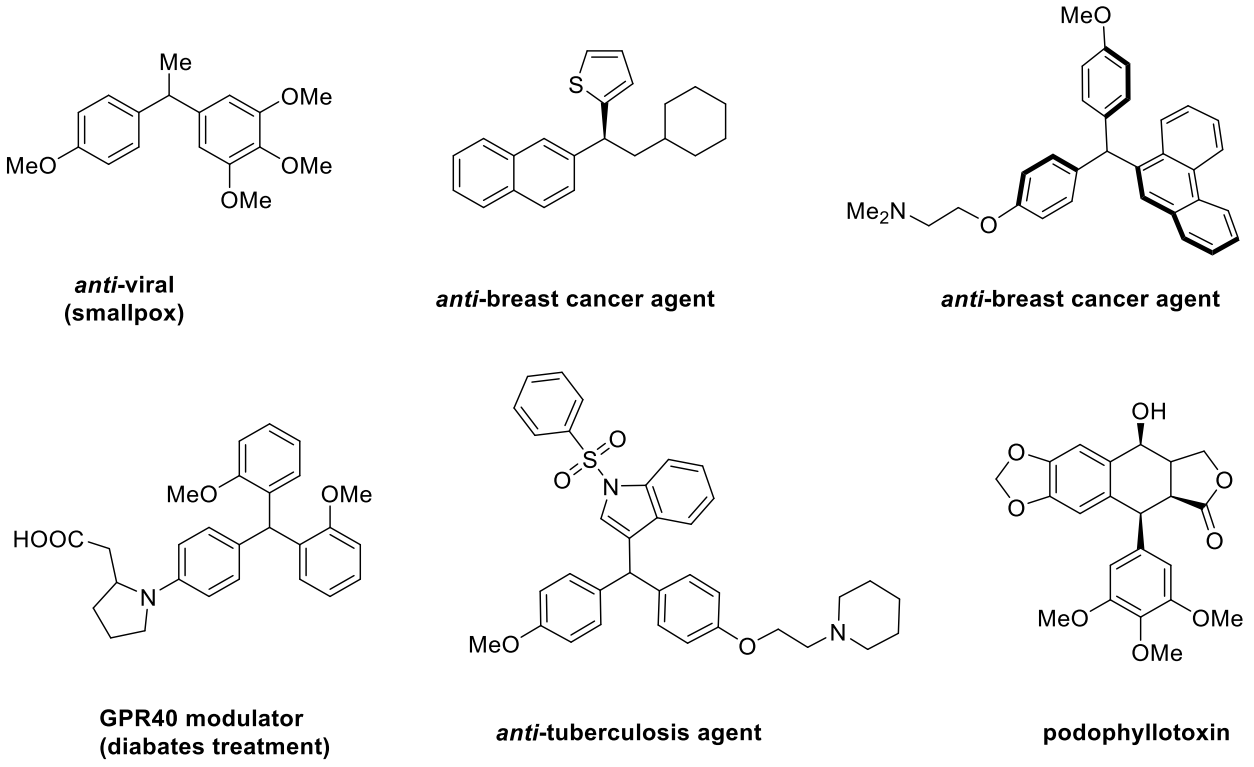

Figure 3.1 Representative important bioactive relevant molecules

Traditionally, Friedel–Crafts arylations of diarylmethanols have been employed for their synthesis; however, this methodology poses limitations concerning nucleophilic and electron-rich arenes, occasionally leading to the formation of regioisomers.[59] To circumvent these drawbacks, Walsh et al. pioneered a groundbreaking approach utilizing Pd-catalyzed cross-couplings of aryl halides (Ar–Br, Ar–Cl) with diarylmethanes, affording triarylmethanes at ambient temperature conditions.[60] This method, employing $Pd(OAc)_2$, NiXantphos, and KHMDS, notably overcomes the constraints of traditional cross-coupling procedures, often necessitating high reaction temperatures (Scheme 3.1 top). Subsequent advancements have witnessed the emergence of several mild-condition protocols for synthesizing triarylmethanes or diarylalkanes, predominantly relying on transition-metal catalysis.[61] Although these methodologies commonly necessitate aryl halides (Ar–X, X=I, Br, Cl) as precursors, aryl fluorides (Ar–F) do not conventionally find utility due to the inherent inertness and high bond dissociation energy of the C–F bond within this series. Effecting chemical transformations on fluorinated moieties poses a considerable challenge,[62] which was further exemplified in 2018 when Walsh et al. expanded

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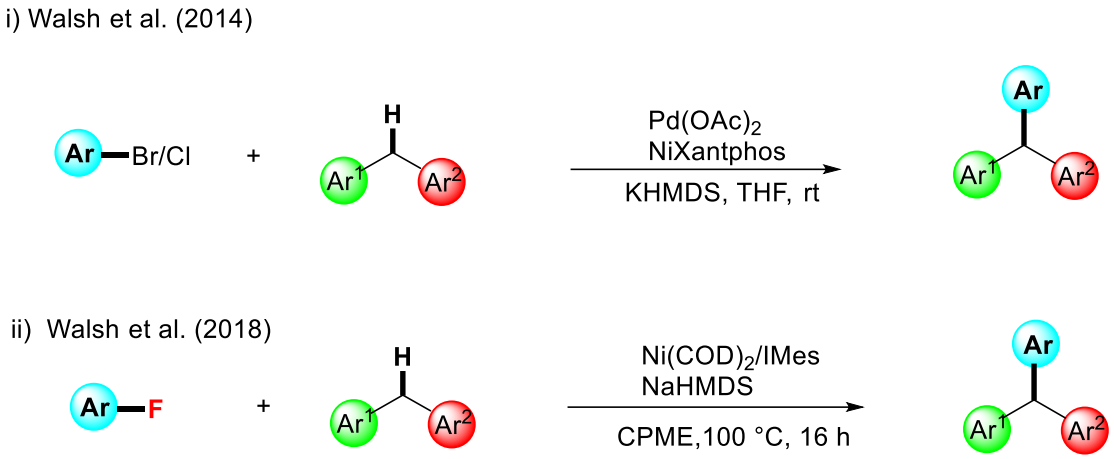
[61] M. Nambo, C. M. Crudden, Recent Advances in the Synthesis of Triarylmethanes by Transition Metal Catalysis, *ACS Catal.* **2015**, *5*, 4734–4742.

[62] (a) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, Activation of Carbon-Fluorine Bonds by Metal Complexes, *Chem. Rev.* **1994**, *94*, 373–431; (b) H. Amii, K. Uneyama, C–F Bond Activation in Organic Synthesis, Main-Group Lewis Acids for C–F Bond Activation, *Chem. Rev.* **2009**, *109*, 2119–2183; (c) T. Stahl, H. F. Klare, M. Ostreich, *ACS Catal.* **2013**, *3*, 1578–1587; (d) T. Ahrens, T. J. Kohlmann, M. Ahrens, Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation to Access Fluorinated Building Blocks, *Chem. Rev.* **2015**, *115*, 931–972; (e) J. D. Hamel, J. F. Paquin, Activation of C–F Bonds α to C–C Multiple Bonds, *Chem. Commun.*, **2018**, *54*, 10224–10239.

their cross-coupling methodology to include aryl fluorides. While their findings led to the identification of suitable conditions [$Ni(cod)_2$ (10 mol%) and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes, 20 mol%) in the presence of NaHMDS (3 equiv.) in cyclopentyl methyl ether (CPME)] for product generation, it necessitated high temperatures and extended reaction times (16 h) (Scheme 3.1 bottom).[63]



Scheme 3.1 Approaches for the synthesis of di- or tri-arylmethanes

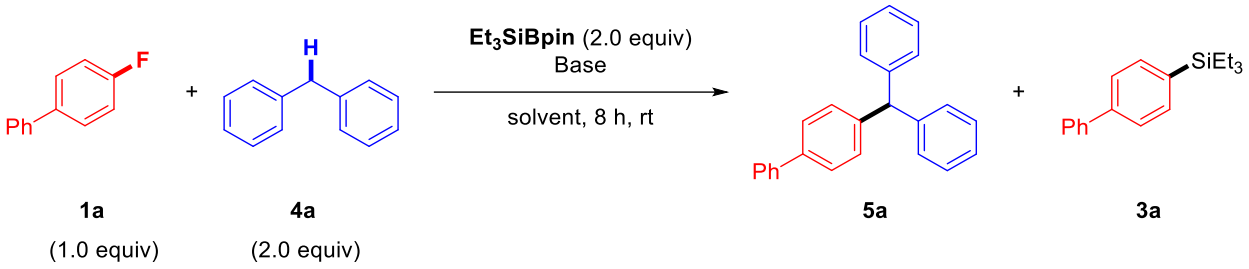
Acknowledging the potential for advancing the synthesis of triarylmethanes or diarylalkanes compounds further, and building upon our prior success in C-F bond activations, we herein devised a novel silylboronate-mediated radical cross-coupling reaction. This innovative approach involves the interaction between aryl fluorides **1** and arylalkanes **4**, thereby effecting the cleavage of both C–F and C–H bonds.

Optimization of Reaction Conditions

The investigation commenced with an exploration of the reaction involving 4-fluorobiphenyl (**1a**) and diphenylmethane (**4a**), serving as a model reaction to discern optimal conditions (Table 3.1). Our initial approach involved the use of $Et_3SiBpin$ (2.0 equiv.), $Ni(cod)_2$ (10 mol%), and KOtBu (3.0 equiv.) in THF at room temperature, akin to the conditions employed in our previous defluorosilylation of aryl fluorides.[49] Expectedly, the reaction yielded 4-benzhydrylbiphenyl (**5a**) in 37% yield alongside the defluorosilylated byproduct, biphenyl-4-yltriethylsilane (**3a**) (entry 1). Interestingly, the exclusion of $Ni(cod)_2$ improved the yield of **5a** to 47% (entry 2). Subsequent exploration involved a screening of various bases (entries 3–6). While weaker bases proved unsuitable (entries 3 and 4), the utilization of strong bases like NaOtBu and KHMDS did not enhance the yield (entries 5 and 6). A modest increase to 49% yield was observed with 4 equiv. of KOtBu (entry 7). Notably, solvent choice significantly impacted the yield of **5a** (entries 8–16), with diglyme yielding the highest output (95%, entry 16) while effectively reducing the formation of byproduct **3a**. Diglyme's efficacy could be attributed to the encapsulation of K^+ ions, rendering a more potent and unencumbered base.[64] Control experiments established that no reaction took place in the absence of KOtBu or $Et_3SiBpin$ (entries 17 and 18). Subsequently, the scalability of the coupling process was examined using 0.2 mmol and 4.0 mmol of **1a** under the conditions from entry 16. The successful isolation of product **5a** was achieved in 96% (93% isolated yield, entry 19) and 85% isolated yield (entry 20) respectively, further confirming the feasibility of the developed protocol at different scales.

[63] J. Li, C. Wu, B. Zhou, P. J. Walsh, Nickel-Catalyzed C(sp^3)−H Arylation of Diarylmethane Derivatives with Aryl Fluorides, *J. Org. Chem.*, **2018**, *83*, 2993–2999.
[64] T. Saito, J. Wang, E. Tokunaga, S. Tsuzuki, N. Shibata, *Sci. Rep*. **2018**, *8*, 11501–11508.

Table 3.1 Optimization of the defluoronative cross-coupling conditions[a]



1a (1.0 equiv) + **4a** (2.0 equiv) → **5a** + **3a**

entry	Base (equiv.)	Solvent	5a(%)[b]	3a(+/-)
1[c]	KOtBu (3.0)	THF	37	+
2	KOtBu (3.0)	THF	47	+
3	K_2CO_3 (3.0)	THF	-	-
4	Cs_2CO_3 (3.0)	THF	-	-
5	NaOtBu (3.0)	THF	28	+
6	KHMDS (3.0)	THF	30	+
7	KOtBu (4.0)	THF	49	+
8	KOtBu (4.0)	c-hexane/THF (8/1, v/v)	34	+
9	KOtBu (4.0)	c-hexane	9	+
10	KOtBu (4.0)	toluene	11	+
11	KOtBu (4.0)	dioxane	trace	+
12	KOtBu (4.0)	DME	36	+
13	KOtBu (4.0)	CPME	18	+
14	KOtBu (4.0)	MTBE	12	+
15	KOtBu (4.0)	DTBE	trace	+
16	KOtBu (4.0)	diglyme	95	-
17	-	diglyme	0	-
18[d]	KOtBu (4.0)	diglyme	0	-
19[e]	KOtBu (4.0)	diglyme	96 (93)	-
20[f]	KOtBu (4.0)	diglyme	(85)	-

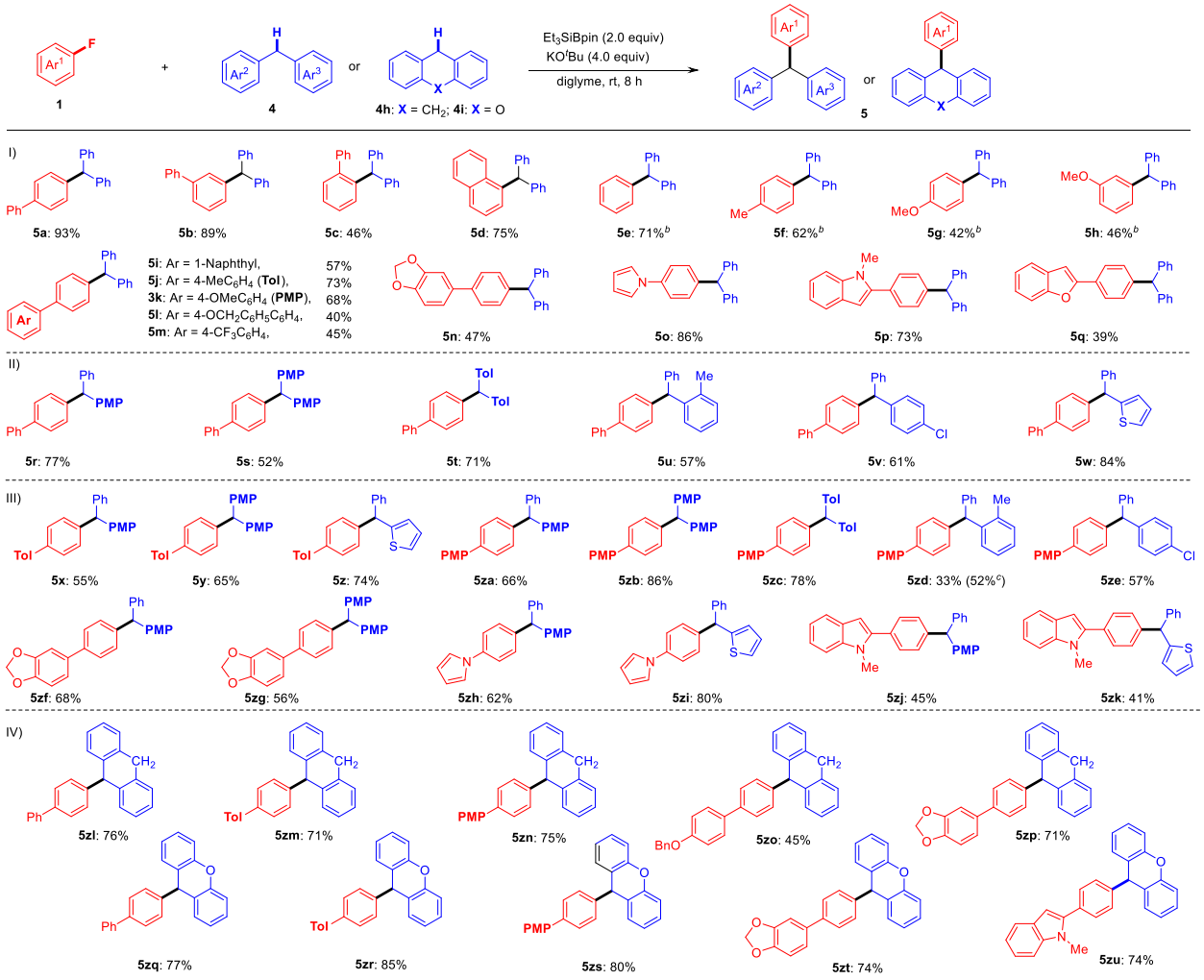
[a]Reactions were attempted under indicated reagents and conditions: **1a** (17.2 mg, 0.1 mmol), **4a**, KOtBu $Et_3SiBpin$, and solvent (1.0 mL) reacted at room temperature for 8 h. [b]Determined by ^{19}F NMR and ^{1}H NMR spectroscopy using 3-fluoropyridine as an internal standard. The number in parentheses referred to the isolated yield. [c]Performed without $Et_3SiBpin$. [d]0.2 mmol scale was performed.

Substrate Scope

Upon establishing the optimized reaction conditions (entry 20, Table 3.1), a thorough exploration of the substrate scope for the silylboronate-mediated defluorinative cross-coupling reaction was conducted (Table 3.2). The investigation encompassed a diverse array of substituted aryl fluorides **1** paired with **4a** to assess the method's generality (Table 3.2-I). Notably, an expansive spectrum of fluoroarenes, spanning π-extended systems **1a**–**1d**, fluorobenzene **1i**, and methyl- as well as methoxy-substituted fluorobenzenes **1s**, **1j**, and **1t**, underwent efficient coupling with **4a**, yielding the corresponding triarylmethanes **5a**–**5h** in yields of up to 93%. While the yields of **5** were slightly reduced in cases where steric hindrance (**5c**: 46%) or electron-rich

substituents were present (**5g**: 42%; **5h**: 46%), the coupling reactions of *p*-substituted 4′-fluorobiphenyls **1e**, **1f**, **1g**, **1w**, and **1v** and dioxole **1h** furnished the corresponding triarylmethanes in moderate to good yields under standard conditions: **5i**: 57%, **5j**: 73%, **5k**: 68%, **5l**: 40%, **5m**: 45%, and **5n**: 47%. Encouragingly, these outcomes underscore the commendable tolerance of functional groups like OMe, OBn, and CF_3 in this transformation. Moreover, the assessment extended to aryl fluorides **1n**, **1q**, and **1u** containing attached heterocycles, considering the potential competitive induction of C–H activation by the heterocyclic moiety. Impressively, pyrrole- or indole-containing aryl fluorides **1n** and **1q** led to the formation of 1*H*-pyrrole derivative **5o** (86%) and *N*-methyl-1*H*-indole derivative **5p** (73%), respectively, without any detectable C–H activation product. Additionally, while benzofuran-bearing fluoroarene **1u** engaged in this cross-coupling reaction, the yield of coupling product **5q** reached 39%, albeit relatively modest.

Table 3. 2 Substrate scope of **1** and **4**[a]



[a]Unless otherwise noted, reactions were conducted using **1** (0.2 mmol), **4a** (2.0 equiv.), $Et_3SiBpin$ (2.0 equiv.), KOtBu (4.0 equiv.), and diglyme (2.0 mL) at room temperature for 8 h, with isolated yields shown. [b]Reaction performed using 0.4 mmol of 1. [c]Reaction performed using $Et_3SiBpin$ (3.0 equiv.) and KOtBu (6.0 equiv.).

We then expanded the exploration to assess the substrate scope of diarylmethanes **4** in their cross-couplings with 4-fluorobiphenyl (**1a**) (Table 3.2-II). Electron-rich phenyl-(4-methoxyphenyl)methane (**4b**), bis(4-methoxyphenyl)methane (**4c**), and bis(tolyl)methane (**4d**) engaged smoothly with 1a under standard conditions, affording the desired triarylmethanes **5r** (77%), **5s** (52%), and **5t** (71%), respectively. Even the sterically

encumbered *ortho*-methyl-diphenylmethane (**4e**) yielded the coupling product **5u** in a 57% yield, showcasing the robustness of the process. Remarkably, the presence of a chlorine substituent in diphenylmethane **4f** was well-tolerated under the same conditions, selectively yielding the defluorinative coupling product **5v** (61%). Additionally, 2-benzylthiophene (**4g**) effectively underwent the cross-coupling with **1a** under identical reaction conditions, resulting in a high yield of **5w** (84%). These findings further underscore the versatility and compatibility of various diarylmethane substrates in this defluorinative coupling approach.

We extended our investigation by exploring the coupling reactions involving a variety of substituted fluoroarenes (**1f**, **1g**, **1h**, **1n**, **1q**) and substituted diarylmethanes (**4b–g**) to broaden the applicability of this method (Table 3.2-III). Fluoro-biphenyls bearing Me (**1f**) or OMe (**1g**) substituents underwent successful reactions with diarylmethanes **4b–f** under the optimized conditions, yielding the desired triarylmethanes in moderate to good yields (**5x**: 55%; **5y**: 65%; **5z**: 74%; **5za**: 66%; **5zb**: 86%; **5zc**: 78%; **5zd**: 33%; **5ze**: 57%). The diminished yield of **5zd** can be attributed to the steric hindrance caused by the *o*-Me group in **4e**, which was ameliorated to 52% with the addition of excess $Et_3SiBpin$ (3.0 equiv.) and KOtBu (6.0 equiv.). Moreover, the dioxole-bearing fluoroarene 1n exhibited successful reactivity with 4-methoxydiphenylmethane (**4b**) and dianisylmethane (**4c**), yielding triarylmethanes **5zf** (68%) and **5zg** (56%), respectively. Interestingly, despite featuring multiple reactive C(sp2)–H bonds within their heterocyclic frameworks, the cross-coupling reactions of pyrrole aryl fluoride **1n** and indole aryl fluoride **1q** progressed smoothly, generating heteroaryl-containing products **5zh** (62%), **5zi** (80%), **5zj** (45%), and **5zk** (41%) via C–F bond cleavage, without engaging in the expected C–H cross-coupling reactions within the heteroaromatic structure.

This protocol's notable feature is its successful utilization of dihydroanthracene (DHA, **4h**) as a cross-coupling partner alongside fluoroarenes (Table 3.2-IV). Conventionally, DHA functions as a radical inhibitor.[65] Despite this transformation presumably involving a radical process (as discussed below), the cross-coupling of aryl fluorides **1** with **4h** proceeded smoothly under standard conditions, yielding the desired cross-coupling products in good yields (**5zl**: 76%; **5zm**: 71%; **5zn**: 75%; **5zo**: 45%; **5zp**: 71%). Similarly, 9*H*-xanthene (**4i**) demonstrated commendable compatibility with aryl fluorides **1** under identical conditions (**5zq**: 77%; **5zr**: 85%; **5zs**: 80%; **5zt**: 74%; **5zu**: 74%).

We then delved into exploring potential limitations of this methodology, focusing on arylalkanes **4** (Table 3.3 top). The cross-coupling of **1a** with 1,1-diphenylalkanes **4j–l** under the optimized conditions yielded products **5zv** (79%), **5zw** (64%), and **5zx** (51%), bearing a quaternary carbon center, with commendable yields. However, cumene (**4m**) yielded product **5zy** in a significantly lower yield of 23%. Other arylalkanes containing a single aromatic group (**4n–p**) resulted in corresponding cross-coupling products with yields ranging from 20% to 25% (**5zz**: 25%; **5zza**: 22%; **5zzb**: 20%). Slightly enhanced yields of 3 were achieved by using excess reagents (**5zz**: 37%; **5zza**: 41%; **5zzb**: 35%; **5zzb**: 33%). These outcomes underscore the notable dependence of successful conversion on the stability of the reactive benzylic species. Interestingly, when we attempted the reaction of allylbenzene (**4q**), we obtained **5zzc** (Z/E = 1: 1.3) in a 34% yield instead of the anticipated coupling product **5zzc'**. One possibility for this is its isomerization to **5zzc** under the optimized conditions. Indeed, treating independently prepared **5zzc'** under KOtBu/$Et_3SiBpin$ conditions yielded **5zzc** (Z/E = 1: 1.3). Furthermore, the isomerization of **5zzc'** under the base (KOtBu) led to **5zzc** with a different ratio (Z/E = 1: 1) (see details in the experimental section†). To affirm this hypothesis, we attempted the reaction of **1a** with toluene, observing no desired coupling product. However, when *p*-phenyl-substituted

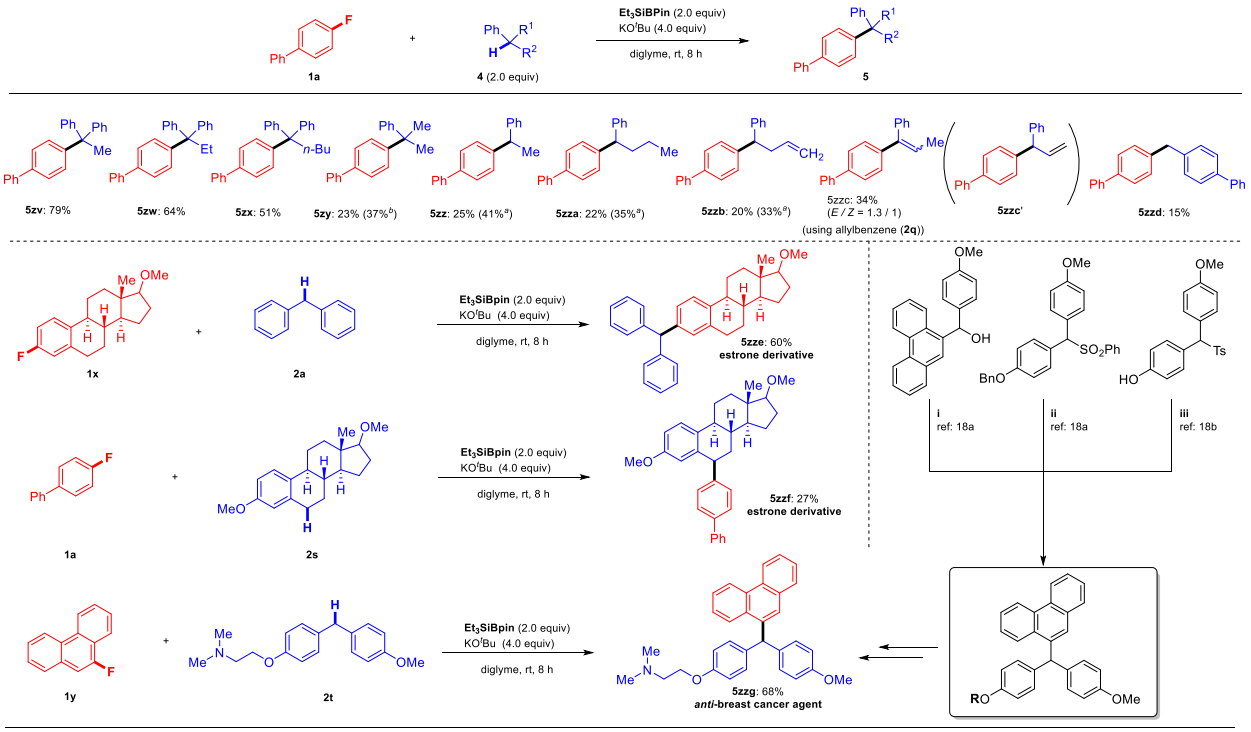
[65] (a) E. Yamamoto, K. Izumi, Y. Horita, S. Ukigai, H. Ito, Formal Nucleophilic Boryl Substitution of Organic Halides with Silylborane/Alkoxy Base System, *Top. Catal.* **2014**, *57*, 940–945; (b) B. Górski, A. Barthelemy, J. J. Douglas, F. Juliá, D. Leonori, Copper-Catalysed Amination of Alkyl Iodides Enabled by Halogen-Atom Transfer, *Nat. Catal.* **2021**, *4*, 623-630; (c) S. Das, S. Roy, A. Bhowmik, W. Sarkar, I. Mondal, A. Mishra, S. J. Saha, S. Karmakar, I. Deb, A radical–radical cross-coupling reaction of xanthene with sulfonyl hydrazides: facile access to xanthen-9-sulfone derivatives, *Chem. Commun*. **2022**, *58*, 2902–2905.

toluene (**4r**) was employed, the desired coupling product **5zzd** was obtained in a 15% yield, providing support for the formation of a benzylic radical species (see the Discussion section). Despite successful utilization of various substrates **1**, **4**, and **5** bearing functional groups and heterocycles (Table 3.2 and 3.3), certain limitations arose with functionalities like carbonyls, amines, and free H (OH, NH_2, etc.).

Application of silylboronate-mediated defluorinative coupling reaction

To underscore the practical applications of this silylboronate-mediated defluorinative coupling reaction, we delved into the functionalization of several drug derivatives featuring a fluoroarene moiety or benzylic C–H moiety (Table 3.3, bottom). Beginning with an estrone-derived fluoroarene **1x**, the coupling reaction with diphenylmethane **4a** yielded the desired estrone derivative **5zze** in a respectable 60% yield. Moreover, the motif **4s**, possessing two benzylic C–H bonds derived from estrone, was effectively functionalized at the secondary C–H site using this transformation with **1a** to produce **5zzf** in a 27% yield. Notably, this modular approach facilitates the rapid synthesis of the anti-breast-cancer agent **5zzg** in a single step rather than through multiple steps. [66] Employing 9-fluorophenanthrene **1y** and 2-(4-(4-methoxybenzyl)phenoxy)-*N*,*N*-dimethylethan-1-amine **4t** under standard reaction conditions resulted in the facile production of the desired product **5zzg**, achieved with an impressive 68% yield.

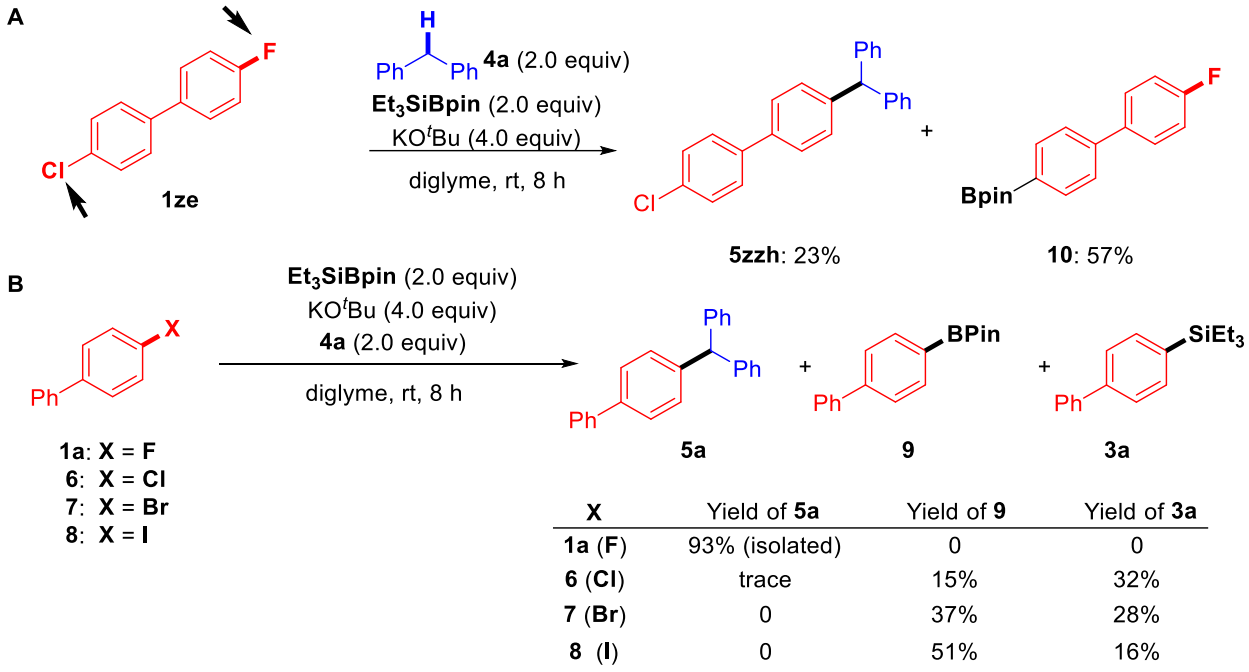
Table 3.3 Further scopes and limitations of arylalkanes 2[a]



[a]Unless otherwise noted, reactions were conducted with **1** (0.2 mmol), **4** (2.0 equiv.), $Et_3SiBpin$ (2.0 equiv.), KOtBu (4.0 equiv.), and diglyme (2.0 mL) at room temperature for 8 h, with isolated yields shown. [b]Reaction performed using $Et_3SiBpin$ (3.0 equiv.) and KOtBu (6.0 equiv.)

[66] (a) M. Nambo, C. M. Crudden, Transition Metal-Catalyzed Cross-Couplings of Benzylic Sulfone Derivatives, *Chem. Rec.* **2021**, *21*, 3978–3989; (b) M. Miao, W. Yin, L. Wang, Z. Chen, J. Xu, H. Ren, Transition-Metal-Free Arylation and Alkylation of Diarylmethyl *p*-Tolyl Sulfones with Zinc Reagents, *J. Org. Chem.*, **2018**, *83*, 10602–10612.

It's worth noting that the chemoselectivity of our coupling reaction, particularly in the case of 4-chloro-4'-fluoro-1,1'-biphenyl (**1ze**), exhibited lower efficiency in transforming it into the desired product **5zzh** (yield: 23%). Instead, a preference for the borylated product **10** (yield: 57%) was observed, highlighting the prevalent C–Cl bond cleavage in this instance (Fig. 3.2 A). However, contrasting with this, the selectivity of the C–F bond over C–Cl/Br/I bonds displayed exceptional efficiency in parallel experiments (Fig. 3.2 B). For instance, when conducting cross-coupling reactions of diphenylmethane (**4a**) with biphenyl chloride (**6**), biphenyl bromide (**7**), and biphenyl iodide (**8**), the observed outcomes indicated mixtures of borylated product **9** and silylated product **3a**, with minimal traces of the desired cross-coupling product **5a** detected under the standard conditions.



X	Yield of **5a**	Yield of **9**	Yield of **3a**
1a (**F**)	93% (isolated)	0	0
6 (**Cl**)	trace	15%	32%
7 (**Br**)	0	37%	28%
8 (**I**)	0	51%	16%

(A) Chemoselectivity of Ar–F over Ar–Cl. (B) Coupling reactions of **4a** with **1a** (X = F), **6** (X = Cl), **7** (X = Br), and **8** (X = I).

Figure 3.2 Chemoselectivity and parallel experiments

Mechanistic Study

Several key observations in our study led us to favor a single-electron transfer (SET) radical process rather than nucleophilic substitution pathways, such as traditional nucleophilic aromatic substitution (S_NAr) and S_N2 mechanisms, where aryl fluorides may act as electrophiles or benzyne precursors.[67] These conventional S_NAr and S_N2 protocols typically necessitate electron-deficient aryl fluorides under strongly basic conditions. To gain deeper insights into the reaction mechanism (Fig. 3.3), we conducted several additional experiments. Initially, we investigated the coupling reaction between aryl fluoride **1a** and diphenylmethane **4a** in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (Fig. 3.3A(i)). Despite obtaining the coupling

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product **5a** in 93% yield under standard conditions, the yields notably diminished with increasing amounts of TEMPO: 52% (1.0 equiv. of TEMPO), 20% (2.0 equiv. of TEMPO), and trace amounts (4.0 equiv. of TEMPO). Interestingly, elevating the TEMPO quantity resulted in a rise in the yield of 1-(benzhydryloxy)-2,2,6,6-tetramethylpiperidine (**Int-TEMPO**) from 11% (1.0 equiv. of TEMPO) to 68% (2.0 equiv. of TEMPO) and 80% (4.0 equiv. of TEMPO). These findings strongly suggest the involvement of radical species in the cross-coupling reaction. Additionally, Ohmiya and co-workers reported the cross-coupling of aryl fluorides using tertiary benzylic organoboronates with KOtBu at a high temperature of 120 °C via S_NAr mechanisms.[68] In line with this, we attempted the reaction of **1a** with $pinBCHPh_2$ (**11**) in the presence of KOtBu in diglyme at room temperature (Fig. 3.3A(ii)). However, we only detected 9% of **5a**, with the majority of **1a** remaining unchanged. These outcomes signify the formation of a carbanion from $pinBCHPh_2$ and indicate the unlikelihood of the S_NAr process being involved.[69]

A standard radical clock experiment was conducted using 1-(but-3-en-1-yl)-2-fluorobenzene (**1z**) and **4a** under the same cross-coupling conditions (Fig. 3.3A(iii)). Notably, the resulting cross-coupling products **5zzi** (without cyclization) were obtained with a yield of 68%. This outcome strongly implies that the C–F bond cleavage takes place through a sequential, concerted process in the final phase of the reaction mechanism, without generating a free aryl radical. To further elucidate the reaction process, two additional radical clock experiments were undertaken. Firstly, the reaction between 1a and the cyclopropyl benzyl derivative **4u** did not yield the expected cross-coupling product. Instead, the ring-opening product **4u'** was isolated (26% yield), likely resulting from the formation of a cyclopropyl benzyl radical **˙4u**. This reaction also generated associated by-products such as **3a** and hexaethyldisilane ($(Et_3Si)_2$) (Fig. 3.3A(iv)). Furthermore, an intramolecular cross-coupling reaction was accomplished by treating diphenylpropyl-substituted fluorobenzene **1za** under identical conditions, producing cyclization product **5zzj** with a notable 89% yield (Fig. 3.3A(v)).

Finally, ESR experiments were conducted to affirm the generation of radicals under the optimized conditions (Fig. 3.3B). Initially, an ESR experiment using the spin trap tri-tert-butylnitrosobenzene (TTBNB) was performed. The resulting ESR spectrum (triple–triplet) from the reaction between $Et_3SiBpin$ and KOtBu in diglyme at room temperature (Fig. 3.3B(i)(a)) corresponded to the spin adduct of the triethylsilyl radical ($^{\cdot}SiEt_3$) trapped by TTBNB. The observed hyperfine splitting (*hfs*) constant due to nitrogen (A_N; spin quantum number $I = 1$) was 1.03 mT, while the smaller splitting constant due to the two hydrogens at the *meta* position of the TTBNB benzene ring (A_{Hm}; $I = 1/2$) measured 0.175 mT. The g-value of 2.0047 was associated with an anilino-type radical [70] (Fig. 5B(i)), which has been previously reported for $SiEt_3$-TTBNB, confirming consistency with past observations.[71] Subsequently, the reaction involving diphenylmethane (**4a**), $Et_3SiBpin$, and KOtBu in diglyme at room temperature was explored (Fig. 3.3B(ii)(b)). The observed ESR spectrum (double-triplet; sextet line) indicated the presence of a benzyl-type radical ($^{\cdot}CHPh_2$) trapped by TTBNB, with *hfs* constants A_N and $A_{H\alpha}$ (due to an α-proton) measured at 0.62 and 0.34 mT, respectively. Additionally, the g-value of 2.00266 was assigned to an anilino-type radical (Fig. 3.3B(ii)), further supporting our experimental observations.[70] Furthermore, the reaction between $Et_3SiBpin$ and KOtBu in diglyme at room temperature displayed a quartet line with a *g*-value of 2.0060, attributed to a silyl radical $^{\cdot}SiEt_3$ (Fig. 3.3B(iii)(c)). This

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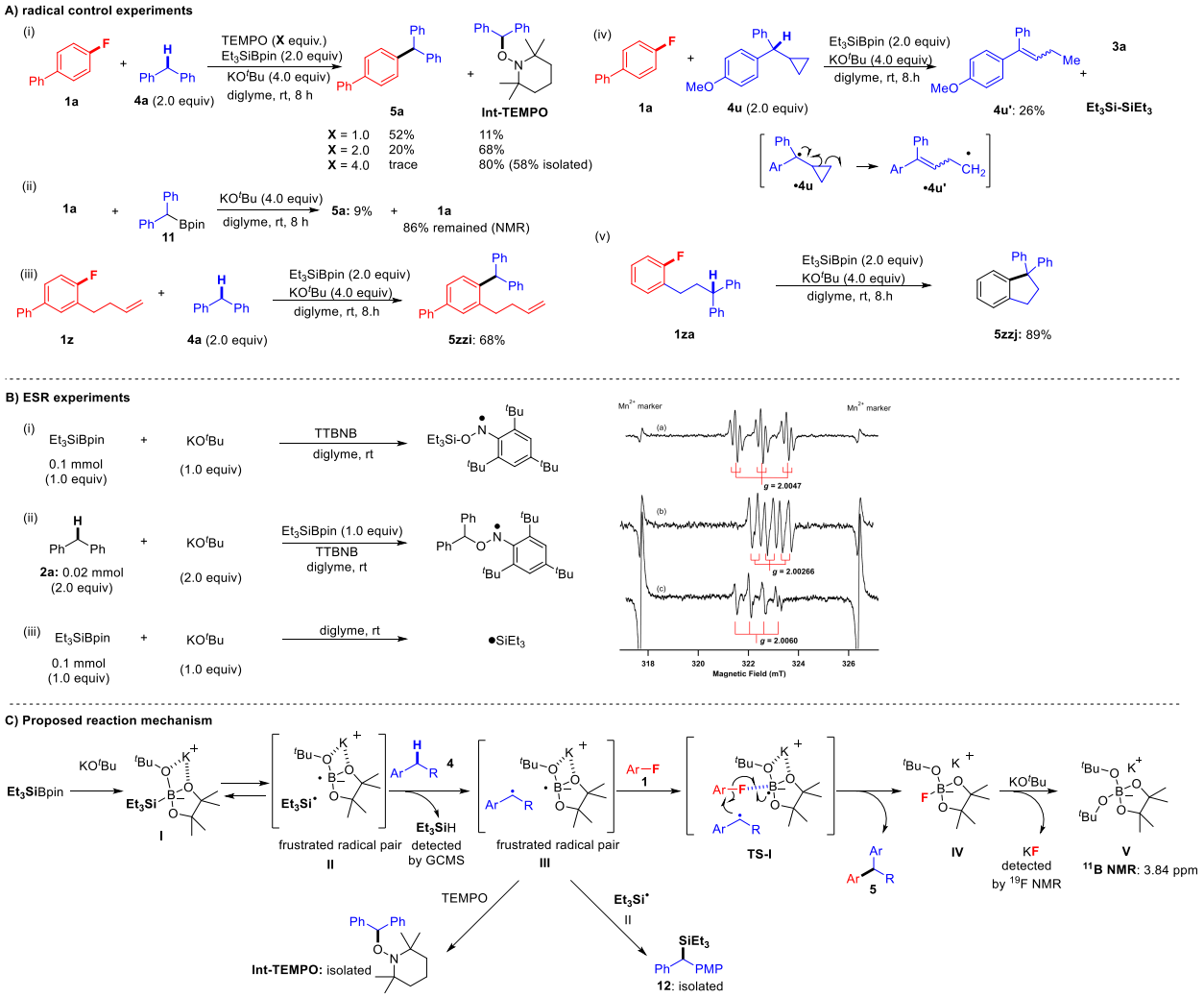
detection provided direct evidence of the generated silyl radical ˙$SiEt_3$ (for more details, refer to the ESI† for a comprehensive discussion of the ESR experiments).



(A) Radical control experiments. (i) Effect of TEMPO in the silylboronate-mediated coupling reaction. (ii) S_NAr conditions using pinBCHPh$_2$ **11** in the presence of KOtBu. (iii) Radical cyclization experiments. (iv) Radical ring-opening experiment. (v) Radical cyclization experiment. (B) ESR experiments and chemical structure. (i) and (a) Spin-adduct of TTBNB with triethyl silyl radical (anilino-type), (ii) and (b) spin-adduct of TTBNB with diphenyl methyl radical (anilino-type). (iii) and (c) triethyl silyl radical. (C) Proposed reaction mechanism.

Figure 3.3 Control experiments study and proposed mechanism

Based on our experimental findings and prior research[37,49], a proposed mechanism involving a radical-mediated defluorinative cross-coupling reaction is presented (Fig. 3.3C).[72] The schematic depicts the mechanism for the representative reaction between aryl fluorides **1** and diarylmethanes **4**. Initially, $Et_3SiBpin$ reacts with KOtBu to generate intermediate **I**, which was previously confirmed by the Avasare group using density functional theory calculations.[50] We further validated the existence of intermediate **I** through ^{11}B NMR and ^{29}Si NMR spectroscopy.[37,49] Subsequently, owing to steric repulsion, intermediate **I** undergoes homolytic

[72] As the research progressed (ref. 37 and 49), we gradually modified the reaction mechanisms proposed in each paper based on new results and discussions. We believe that the mechanism presented here is the most appropriate for understanding the reaction process so far.

scission of the Si–B bond, giving rise to a sterically challenging and frustrated radical pair **II**[73] composed of a triethylsilyl radical (˙$SiEt_3$) and a boron-radical species. Hydrogen abstraction from diarylmethane **4** by ˙$SiEt_3$ forms a frustrated radical pair **III** and generates $HSiEt_3$ (identified by GC-MS). The cascade process involves aryl fluorides **1** at transition state **TS-I**, activating the C–F bond via the boron atom in Bpin. Then, aryl fluorides **1** transform into aryl radicals by undergoing C–F bond cleavage through SET.[73,74] Simultaneously, the boron-radical side of a frustrated radical pair **III** in **TS-I** triggers a radical reaction. The aryl radicals generated interact with the approaching benzyl radical, completing C–C bond formation, releasing **IV** ([Bpin(OtBu)F]K), and producing the desired cross-coupling product 3.[37,49] Finally, **IV** ([Bpin(OtBu)F]K) further reacts with a second mole of KOtBu, yielding a stable **V** ([$Bpin(OtBu)_2$]K) (detected by ^{11}B NMR) and KF (detected by ^{19}F NMR). Occasionally detected as a by-product in experiments, the benzyl radical species in the frustrated radical pair **III** are occasionally captured by ˙$SiEt_3$ from **II**, forming **12**. The presence of benzyl radicals in **III** is further confirmed by the formation of **Int-TEMPO**. The reduced yields observed in coupling reactions involving monoarylalkanes can be attributed to the lower stabilities of corresponding radical species.

Conclusion

In conclusion, we've introduced the pioneering silylboronate-mediated radical cross-coupling reaction between aryl fluorides and arylalkanes, orchestrating the simultaneous cleavage of a C–F bond alongside an initial C–H bond cleavage to forge a fresh C–C bond. This methodology adeptly synthesizes an array of triaryl- and diarylalkanes with impressive efficiency, yielding moderate to excellent outputs under exceedingly mild conditions at room temperature. An outstanding aspect of this coupling system lies in its activation of C–F and C–H bonds at ambient temperatures, eliminating the necessity for high reaction temperatures, transition metals, or specialized ligands. Our empirical evidence supports a radical reaction mechanism, corroborated by ESR analysis. The resulting array of arylalkanes from this method serves as a valuable foundation for pharmaceuticals and functional materials. Considering the ready availability of numerous organic fluorides, including intricate pharmaceuticals and agrochemicals, we foresee the radical coupling of organic fluorides with arylalkanes as a pivotal method for facilely crafting diverse materials, encompassing potential drug candidates and specialized substances.

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Chapter 4. Transition-metal-free silylboronate-mediated cross-couplings of organic fluorides with amines

Introduction

Aromatic tertiary amine structures represent pivotal elements within molecules utilized across pharmaceuticals, agroscience, bioactive natural products, and materials science (Fig. 4.1a).[75] Until now, the most dependable methods for preparing aromatic tertiary amines involve transition-metal-catalyzed C(sp2)–N couplings of aryl (pseudo)halides with amine nucleophiles, such as the Ullmann coupling[76] the Buchwald–Hartwig reaction[77] and metallaphotoredox amination[78] (Fig. 4.1b). Despite being among the top five globally performed reactions for synthesizing high-value products[79], efficient syntheses of aromatic tertiary amines, conducive to green chemistry, necessitate transition-metal-free systems. Nevertheless, transition-metal-free aminations of aryl (pseudo)halides often face constraints like low regioselectivities, requiring strong bases and high temperatures.[80] Additionally, the use of inert C–F-containing organic fluorides in such C–N couplings under mild conditions remains infrequent due to the high bond dissociation energies of C–F bonds. Amination reactions of aromatic C–F bonds using strong bases often yield amination products as regioisomer mixtures,

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proceeding through benzyne intermediates.[81a,b,c] In 2015, Shi group reported a direct S_NAr reaction of aromatic fluorides by aromatic amines using tBuOK in DMSO.[81d] Diness and coworkers disclosed the S_NAr reaction of aromatic fluorides with alkyl amines using LiHMDS.[81e] However, both methods necessitate high reaction temperatures of 90–100 °C, except for selected perfluorinated benzenes.[81d,e] Further, S_NAr reactions of perfluorinated benzenes with pyrroles by NaH[81f] and *N*-heterocycle-assisted S_NAr reaction of *ortho*-heterocyclic aryl fluorides with aryl amines using LiH were reported[81g], requiring temperature conditions of 110–153 °C. Recent advancements achieved amination of electron-rich aryl fluorides at 20–50 °C using photocatalysts and blue LEDs; however, these methods mandate electron-rich moieties, such as the OMe group, on aromatic moieties for substrate activation.[34,81] Consequently, these methods aren't conducive for electron-poor aryl fluorides, unlike traditional S_NAr reactions favoring electron-poor substrates. Additionally, aminations involving C(sp3)–F bond cleavage of alkyl fluorides pose challenges, primarily limited to active benzyl or allylic fluorides, often requiring strong Lewis acids, such as $La[N(SiMe_3)_2]_3$ and YbI_3.[82]

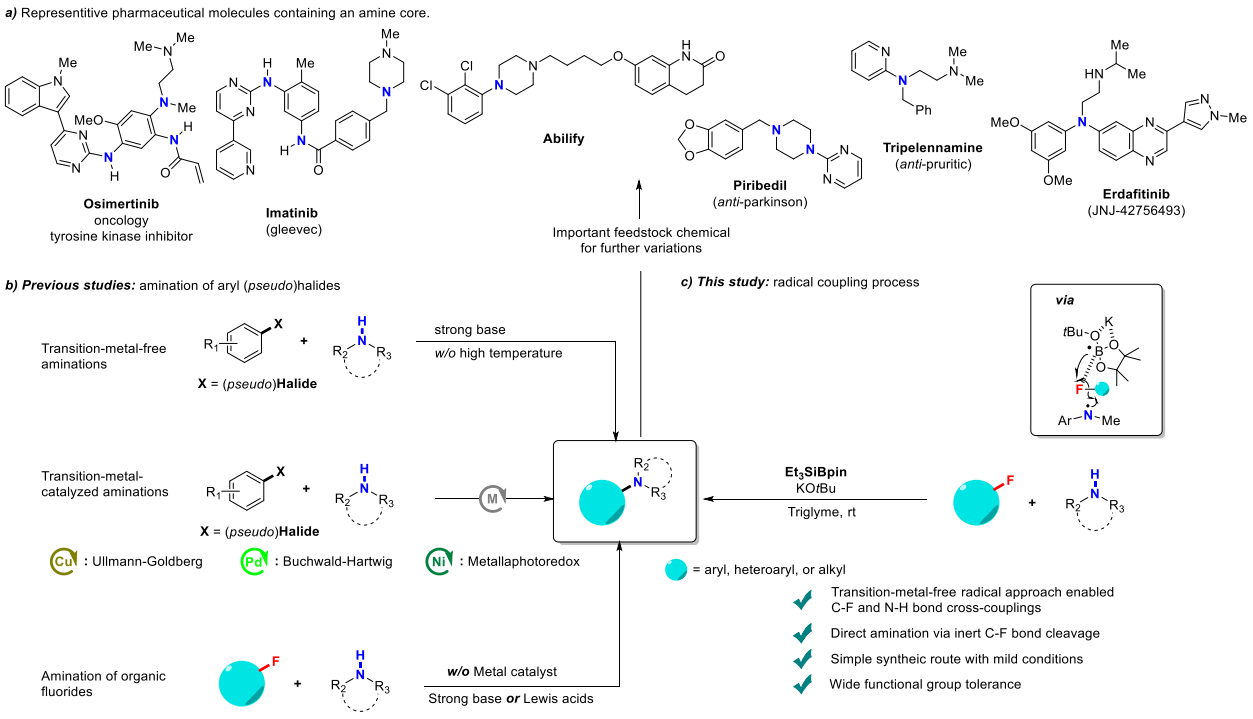

Figure 4.1 Cross-couplings and related reactions of aryl or alkyl halides with secondary amines

As a seamless extension of our ongoing investigations into C–F bond functionalization,[37,49] we present our new findings on transition-metal-free defluorinative aminations of aryl fluorides utilizing secondary amines. This transformation occurs in the presence of triethylsilylboronate ($Et_3SiBpin$) and potassium tert-butoxide (KOtBu, Fig. 4.1c). Diverse aryl fluorides readily engage with both secondary acyclic and cyclic *N*-alkylanilines or dialkylamines under mild conditions, operating at room temperature. This innovative process

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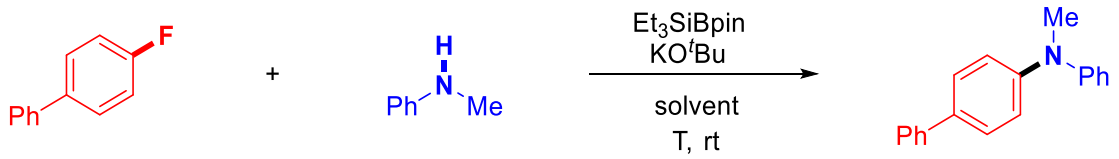
delivers aromatic tertiary amines in consistently good-to-excellent yields, achieved via selective cleavage of C(sp2)–F bonds facilitated by $Et_3SiBpin$, completely bypassing the need for transition-metal catalysis or a photoredox system. The reaction effectively involves (hetero)aryl fluorides in conjunction with both unsubstituted *N*-alkylanilines and substituted *N*-methylanilines, thereby enabling the synthesis of a diverse array of structurally intricate aromatic tertiary amines. These synthesized compounds exhibit precise regioselectivity, incorporating aryl, heteroaryl, and/or alkyl groups at the N centers with remarkable efficiency. The defluoroamination reaction demonstrates exceptional regio- and chemoselectivity, leaving untouched the potentially cleavable C–O bonds of ethers, C–Cl and C–CN bonds, as well as C(sp2)–H bonds present in heteroaromatic compounds. Furthermore, the protocol exhibits non-reactivity towards C(sp3)–F bonds in CF_3 and OCF_3 groups, whereas this cross-coupling strategy can extend its applicability to alkyl fluorides possessing C(sp3)–F bonds, yielding defluoroamination products that incorporate newly formed C(sp3)–N bonds.

Optimization of Reaction Conditions

We initiated our exploration of defluoroamination by employing 4-fluorobiphenyl (**1a**) and *N*-methylaniline (**13a**) as model substrates. The target compound, *N*-methyl-*N*-phenyl-4-biphenylamine (**14a**), was obtained, initially yielding 41% under specific conditions [using $Et_3SiBpin$ (1.5 equiv.) and KOtBu (2.5 equiv.) in diglyme at room temperature, entry 1, Table 4.1]. Subsequent adjustments in the amounts of $Et_3SiBpin$ (2.0 equiv.) and KOtBu (4.0 equiv.) marginally improved the yield to 44% (entry 2), while elevating the amount of 3a to 3.0 equiv. significantly enhanced the yield to 58% (entry 3). Intriguingly, altering the solvent yielded varying results, with a remarkable increase in yield to 81% achieved by switching to triglyme under conditions similar to entry 3 (entry 4). Contrastingly, a sharp decline to 5% yield was observed in THF (entry 5), but the addition of 18-crown-6 increased the yield to 75% (entry 6). Extending the reaction time to 24 h in triglyme resulted in an improved yield of 91% (88% isolated, entry 7). Control experiments validated the indispensability of $Et_3SiBpin$ and KOtBu (entries 8 and 9). Manipulations in reactant ratios failed to enhance yields (entries 10−14). Reproducing the optimal conditions (entry 7) on a larger scale resulted in a 93% yield (89% isolated) of **14a** (entry 15). A gram-scale reaction using 5.0 mmol of 1a corroborated the reproducibility of the reaction, yielding 1.13 g (87%). Further exploration with different silylboronates ($tBuMe_2SiBpin$, $PhMe_2SiBpin$, $(Me_3Si)_3SiBpin$) revealed decreased yields with increased steric hindrance (entries 16–18), leaving some starting material (**1a**) unreacted. Additional details on the optimization of reaction conditions are available in the Supplementary Information (Supplementary Tables 1–5).

Table 4.1 Optimization of the defluoroamination conditions[a]



1a **13a** **14a**

Entry	13a	Si-B	KOtBu	Solvent	Time (h)	14a (%)[b]
1	1.5	1.5	2.5	diglyme	8	41
2	1.5	2.0	4.0	diglyme	8	44
3	3.0	2.0	4.0	diglyme	8	58
4	3.0	2.0	4.0	triglyme	8	81
5	3.0	2.0	4.0	THF	8	5

6	3.0	2.0	4.0	THF with 18-crown-6 (4.0 equiv.)	8	75
7	3.0	2.0	4.0	triglyme	24	91 (88)
8	3.0	--	4.0	triglyme	24	0
9	3.0	2.0	--	triglyme	24	0
10	3.0	2.0	2.0	triglyme	24	7
11	3.0	2.0	5.0	triglyme	24	88
12	3.0	1.5	4.0	triglyme	24	80
13	1.5	2.0	4.0	triglyme	24	53
14	2.0	3.0	4.0	triglyme	24	64
15[c]	3.0	2.0	4.0	triglyme	24	93 (89)
16[d]	3.0	2.0	4.0	triglyme	24	70
17[e]	3.0	2.0	4.0	triglyme	24	44
18[f]	3.0	2.0	4.0	triglyme	24	13

[a]Reactions were conducted with the indicated reagents under the indicated conditions: **1a** (17.2 mg, 0.1 mmol), **13a**, KOtBu, and the solvent (0.5 mL) reacted at room temperature for the indicated hours; [b]Determined using ^{19}F and ^{1}H nuclear magnetic resonance (NMR) spectroscopy with 3-fluoropyridine as an internal standard. The number in parentheses refers to the isolated yield, and those in the columns titled **13a**, Si-B, and KOtBu refer to molar equivalents. [c]Reaction was performed at the 0.2-mmol scale. [d]$tBuMe_2SiBpin$ was used instead of $Et_3SiBpin$. [e]$PhMe_2SiBpin$ was used instead of $Et_3SiBpin$. [f]$(Me_3Si)_3SiBpin$ was used instead of $Et_3SiBpin$.

Substrate scope

The substrate scope of this silylboronate-mediated direct amination underwent comprehensive evaluation employing the optimized reaction conditions (entry 7, Table 4.1). Table 4.2 showcases the reaction of various electronic property-bearing aryl fluorides **1** with **13a**. The reaction demonstrated remarkable efficiency across diverse π-extended aryl fluorides (**1a**–**1d**), including the sterically hindered *ortho*-substituted substrate **1c**, which yielded the corresponding cross-coupling amination products (**14a–14d**) in high yields (80–89%). Non-substituted (**1i**) and *para*-substituted fluorobenzenes carrying electron-donating (Me, **1s**; MeO, **1j**) or electron-withdrawing groups (CF_3, **1zb**) also furnished their respective products (**14e**, 79%; **14f**, 74%; **14g**, 66%; **14h**, 82%) via defluoroamination with **13a**. Excellent chemoselectivity was evident with other halide-substituted aryl fluorides (Cl, **1zc**; Br, **1zd**) to yield products (**14i**, 51%; **14j**, 39%). Fluoroarenes **1e**, **1f**, **1g**, **1w**, **1ze**, **1zf**, **1zg**, **1v**, **1zh**, and **1zi** diverse in their π-extension and electronic properties, were efficiently converted to the corresponding cross-coupling amination products **14k–14t** (51–86%), showcasing independence from attached functional groups. Notably, the process exhibited exceptional chemoselectivity, tolerating functional groups like ethers (OMe, **1g**; OBn, **1w**) and halides (Cl, **1ze**; Br, **1zf**; CN, **1zg**; CF_3, **1v**, **1zh**, and **1zi**), prone to C–F bond activation, yielding diverse products such as 4-(naphthalen-1-yl)phenyl-(**14k**: 77%), 4-methylphenyl-(**14l**: 86%), ether-containing biphenyl products (**14m**: 83%; **14n**: 61%), and biphenyl products containing electron-withdrawing groups (**14o**: 77%; **14p**: 59%; **14q**: 51%; **14r**: 84%; **14s**: 82%; **14t**: 54%). Moreover, aryl fluoride-containing benzo[1,3]dioxole, **1h**, yielded the defluoroamination product **14u** at 81% yield without C–O bond cleavage. *N*-containing heteroaromatic fluorides (**1o**, **1zq**, **1zj**, **1zp**, **1n**, and **1p**) also underwent successful defluoroamination using **13a** under the same conditions, yielding higher yields (≤97%). The cross-coupling reactions delivered pyridine derivatives (**14v**: 93%; **14w**: 91%; **14x**: 94%; **14y**: 94%) and a 1*H*-pyrrole derivative (**14z**: 97%). Indole-(**1p** and **1q**) and benzofuran-containing (**1u**) aryl fluorides exhibited efficient functionalization, selectively yielding defluorinative amination products (**14za**: 85%; **14zb**: 96%; **14zc**: 90%) via C–F bond cleavage without forming corresponding C–H bond-activated byproducts. These

results unequivocally highlight the outstanding functional group tolerance in silylboronate-mediated cross-coupling amination reactions of aryl fluorides and amines.

Subsequently, we investigated substituted *N*-methylanilines **13** in coupling reactions with **1a** under standard conditions. The impact of methyl substituents at *para*- (**13b**), *meta*- (**13c**), or *ortho*- (**13d** and **13e**) positions of *N*-methylaniline was evaluated in conjunction with **1a**. Notably, high yields of coupling products (**14zd**: 87%; **14ze**: 82%) were achieved using **13b** or **13c** with **1a**. However, yields for sterically hindered products (**14zf**: 31%; **14zg**: 32%) were comparatively lower. *N*-Methylanilines harboring electron-donating (4-OMe: **13f**, 1,3-dioxole: **13g**) or electron-withdrawing (4-OCF_3: **13h**; 4-Cl: **13i**; 3-Cl: **13j**; 4-Br: **13k**) groups underwent defluoroamination, yielding desired products with good yields (**14zh**: 61%; **14zi**: 67%; **14zj**: 49%; **14zk**: 60%; **14zl**: 54%; **14zm**: 33%).

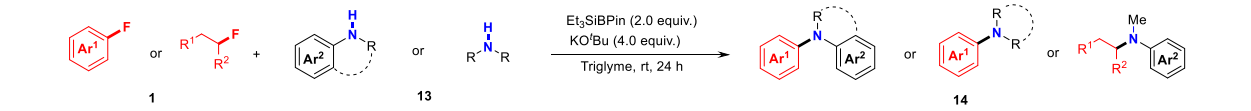
The extensive applicability of both compounds **1** and **13** in this coupling reaction led us to explore a wider scope for defluoroamination using diverse combinations of **1** and **13**. Phenyl (**1b**, **1c**), naphthyl (**1d**), and fluorobenzenes possessing electron-donating 4-OMe (**1j**) or electron-withdrawing 4-CF_3 (**1zb**) substituents were effectively coupled with various *N*-methylanilines (**13c**, **13d**, **13h**), yielding the desired amines **14** in commendable yields (**14zn**: 76%; **14zp**: 54%; **14zq**: 68%; **14zr**: 45%), despite encountering the formation of the sterically unfavorable product (**14zo**: 22%). Additionally, biphenyl fluorides **1** featuring electron-donating (**1f**, **1g**), electron-withdrawing (**1zg**, **1v**, **1zh**, **1zi**), or chloride (**1ze**) functional groups reacted efficiently with anilines **13**, yielding the corresponding products **14** in satisfactory yields (**14zs**: 69%; **14zt**: 54%; **14zu**: 66%; **14zv**: 47%; **14zw**: 92%; **14zx**: 87%; **14zy**: 89%; **14zz**: 91%; **14zza**: 86%; **14zzb**: 85%). Notably, reactions involving *N*-heterocycle-containing aryl fluorides (**1o**, **1zq**, **1n**, **1q**) with chloro- (**13i**, **13j**) or benzo[1,3]dioxole anilines (**13g**) resulted in consistently good-to-high yields (**14zzc**: 97%; **14zzd**: 96%; **14zze**: 65%; **14zzf**: 98%).

Investigating the limitations of defluorinative coupling using aryl fluorides **1** concerning various secondary amines, representative secondary amines, including *N*-alkylanilines (**13l**, **13m**), cyclic anilines (**13n**–**13q**), and cyclic and acyclic alkylamines (**13r–13u**), were reacted with **1a** under standard conditions. Notably, all instances resulted in the generation of desired products via defluoroamination with **1a**, albeit with varying yields, contingent upon the type of amine (Table 4.2, IV). *N*-Ethyl- (**13l**) or *N*-butylaniline (**13m**) exhibited lower yields (**14zzg**: 27%; **14zzh**: 27%) when coupled with **1a**. Conversely, cyclic *N*-alkylanilines demonstrated moderately favorable reactivity, yielding corresponding products in moderate yields (**14zzi**: 47%; **14zzj**: 46%; **14zzk**: 59%; **14zzl**: 35%). Steric hindrance around the N center strongly influences reactivity, evident in lower yields from bulkier anilines. Additionally, this coupling extends to non-aryl cyclic and acyclic dialkyl secondary amines such as morpholine (**13r**), pyrrolidine (**13s**), 1,2,3,4-tetrahydroisoquinoline (**13t**), and diethylamine (**13u**), yielding corresponding products (**14zzm**: 21%; **14zzn**: 11%; **14zzo**: 26%; **14zzp**: 18%). However, in these cases, partial consumption of **1a** was observed alongside byproduct formation, primarily the defluorosilylation product, PhC_6H_4-$SiEt_3$ (**2a**), indicating relatively lower reactivities of the reactants and steric hindrance of the aniline moieties leading to diminished yields.

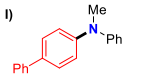
To conclude our investigation, we endeavored defluorinative aminations of alkyl fluorides **1** containing C(sp3)–F bonds utilizing **3a** under optimal reaction conditions (Table 4.2 V). Primary benzyl fluorides (**1zzd**–**1zzf**) efficiently underwent defluoroamination with **13a**, yielding desired coupling products with yields of ≤87% (**14zzq**: 81%; **14zzr**: 76%; **14zzs**: 87%). Remarkably, the C(sp3)–F bond in **1zze** was selectively cleaved without affecting the OCF_3 substituent. Furthermore, employing the secondary benzyl fluoride 2-(1-fluoroethyl)naphthalene (**1zzg**) resulted in the defluoroamination product **14zzt** with a yield of 43%. Conversely, **14zzu** was obtained with a yield of 20% when utilizing 1-fluorodecane (**1zzh**) and **3a** under identical standard reaction conditions. Consequently, the scope of non-activated alkyl fluorides in this method appears limited, although yields might be enhanced through comprehensive optimization of reaction conditions.

Interestingly, while benzyl fluoride **1zzd** produced amination product **14zzq** in an 86% yield even without $Et_3SiBpin$, 1-fluorodecane (**1zzh**) remained unreacted.

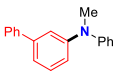
Table 4.2 Substrate scope of defluoroamination



I)

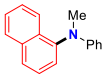


14a: 89%
87% (1.13 g)



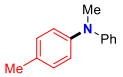
14b: 85%

14c: 80%

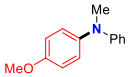


14d: 82%

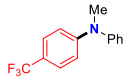
14e: 79%[b]



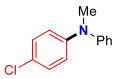
14f: 74%[b]



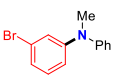
14g: 66%[b]



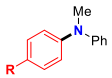
14h: 82%[b]



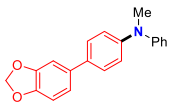
14i: 51%[b]



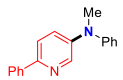
14j: 39%[b]



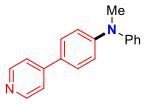
14k: R = 1-Naphthyl, 77%
14l: R = 4-Me-Ph (**Tol**), 86%
14m: R = 4-OMe-Ph (**PMP**), 83%
14n: R = 4-OBn-Ph, 61%
14o: R = 4-Cl-Ph, 77%
14p: R = 4-Br-Ph, 59%
14q: R = 4-CN-Ph, 51%
14r: R = 4-CF_3-Ph, 84%
14s: R = 3-CF_3-Ph, 82%
14t: R = 3,5-di-CF_3-Ph, 54%



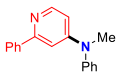
14u: 81%



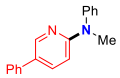
14v: 93%



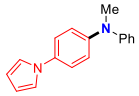
14w: 91%



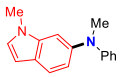
14x: 94%



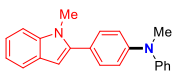
14y: 94%



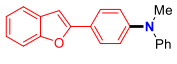
14z: 97%



14za: 85%

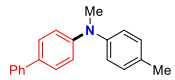


14zb: 96%

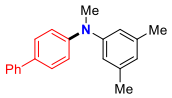


14zc: 90%

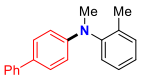
II)



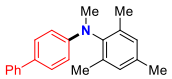
14zd: 87%



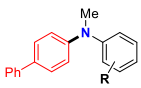
14ze: 82%



14zf: 31%

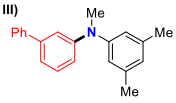


14zg: 32%

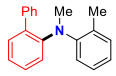


14zh: R = 4-OMe, 61%
14zi: R = 1,3-dioxole, 67%
14zj: R = 4-OCF_3, 49%
14zk: R = 4-Cl, 60%
14zl: R = 3-Cl, 54%
14zm: R = 4-Br, 33%

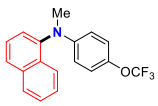
III)



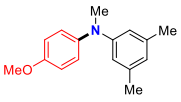
14zn: 76%



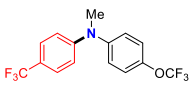
14zo: 22%



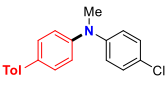
14zp: 54%



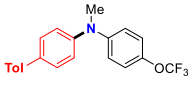
14zq: 68%[b]



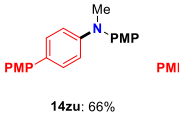
14zr: 45%[b]



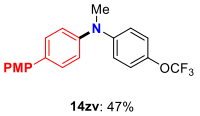
14zs: 69%



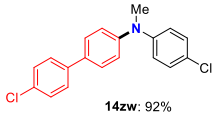
14zt: 54%



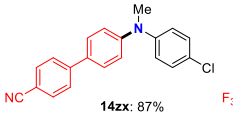
14zu: 66%



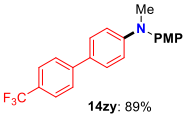
14zv: 47%



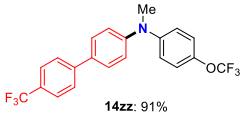
14zw: 92%



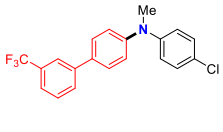
14zx: 87%



14zy: 89%



14zz: 91%



14zza: 86%

14zzb: 85%

14zzc: 97%

14zzd: 96%

14zze: 65%

14zzf: 98%

IV)

14zzg: 27%

14zzh: 27%

14zzi: 47%

14zzj: 46%

14zzk: 59%

14zzl: 35%

14zzm: 21%

14zzn: 11%

14zzo: 26%

14zzp: 18%

V)

14zzq: 81%; 86%[c]

14zzr: 76%

14zzs: 87%

14zzt: 43%

14zzu: 20%; 0%[c]

[a]Unless otherwise noted, all reactions were conducted using **1** (0.2 mmol), **13** (3.0 equiv.), $Et_3SiBpin$ (96.8 mg, 2.0 equiv.),

KOtBu (89.6 mg, 4.0 equiv.), and triglyme (1.0 mL) at room temperature for 24 h, with isolated yields shown. [a]Reaction performed using 0.4 mmol of **1**. [b]Reaction performed without Et3SiBpin, and yield was determined by ^{1}H NMR.

Application of silylboronate-mediated defluorinative coupling reaction

To underscore the synthetic versatility of the silylboronate-mediated defluorinative coupling reaction, we explored the functionalization of various drug derivatives with fluoroarene moieties (Fig. 4.2). The (±)-α-tocopherol-derived fluoroarene **1zk** underwent coupling with **13a**, yielding the (±)-α-tocopherol derivative **14zzv** in an 83% yield. Additionally, the bioactive motif derived from (-)-menthol, *N*-methylaniline **13v**, was effectively functionalized using this reaction with either **1a** or the fluoro-containing estrone derivative **1x**, generating **14zzw** and **14zzx** in yields of 75% and 62%, respectively. Moreover, we expanded the application of this protocol to the late-stage synthesis of deuterated *N*-alkyl pharmaceuticals. Given that >50% of best-selling drugs contain *N*-alkyl groups[83], the development of deuterated *N*-alkyl pharmaceuticals is gaining substantial attention. Isotope labeling holds significant importance in medicinal chemistry, as C–D bonds are more stable than C–H bonds.[84] Consequently, the incorporation of deuterated *N*-methyl (*N*-CD_3) moieties into pharmaceuticals is anticipated to enhance pharmacodynamic properties.[85] In light of this, several representative fluoro-containing derivatives of bioactive molecules, **1zk**, **1x**, **1zl**, and **1zm**, were reacted with deuterated *N*-methylaniline ***d*^{3}–13a** under standard conditions. Initially, **1x** and ***d*^{3}–13a** were employed in the presence of $Et_3SiBpin$ and KOtBu in triglyme, resulting in the synthesis of the estrone derivative ***d*^{3}–14zzy** in a 77% yield. Similarly, the reaction with (-)-menthol-derived fluorobenzene **1zl** produced the deuterated product ***d*^{3}–14zzz** in an 88% yield. The deuterated (*R*)-naproxen derivative ***d*^{3}–14zzza** was also synthesized in a 70% yield using the fluoro-propanoate **1zm**. Furthermore, **1zk** was revisited in reaction with ***d*^{3}–13a** under standard conditions, yielding the corresponding deuterated (±)-α-tocopherol derivative ***d*^{3}–14zzv** with a yield of 79%.

Reaction mechanism

To unravel the reaction mechanism, several control experiments were meticulously conducted (Fig. 4.3, left). Initially, the silylated compound **3a** was engaged in the coupling reaction with **13a** under optimal conditions; however, no detection of the amination product **14a** occurred (Fig. 4.3a), indicating that **3a** remained uninvolved in the reaction. Subsequently, investigating the defluoroamination of **1a** with **13a** in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, Fig. 4.3b) revealed a noteworthy trend: while **14a** was achieved in an 89% yield under standard conditions, its yields significantly decreased as the amount of TEMPO increased: 40% (1.0 equiv. of TEMPO), 26% (2.0 equiv. of TEMPO), and 9% (4.0 equiv. of TEMPO). Similarly, the addition of TEMPO (2.0 equiv.) inhibited the reaction of benzyl fluoride **1zzd** (Figure 4.3c). Attempting the reaction of **1** with the freshly prepared potassium salt of **13a** in the presence of tBuOBpin[27] yielded no reaction (Fig. 4.3d), indicating the unlikelihood of potassium anilide formation in the process. Employing ***d*^{3}–13a** under optimal conditions resulted in the isolation of the corresponding defluoroamination product ***d*^{3}–14a** with an 84% yield (Fig. 4.3e), while ***d*^{2}–14a** was not obtained, indicating the non-involvement of the *N*-methyl moiety in the process. Additionally, a radical clock experiment involving **1a** and *N*-cyclopropylaniline (**13w**) was conducted, leading to almost 90% recovery of **1a**, while **13w** disappeared, producing a complex mixture (Fig. 4.3f). Similarly, treating only **13w** under standard conditions yielded the

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same complex mixture, yet **13w** was recovered under the same treatment without $Et_3SiBPin$ (Fig. 4.3g), suggesting the ring-opening of aminyl radical **13w'** into primary carbon radical **13w"**, vulnerable to decomposition under $Et_3SiBpin$/tBuOK conditions.[86] Notably, the reaction of **13a** without **1a** resulted in the formation of hydrazine **15** with an isolated yield of 27% (Fig. 4.3h), indicating the dimerization of *N*-methylanilino radical PhN•Me. These control experiments collectively support the defluorinative C–N cross-coupling proceeding via a radical pathway. Furthermore, comparison studies revealed the uniqueness of this reaction using aryl fluorides **1** over conventional aryl halides Ar–X **6-8** (X = Cl, Br, or I) in the silylboronate-mediated cross-coupling (Fig. 4.3i). While 4-chlorobiphenyl (**6**) converted to the desired coupling product **14a** under identical conditions, the yield of 8% was insufficient. Contrastingly, employing bromo- or iodo-substituted biphenyl (Br: **7**; I: **8**) produced a mixture of amination product **14a** and silylation product **3a**: **14a** (Br: 6% and I: trace) and 4-biphenylyl(trimethyl)silane **3a** (Br: 9% and I: 26%), respectively. Hence, the exceptional chemoselectivity of this cross-coupling reaction favoring the C–F bond over C–Cl/Br/I bonds is evident.

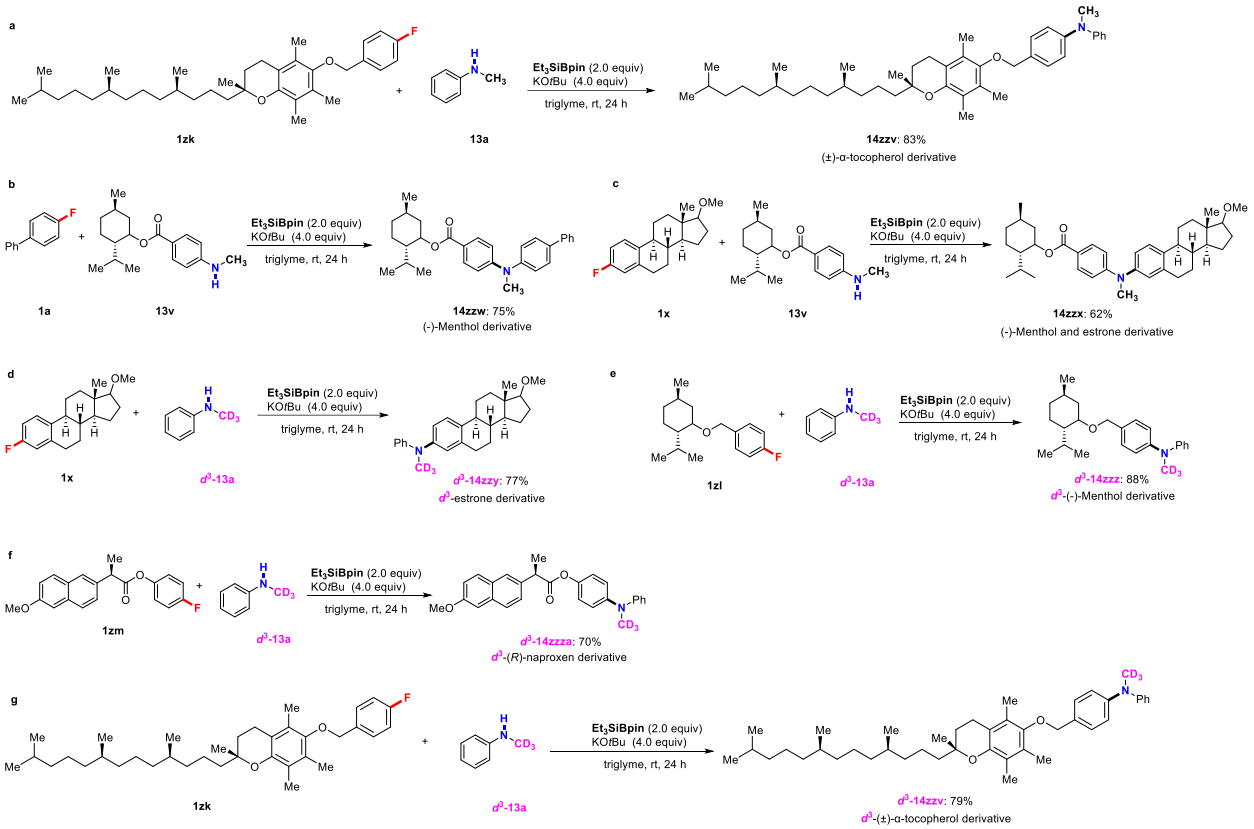

Figure 4.2 Synthetic applications

We proceeded to compare the reactivity of alkyl halides under standard conditions, both in the presence and absence of $Et_3SiBpin$. Alkyl bromide reacted with *N*-Me-aniline **13a** under standard conditions, yielding the desired amination product in a 91% yield (Fig. 4.3j). Intriguingly, even in the absence of $Et_3SiBpin$, the

[86] (a) Y. Maeda, K. U. Ingold, Kinetic applications of electron paramagnetic resonance spectroscopy. 35. the search for a dialkylaminyl rearrangement. ring opening of *N*-cyclobutyl-*N*-*n*-propylaminyl, *J. Am. Chem. Soc.* **1980**, *102*, 328–331; (b) M. Wang, T. V. T. Nguyen, J. Waser, Activation of aminocyclopropanes via radical intermediates, *Chem. Soc. Rev.* **2022**, *51*, 7344–7357; (c) S. A. Morris, J. Wang, N. Zheng, The prowess of photogenerated amine radical cations in cascade reactions: from carbocycles to heterocycles. *Acc. Chem. Res*. **2016**, *49*, 1957–1968.

amination product was obtained quantitatively (Fig. 4.3j). Similarly, alkyl chloride produced the desired amination product in high yield without the use of $Et_3SiBpin$ (Fig. 4.3k). Contrastingly, alkyl fluoride **1zzh** resulted in **14zzu** under standard conditions, but no reaction took place in the absence of $Et_3SiBpin$ (Fig. 4.3l). It's noteworthy that while alkyl bromides and chlorides easily react with the nucleophilic species through a common S_N2 reaction[2b], alkyl fluorides demonstrate distinct reactivity. These findings underscore a clear disparity between the reactivity of C–F bonds compared to C–X (Br, Cl) bonds, highlighting the significant challenges associated with C–F bond cleavage.

Drawing from our findings and insights gleaned from previous studies, we propose a mechanism for single-electron-transfer/radical-mediated defluorinative amination using frustrated radical pair chemistry[73] (Fig. 4.3m). Initially, $Et_3SiBpin$ reacts with KOtBu, forming an intermediate, **A**. Avasare et al. proposed the formation of this intermediate based on density functional theory calculations[50], and its existence was confirmed via ^{11}B and ^{29}Si nuclear magnetic resonance (NMR) studies.[82a,b] The steric hindrance of $R_3SiBpin$ moieties correlated with reduced conversion and reaction yields (Table 4.1, entries 16–18), suggesting that the initial nucleophilic addition of *t*-butoxy anion (−OtBu) to $R_3SiBpin$ is largely influenced by steric factors, independent of radical stability in the subsequent steps. These observations align with the solvent effect (Table 4.1, entries 4–6). It's known that the encapsulation of potassium cation by glymes and 18-crown-6 generates a reactive −OtBu[64,87]. This naked −OtBu anion likely expedites the formation of intermediate A. Subsequently, owing to the single electron reductant property of −OtBu[74], intermediate **A** undergoes homolytic cleavage of the Si–B bond, producing a sterically demanding frustrated radical pair, **B**, comprising the triethylsilyl radical ($•SiEt_3$) and a boron-radical species (B•). Hydrogen abstraction from *N*-methylaniline **13** by $•SiEt_3$ in **B** yields frustrated radical pair **C**, consisting of a *N*-methylanilino radical (Ar-N•-Me) and the boron-radical species, accompanied by the formation of $HSiEt_3$ (detected via gas chromatography-mass spectrometry). The low yields of **14a** under optimal reaction conditions with increased TEMPO equivalents support the generation of the *N*-methylanilino radical. Subsequently, frustrated radical pair **C** preferentially attracts organic fluoride **1** leading to the formation of **TS-I** due to favorable F-B interactions. The activated C–F bond in **1** via the B atom interaction in **TS-I** facilitates selective attack by the *N*-methylanilino radical at the carbon center of the C–F bond as depicted in **TS-I**. Ultimately, this leads to the desired cross-coupling product **14** formation via C–N bond formation, along with the release of **D** ([Bpin(OtBu)F]K, which rapidly reacts with KOtBu to yield a stable ([Bpin$(OtBu)_2$] species (detected via ^{11}B NMR spectroscopy) and KF (detected via ^{19}F NMR spectroscopy) (refer to experimental section). The observed fluorine-selective reaction over other halogens might be explained based on bond dissociation energy (BDE).[88] The C–F bond in Ph–F (BDE: 125.6 kcal/mol) is more stable than C–Br (BDE: 80.4 kcal/mol) and C–Cl (95.5 kcal/mol) bonds in Ph–X. However, the B–F (boron-fluorine) bond is the strongest among the other B–X bonds (X = F, Cl, Br) based on reported values (B(O)-X; X–F: 163.0 kcal/mol, X–Cl: 104.6 kcal/mol, X–Br: 86.7 kcal/mol)[2b] and predicted values of corresponding intermediate structures (PinB-(X)OtBu; X = F: 105.2 kcal/mol, X = Cl: 91.9 kcal/mol, X = Br: 83.9 kcal/mol).[89] Hence, the B atom in the intermediate preferentially interacts with the F atom compared to Cl or Br on the substrates, leading to the preferential attack of the amino radical at the carbon linked to the F atom over other halogen-attached carbons. Such interactions between F and B centers are pivotal for C–F bond cleavage rather than interactions between B centers and other halogens. Another possible mechanistic pathway

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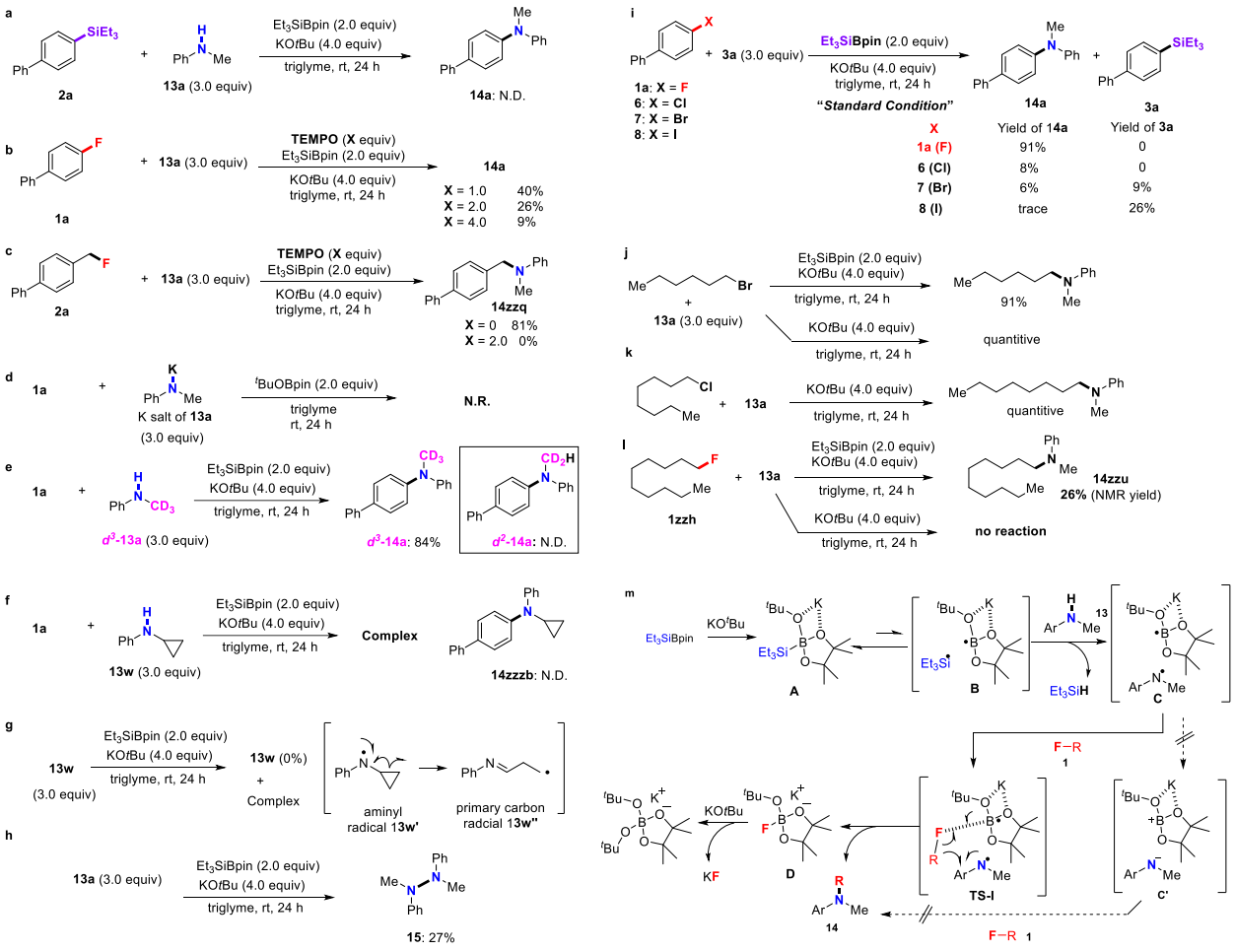
involving nucleophilic S_NAr reaction of organic fluoride **1** with the anilino anion in the frustrated ion pair **C'** was ruled out based on control experiments depicted in Fig. 4.3d.



a. Stepwise attempted reaction. b, c. Effect of TEMPO on the silylboronate-mediated coupling reaction. d. Reaction of **1a** with the potassium salt of **13a** (PhNKMe) in the presence of tBuOBpin. e. Reaction between **1a** and the deuterated **13a** (***d*^{3}-13a**). f, g. Radical clock experiments. h. Evidence suggesting the generation of an *N*-methylanilino radical. i. Chemoselectivites of organic halides Ar–X. j–l. Different reactivities of alkyl halides under the standard conditions in the presence and absence of $Et_3SiBipn$. m. Proposed reaction mechanism.

Figure 4.3 Mechanistic studies

Conclusion

In summary, we've pioneered a silylboronate-mediated radical coupling methodology that enables the inert activation of C–F bonds at room temperature, facilitating the coupling of diverse organic fluorides with secondary amines. This process effectively generates a broad array of aromatic tertiary amines in yields ranging from moderate to excellent under exceptionally mild conditions. Notably, this protocol accommodates a wide range of secondary acyclic and cyclic *N*-alkylanilines and dialkylamines, offering versatility by accommodating substrates with functional groups like -OR, Cl-, CN-, or CF_3. Unlike the Buchwald–Hartwig amination, renowned for its efficacy with aryl halides and Pd catalyst systems, this method uniquely allows the use of aryl fluorides, providing a practical approach, especially in the context of the growing application of

fluorine-containing drugs in pharmaceutical and agrochemical industries. Our strategy offers potential in the synthesis of new drug candidates, including late-stage syntheses of *N*-alkyl pharmaceuticals, including deuterated analogs, demonstrating the adaptability and mild nature of this reaction. Given its ease of execution, broad substrate compatibility, and the ability to generate complex pharmaceuticals, this silylboronate-mediated C–F and N–H bond coupling holds promise for organic syntheses, pharmaceuticals, and agrochemical applications. Ongoing studies aim to further explore and expand upon this defluorinative functionalization methodology.

Chapter 5. An Innovative Approach to α-Arylation of acetonitrile

Introduction

The α-arylation of nitriles stands as a crucial chemical process wherein an aryl (aromatic) group seamlessly integrates into the α-position of nitrile compounds. The ubiquity and versatility of α-(hetero)aryl nitriles in organic synthesis make them indispensable, notably reflected in their pivotal roles as core structures in pharmaceuticals.[90] Over recent decades, methodological endeavors targeting the α-arylation of nitriles have been categorized into four primary groups: a) radical nucleophilic aromatic substitution ($S_{RN}1$) reactions[91], b) aryne pathways[92], c) nucleophilic aromatic substitution (S_NAr) methodologies[93], and d) transition-metal-catalysis processes[94] (Scheme 5.1a). $S_{RN}1$ methods involve radical pathways mediated by *in situ* generated sodium or potassium amides in liquid ammonia, often requiring photostimulation. However, these pathways exhibit critical limitations concerning substrate scope and compatibility with phenyl halides, resulting frequently in lackluster yields overshadowed by byproducts. Aryne strategies rely on arynes and benzynes generated *in situ* under highly basic conditions but are plagued by regioselectivity issues. S_NAr approaches typically employ aryl fluorides, necessitating auxiliary activating groups or complexation with tricarbonyl chromium. Highly reactive nitrile carbanions derived from (di)phenylacetonitriles, cyanoacetates, and α-iminonitriles under basic conditions are also required. Caron[93a] and colleagues demonstrated S_NAr reactions

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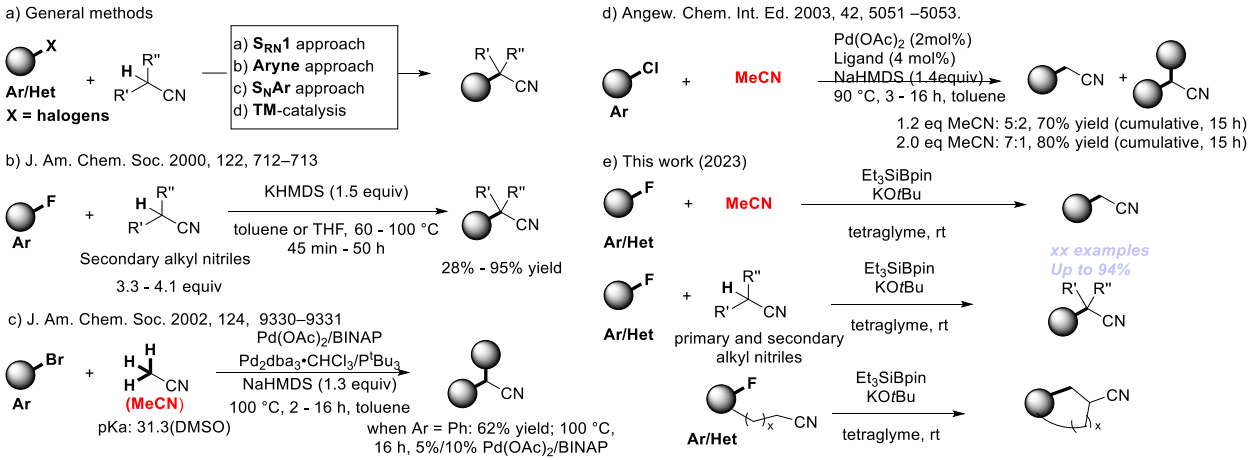
using non-activated aryl fluorides and non-activated secondary alkyl nitriles to provide tertiary benzylic nitriles. However, primary nitriles did not undergo substitution (Scheme 5.1b). Transition-metal-catalyzed methods, exemplified by pioneering works from Takahashi, Migita[94i], Hartwig[94a], Verkade[94b,c], and Liu[94g], have emerged as promising avenues for synthesizing α-aryl nitriles from aryl halides. Nevertheless, these methods necessitate reactive nitrile sources such as malononitrile, α-silyl nitriles, and cyanoacetates, among others (Scheme 5.1a).

It should be noted that Hartwig et al. delineated strategies employing BINAP or P(*t*Bu)$_3$-ligated Pd, which are effective for the cross-coupling of aryl bromides with non-activated alkyl nitriles (Schemes 5.1a and 5.1c). Verkade and You used bicyclic proazaphosphatrane ligands with Pd catalysts to facilitate the α-arylation of aryl chlorides with non-activated alkyl nitriles. However, elusive acetonitrile, which presents inherent challenges associated with its low reactivity and high stability, remains a cumbersome substrate (Schemes 5.1a and 5.1d). Acetonitrile (MeCN) is a popular solvent for many organic reactions because of its inertness (pKa:31.2 (DMSO)). Moreover, there are three hydrogen atoms, and issues such as diarylation over monoarylation have persistently plagued this field of research. Notably, Hartwig's approach yielded α-diarylated products using acetonitrile (Scheme 5.1c), while Verkade's protocol yielded a mixture of both mono- and diarylated derivatives (Scheme 5.1d).

To address this intricate challenge for 20 years, we have introduced a paradigm-shifting method for the α-arylation of acetonitrile with traditionally considered unreactive aryl fluorides (Scheme 5.1e). Our strategic innovation lies in employing a potential frustrated radical pair approach based on a silylboronate/potassium (K)-base system, which directly facilitates cross-coupling between aryl fluorides and acetonitrile through C-F bond activation, thus selectively producing α-aryl nitriles in appreciable yields. The advantages of this method are further underscored by its ability to engage a broad spectrum of aryl fluorides and its exceptional selectivity, which prevents the diarylation of acetonitrile. Moreover, our approach generously accommodates an array of unactivated alkyl nitriles. Given the prevalence of aryl fluoride motifs in pharmaceuticals[1a,b,e], our method represents a practical approach for late-stage functionalization in drug development and modification.

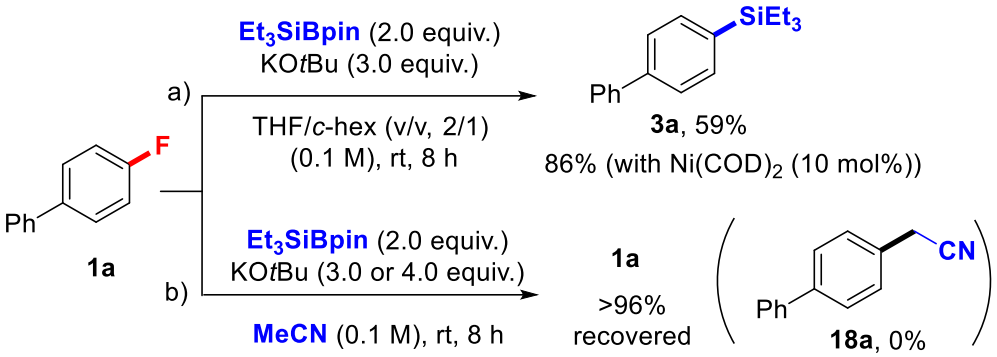


Scheme 5.1 a) General Approach to α-(hetero)aryl Nitriles; b) S$_N$Ar Reaction of Aryl fluorides with Secondary Alkyl Nitriles; c) Pd-Catalyzed α-Arylation of Nitriles with Aryl bromides; d) Pd-Catalyzed α-Arylation of Nitriles with Aryl Chlorides; e) This Work.

Optimization of reaction conditions

In 2018, we elucidated the defluorosilylation of aryl fluorides utilizing Et$_3$SiBpin in conjunction with KOtBu under Ni catalysis in a mixed solvent system (THF/*c*-hexane), yielding aryl silanes.[37] Subsequently, after three years, it was observed that this defluoro-silylation could occur even in the absence of a Ni catalyst, albeit with

diminished yields of aryl silanes.[95] Under such Ni-free conditions, the silyl radical species, $Et_3Si•$, is postulated to serve as a silicon donor and generate silylation products through C–F bond cleavage of aryl fluorides. Representative examples of 4-biphenyl fluoride (**1a**) with and without a Ni catalyst are shown (Scheme 2a).



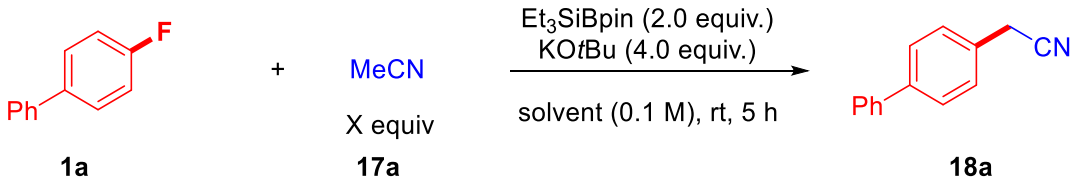
Scheme 5.3 a) Silylboronate-Mediated Defluoro-silylation of Aryl Fluorides with or w/o Ni-Catalyst; b) Initial Trial for Silyl-boronate-Mediated Defluoro-cyanomethylation of Aryl Fluorides using Acetonitrile as Solvent.

Based on these insights, we conjectured that α-arylation of acetonitrile would be feasible if the reaction occurred in acetonitrile. We postulated that the generated Si radical would predominantly abstract hydrogen (H) from acetonitrile over engaging aryl fluorides due to significant disparities in their amounts, leading to the formation of the α-carbon radical of acetonitrile with Et_3SiH. Subsequently, the nascent α-carbon radical of acetonitrile participates in the cross-coupling with aryl fluorides to synthesize the desired α-aryl acetonitriles. To substantiate this theory, we performed the reaction of **1a** with $Et_3SiBpin$ and KOtBu at ambient temperature in acetonitrile (**17a**) for 8 h to synthesize α-aryl acetonitrile (**18a**). However, the reaction remained unproductive, and aryl fluoride **1a** was largely unaltered (Scheme 2b).

Not even aryl silane **3a** was detected (Scheme 2b), we reverted to our baseline conditions in THF/*c*-hexane and added 2.0 equivalents of acetonitrile (Table 5.1, entry 1). However, this also indicated the recovery of aryl fluoride **1a**. Our attention had next shifted to the exploration of ethereal solvents. Although employing THF did not facilitate the reaction (entry 2), the use of dimethoxyethane (DME) yielded **18a** in 25% yield (entry 3). Buoyed by this intriguing solvent effect, our endeavors to optimize the reaction conditions persisted, involving alteration of the ethereal solvents (entries 4-6), and the yield of **18a** increased to 88% (68% in diglyme, 67% in triglyme, and 88% in tetraglyme). Prolonging the reaction time to 24 h using tetraglyme did not increase the yield (entry 7). The quantity of acetonitrile was influential, with optimal results for **18a** observed at 2.0 equiv., whereas 1.0 or 3.0 equiv. compromised the yields. Given the residual presence of **1a** in the reaction, the quantities of $Et_3SiBpin$ and KOtBu were amplified to 2.5 and 5.0, respectively, completely consuming starting material **1a** and yielding product **18a** in a 97% yield (entry 10). Control experiments delineated that the absence of KOtBu completely hindered the reaction (entry 11), and the absence of $Et_3SiBpin$ resulted in a mere 3% yield of **18a** (entry 12).

[95] J. Zhou, Z. Zhao, Silylboronate-Mediated Defluorosilylation of Aryl Fluorides with or without Ni-Catalyst, *Front. Chem*. **2021**, *9*, 771473.

Table 5.1 Optimization of reaction conditions[a]



1a **17a** **18a**

Entry	MeCN (equiv.)	Solvent	Yield[e]
1	2.0	THF/c-hex (v/v, 2/1)	0%
2	2.0	THF	0%
3	2.0	DME	25%
4	2.0	diglyme	68%
5	2.0	triglyme	67%
6	2.0	tetraglyme	88%
7[b]	2.0	tetraglyme	84%
8	1.0	tetraglyme	27%
9	3.0	tetraglyme	80%
10[c]	2.0	tetraglyme	97% (92%)
11[d]	2.0	tetraglyme	0%

[a] Reaction was conducted with 0.1 mmol of **1a**; [b]Reaction time was 24 h; [c]2.5 equiv. equiv of $Et_3SiBpin$ and 5.0 equiv. of KOtBu were used; [d]Reaction was conducted in the absence of KOtBu; [e]Determined by ^{19}F and ^{1}H NMR spectroscopy using 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. The numbers in parentheses refer to isolated yields.

Substrate Scope

With the optimal reaction conditions in hand, the substrate scope of the α-arylation of acetonitrile (**17a**) was explored (Table 5.2(I)). The α-arylation of **17a** with *para*- (**1a**), *meta*- (**1b**), and *ortho*- (**1c**) biphenyl fluorides under refined conditions yielded α-aryl nitriles in good-to-high yields of **18a** (92%), **18b** (64%), and **18c** (73%). Subsequently, we evaluated the effect of the substitution on the biphenyl ring. A range of *para*-substituted fluorobiphenyls with Me (**1f**), OMe (**1g**), and Cl (**1ze**) yielded the corresponding acetonitrile derivatives in high yields of 86% (**18d**), 85% (**18e**), and 83% (**18f**), respectively. Naphthyl-phenylacetonitrile (**18g**) was obtained in 94% yield from naphthyl-phenyl fluoride (**1e**) and **17a**.

Phenyl fluorides with *p*-Cl (**1zc**) and *m*-OPh (**1zr**) substitutions reacted with **17a** to provide the corresponding phenyl acetonitriles in 81% (**18h**) and 88% (**18i**) yields. The reaction of 1-naphthyl fluoride (**1d**) with **17a** afforded 1-naphthyl acetonitrile (**18j**) in 82% yield. Aryl fluorides bearing heteroaryl groups, such as benzodioxol (**1h**), benzofuran (**1u**), indole (**1q**), pyridine (**1zq**), and pyrrole (**1n**), were efficiently transformed into the desired products **18k**-**18o** in 54%-90% yields, indicating the efficacy of this methodology for a series of aryl fluorides with heterocycles. Moreover, direct α-heteroarylation of acetonitrile was achieved. Fluoroquinoline **1zs**, fluoro-pyridine **1o**, fluoroindazole **1zn**, fluorobenzofuran **1zt**, and fluorobenzothiophene **1zo** were converted into the respective heteroaryl acetonitriles **18p**-**18t** in 34%-61% yields under standard conditions.

We then broadened the methodology for the α-arylation of nitriles using diverse linear alkyl nitriles, such as propionitrile (EtCN, **17b**), butylonitrile (PrCN, **17c**), and nonadecanenitrile ($C_{18}H_{37}CN$, **17d**). α-Arylation of **17b** using fluorobiphenyl (**1a**), fluorobenzene (**1i**), and *para*-Me-fluorobenzene (**1s**) proceeded smoothly, yielding the desired α-(hetero)aryl propionitriles in excellent yields (**18u**: 89%, **18v**: 96%, **18w**: 96%). The reaction of **1a** with butylonitrile (PrCN, **17c**) or nonadecanenitrile (**17d**) afforded α-aryl butylonitrile **18x** (92%) and α-aryl nonadecanenitrile **18y** (87%) in high yields. Branched alkylnitriles, such as isopropyl (**17e**), cyclopropyl (**17f**), cyclohexyl (**17g**), and adamant (**17h**), were reacted with fluorobiphenyl **1a** to yield the respective products **18z**-**18zc** in yields of up to 89%. Furthermore, the acyclic and cyclic tertiary alkyl nitriles **17i**, **17j**, and **17k** were well tolerated under the reaction conditions with **1a**, producing the desired products in acceptable yields (**18zd**: 46%, **18ze**: 34%, **18zf**: 47%) despite their high steric hindrance.

Alkyl nitriles bearing various heterofunctional groups at the terminal (**17l**-**17q**) were further evaluated. Methoxy (**17l**), dimethylamino (**17m**), trifluoromethyl (**17n**), piperidinyl (**17o**), morpholinyl (**17p**), and *N*-methyl anilinyl (**17q**) groups were all viable, generating the respective products **18zg** (89%), **18zh** (64%), **18zi** (31%), **18zj** (93%), **18zk** (94%), **18zl** (89%) yields. Notably, alkyl nitriles **17r**-**17u** with potentially reactive protons, such as allyl (**17r**), benzyl (**17s** and **17t**), and pyridylmethyl (**17u**), were also tolerated in this α-arylation reaction, providing the desired aryl nitriles in 48-91% yields.

Aryl fluorides **1zu**-**1zw** possessing alkyl nitriles under identical conditions yielded six- and seven-membered (hetero)cyclic nitrile compounds in good yields (**18zq**: 70%, **18zr**: 55%, **18zs**: 63%). All trials in Table 5.2(III) unequivocally suggest that this methodology for the α-arylation of acetonitrile and related non-activated alkyl nitriles is highly effective, with broad general and functional tolerances. However, some functional limitations were encountered (refer to experimental section).

To demonstrate the applicability of silylboronate-mediated α-arylation of acetonitriles with aryl fluorides, late-stage diversification of natural products and drug-conjugated substrates was performed under standard reaction conditions (Table 5.2(IV)). Aryl fluorides **1zr**, **1zs**, and **1zzb** successfully underwent defluoro-α-arylation with propylnitrile **17b**, yielding the precursors of fenoprofen (**18zt**), naproxen (**18zu**), and ibuprofen (**18zv**) in 87%, 82%, and 89% yields, respectively. Additionally, several molecules with complex structures, including blonanserin (a drug used to treat schizophrenia) **1zz**, adapalene-derived fluoroarene **1zza**, estrone-derived fluoroarene **1zy**, and Vitamin E derivative **1zzc** performed well under standard conditions, forming desired products **18zw**, **18zx**, **18zy**, and **18zz** in 71%, 81% 74%, and 34% yields, respectively.

Mechanistic Investigation

Several control experiments were performed to elucidate the reaction mechanism. Initially, reactions were examined under standard conditions with TEMPO, where yields significantly decreased as TEMPO amounts increased: 68% with 1.0 equiv., 45% with 2.0 equiv., and 12% 4.0 equiv. of TEMPO (Figure 5.1a). Additionally, the reaction of 1a was carried out using KOtBu in the absence of $Et_3SiBpin$, resulting in a mere 3% yield of **18a** (Figure 5.1b). These results suggest that the reaction is mediated by radical species, and deny the general S_NAr reaction by the alpha-carbanion of acetonitrile.

To investigate the mediation of $TESCH_2CN$ in the reaction, aryl fluoride **1a** was reacted with the separately prepared $TESCH_2CN$ in the presence of tBuOK in tetraglyme. The desired product was obtained in 20% yield, whereas **1a** was recovered in 59% yield. We also performed the same experiment using $TESCH_2CN$, but in the presence of B_2Pin_2 (Figure 5.1c and d), the product yield was 16%, with **1a** recovered at 65%. These results suggest that in-situ generation of $TESCH_2CN$ may not have occurred during the reaction.

Based on these experiments and prior studies[37,49,96], we propose a single-electron-transfer/radical-mediated defluor-inative cross-coupling mechanism utilizing frustrated radical pair chemistry (Figure 5.1e). First, $Et_3SiBpin$ and KOtBu form intermediate **A**, as confirmed by us and others. Because of the steric repulsion between Si and BPin, intermediate **A** dissociates into a frustrated radical pair (FRP) **B**, consisting of a triethylsilyl radical (•$SiEt_3$) and a boron-radical species (•B(OtBu)Pin), through the homolytic scission of the Si–B bond. The •$SiEt_3$ abstracts hydrogen from alkylnitriles **17**, forming frustrated radical pair **C** and yielding $HSiEt_3$ (GC-MS detected $HSiEt_3$). Subsequently, the frustrated radical pair **C** engages organic fluoride **1** because of the favorable interaction between the fluorine atom and boron center, forming **TS-I**. Interaction with the boron atom in **TS-I** activates the C–F bond of **1**, allowing cyanoalkyl radicals to selectively target the carbon center of the C–F bond of **1**. The final reaction yields the desired cross-coupling product **18** through C–C bond formation, releasing **D** ([Bpin(OtBu)F]K), which reacts with KOtBu to form a stable ([$Bpin(OtBu)_2$] species and KF, detected using ^{11}B and ^{19}F NMR spectroscopy, respectively.

It should be mentioned that, in the reaction using acetonitrile (**17a**), the steric frustration in FRP **C** might not be sufficiently large, resulting in the formation of **C'**. However, the bond dissociation energy (BDE) of **C'** is weak; thus, intermediate **C** should predominantly proceed toward forming stable intermediate **D** via **TS-I**.

Subsequently, comparative experiments with other aryl halides, Ar-X **6**-**8** (X = Cl, Br, I), were performed to confirm the role of fluorine. 4-Chlorobiphenyl (**6**) produced the desired coupling product **18a** under identical conditions, but the yield was only 8%. Utilizing bromo- or iodo-substituted biphenyl (Br: **7**; I: **8**) led to a mixture of desired **18a** (Br: 6% and I: trace) and silylation product **2a** (Br: 9% and I: 26%), respectively. This remarkable advantage of fluorine can be explained by the BDEs of the B–X bonds in intermediate **D** (Figure 5.1f). Among the halogens, fluorine (F) makes the strongest bond with borane (B). Thus, in transition state **I** (**TS-I**), the boron species efficiently cleaves the C-F bond of aryl fluorides rather than other C-X bonds of aryl halides.

Conclusion

In conclusion, we have formulated a universally applicable method for the α-arylation of acetonitrile, addressing a challenge that has persisted for over 50 years. Although numerous approaches to the α-arylation of nitriles exist, which are broadly categorized under SRN_1 reactions, aryne pathways, S_NAr methodologies, and transition metal catalysis processes, the direct α-arylation of acetonitrile has remained formidable. Our pioneering method stands apart from previously reported categories and accomplishes α-arylation of acetonitrile proficiently and selectively, utilizing a frustrated radical pair (FRP) approach. This FRP approach was realized through the synergy of silylboronate, tBuOK, and organic fluorides, including inert C-F bond cleavage. A striking feature of our protocol is the achievement of acetonitrile use and its ability to operate at ambient temperatures within a minimal time frame, thereby pre-venting the need for transition metals and specialized ligands at elevated reaction temperatures. This innovation broadens the substrate spectrum to encompass a plethora of non-activated alkyl nitriles. A significant augmentation of our method is the deployment of inert aryl fluorides as a replacement for conventional aryl halides, facilitating the tolerance of reactants in multistep syntheses and enabling the late-stage alpha-arylation of nitriles with intricate structures. Furthermore, our method is not constrained to aryl fluorides; heteroaryl fluorides are also excellent substrates for this transformative chemical process. Given the widespread availability of many aryl fluorides, including those found in complex pharmaceuticals and agrochemicals, we anticipate that our methodology, emphasizing the radical coupling of aryl fluorides with alkyl nitriles, will become an invaluable tool for the streamlined synthesis of a diverse array of materials such as prospective drug candidates.

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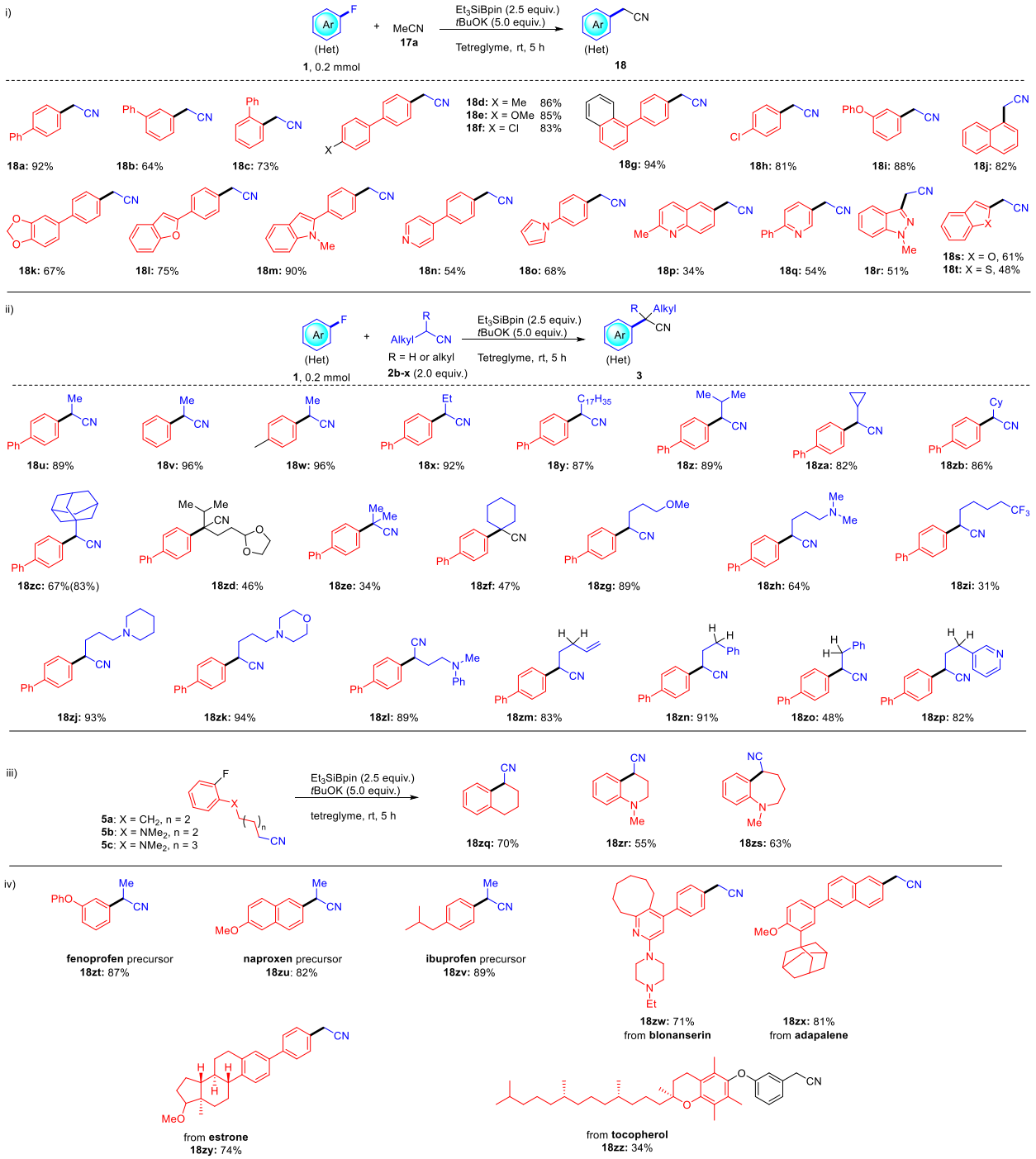
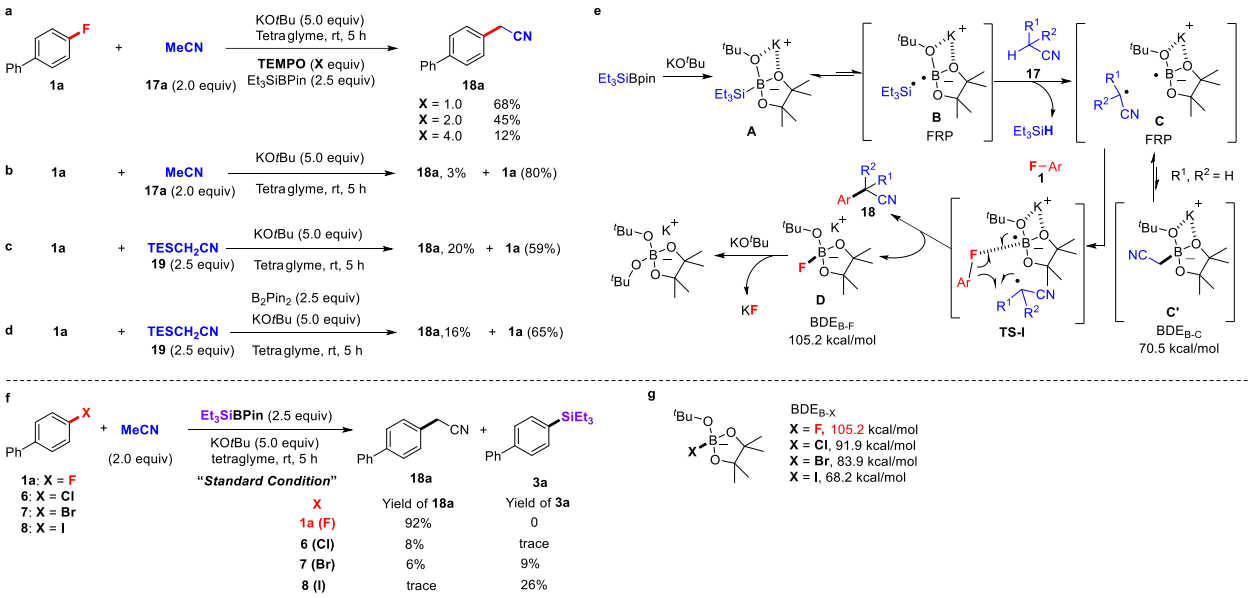
Table 5.2 Substrate Scope of Defluorocyanoalkylation



[a]See the experimental section for details; **1** (0.2 mmol, 1.0 equiv.), **17** (2.0 equiv.), $Et_3SiBpin$ (2.5 equiv.), KOtBu (5.0 equiv.), and tetraglyme (2.0 mL) at room temperature for 5 h.



a. Effect of TEMPO on silylboronate-mediated defluorocyanoalkylation. b. Possiblity of SNAr Pathway; c&d. possible intermediate confirmation experiment; e. Proposed reaction mechanism; f. Differences in the defluorocyanoalkylation of aryl halides (Ar–X; X = F, Cl, Br, or I) with 2a under standard conditions; g. Comparison for Predicted BDE of B–X bond in Bpin(OtBu)X anion.

Figure 5.1 Mechanistic studies

Chapter 6. Mechanochemical Deoxyfluorination of Carboxylic Acids to Acyl Fluorides and Successive Mechanochemical Amide Bond Formation

Introduction

Acyl fluorides (RFC=O) are versatile reagents in organic synthesis that exhibit three types of reactivity to produce valuable products (Scheme 6.1a).[97] Acyl fluorides are traditionally used as acylating agents (RC=O sources), wherein they react with nucleophiles such as alcohols, amines, and thiols to form esters, amides, and thioesters, respectively. Compared to other acylating agents such as acid chlorides or anhydrides, acyl fluorides are less prone to hydrolysis and other side reactions.[97d-g] Furthermore, acyl fluorides have recently been used as the "R" source for transition-metal-catalyzed decarbonylative cross-coupling reactions.[97h-l] Acyl fluorides can also be used as the "F" source in fluorination reactions[97m-o] to synthesize diverse fluorinated compounds that have applications in the pharmaceutical industry, [98] materials engineering, [99] and agrochemical development.[100] The appropriate balance of stability and reactivity of acyl fluorides toward water, protic solvents, and transition metal catalysts make them valuable reagents in organic synthesis.[97]

Mechanochemistry, recognized by the International Union of Pure and Applied Chemistry (IUPAC) as a groundbreaking innovation in chemistry, has been termed Chemical 2.0 owing to its transformative potential.

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This emerging field encompasses the application of mechanical forces to induce chemical reactions, and advances in solid-state chemistry. IUPAC has acknowledged mechanochemistry as one of the ten leading technologies in chemistry, responding to the growing need for environmentally friendly processes and sustainable reaction conditions.[101] A ball mill is a mechanochemical apparatus that employs the controlled movement of a ball at a specified frequency to exert mechanical force on the mixture of reagents, thereby expediting the reaction process. Although many mechanochemical reactions, including fluorination[102] and difluoromethylation [103] reactions, have recently been reported, there is an absence of reported mechanochemical synthesis methods for acyl fluorides.

A suitable choice of deoxyfluorinating reagent is critical for the mechanochemical synthesis of acyl fluorides from carboxylic acids. It is advisable to refrain from using shock-sensitive materials that undergo mechanochemical stress. In addition, mechanochemical stress can produce heat due to material friction, but this heat generation is generally not substantial.[101b] Diethylaminosulfur trifluoride (DAST), [104] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor), [105] and 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead®)[106] are practical and convenient fluorinating reagents for general solution reactions (Scheme 6.1b). However, DAST and Deoxofluor are thermally unstable and are extremely sensitive to moisture. Moreover, DAST is highly explosive,[107] which makes it unsuitable for ball mill reactions. In addition, based on a previous report[108] and our observations, Fluolead® leaves massive residue ArSOF after the reaction, hindering the isolation of the generated acyl fluorides. Besides, these deoxyfluorinating reagents require multiple preparation steps.

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[107] (a) K. A. Jolliffe, *N*,*N*-Diethylaminosulfur trifluoride (DAST, Et_2NSF_3) and related reagents. *Aust. J. Chem.* **2001**, *54*, 75; (b) P. A. Messina, K. C. Mange, W. J. Middleton, Aminosulfur trifluorides: relative thermal stability [1]. *J. Fluorine Chem.* **1989**, *42*, 137-143; (c) A. l'Heureux, F. Beaulieu, C. Bennett, D. R. Bill, S. Clayton, F. O. Laflamme, M. Mirmehrabi, S. Tadayon, D. Tovell, M. Couturier, Aminodifluorosulfinium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling. *J. Org. Chem.* **2010**, *75*(10), 3401–3411.

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Therefore, we were interested in 1,1,2,2-tetrafluoro-*N*,*N*-dimethylethylamine (TFEDMA). TFEDMA, developed by Petrov et al. at Du Pont in 2001, is a thermally stable and industrially scalable reagent for the fluorination of alcohols and ketones.[109] It can be easily accessed by mixing *N*,*N*-dimethylamine with affordable and commercially available tetrafluoroethylene (TFE), a widely abundant starting material (Scheme 6.1c). TFE is an industrial raw material used to manufacture Teflon®, PTFE, ETFE, and other fluoropolymers.[110] This contrasts with common fluorinating reagents, like DAST, whose use involves significant safety concerns owing to their explosive nature, making them unsuitable for mechanochemical reactions. Although the use of TFEDMA must also be handled with extreme caution and appropriate protective measures, such as DAST, owing to its susceptibility to hydrolysis upon exposure to moisture or water, resulting in the generation of hydrogen fluoride (HF), its thermal stability, non-explosive nature, and industrially scalable nature make it attractive as a deoxyfluorinating reagent in our study. It should be pointed out that the usage of fluoride compound in this protocol inevitably generates fluoride waste. The accumulating impact of fluoride pollution on both the human body and the environment has raised significant concerns in recent years,[111] underscoring the necessity for proper fluoride waste management.

As a part of our collaborative research program to expand the industrial utility of TFEDMA,[112] we developed the first mechanochemical deoxyfluorination of carboxylic acids to afford acyl fluorides using TFEDMA (Scheme 6.1d). The substrate scope of carboxylic acids was investigated, and the reaction conditions were optimized. A one-pot two-step mechanochemical synthesis of amides from carboxylic acids and amines using TFEDMA without any additives was explored. Furthermore, the methodology was extended to the coupling reaction of two amino acids for application in peptide synthesis. By comparing our ball-milling system to the reported batch, solution reactions, our mechanochemical method demonstrates clear advantages in terms of solvent usage, reaction time, and green marker values. We emphasize the decreased reliance on solvents (no solvent in the reaction), shortened reaction times (20 min), and advantageous E-factor, which agree with the principles of green chemistry. Also, the purification process can be modified through recrystallization to reduce its environmental impact. Furthermore, TFEDMA guarantees not only the efficacy and efficiency of fluorination but also its compatibility with the tenets of safety and sustainability.

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[110] (a) J. Park, A. Benning, F. Downing, J. Laucius, R. McHarness, Synthesis of Tetrafluorethylene-Pyrolisis of monochlorodifluoromethane. *Ind. Eng. Chem.* **1947**, *39* (3), 354-358; (b) B. Ameduri, B. Boutevin, Copolymerization of fluorinated monomers: recent developments and future trends. *J. Fluorine Chem.* **2000**, *104* (1), 53-62; (c) M. Ohashi, T. Kambara, T. Hatanaka, H. Saijo, R. Doi, S. Ogoshi, Palladium-catalyzed coupling reactions of tetrafluoroethylene with arylzinc compounds. *J. Am. Chem. Soc.* **2011**, *133* (10), 3256-3259; (d) D. A. Hercules, C. A. Parrish, T. S. Sayler, K. T. Tice, S. M. Williams, L. E. Lowery, M. E. Brady, R. B. Coward, J. A. Murphy, T. A. Hey, A. R. Scavuzzo, L. M. Rummler, E. G. Burns, A. V. Matsnev, R. E. Fernandez, C. D. McMillen, J. S. Thrasher, Preparation of tetrafluoroethylene from the pyrolysis of pentafluoropropionate salts. *J. Fluorine Chem.* **2017**, *196*, 107-116.

[111] S. Wu, Y. Wang, M. Iqbal, K. Mehmood, Y. Li, Z. Tang, H. Zhang, Challenges of fluoride pollution in environment: Mechanisms and pathological significance of toxicity – A review. *Environ Pollut.* **2022**, *304*, 119241.

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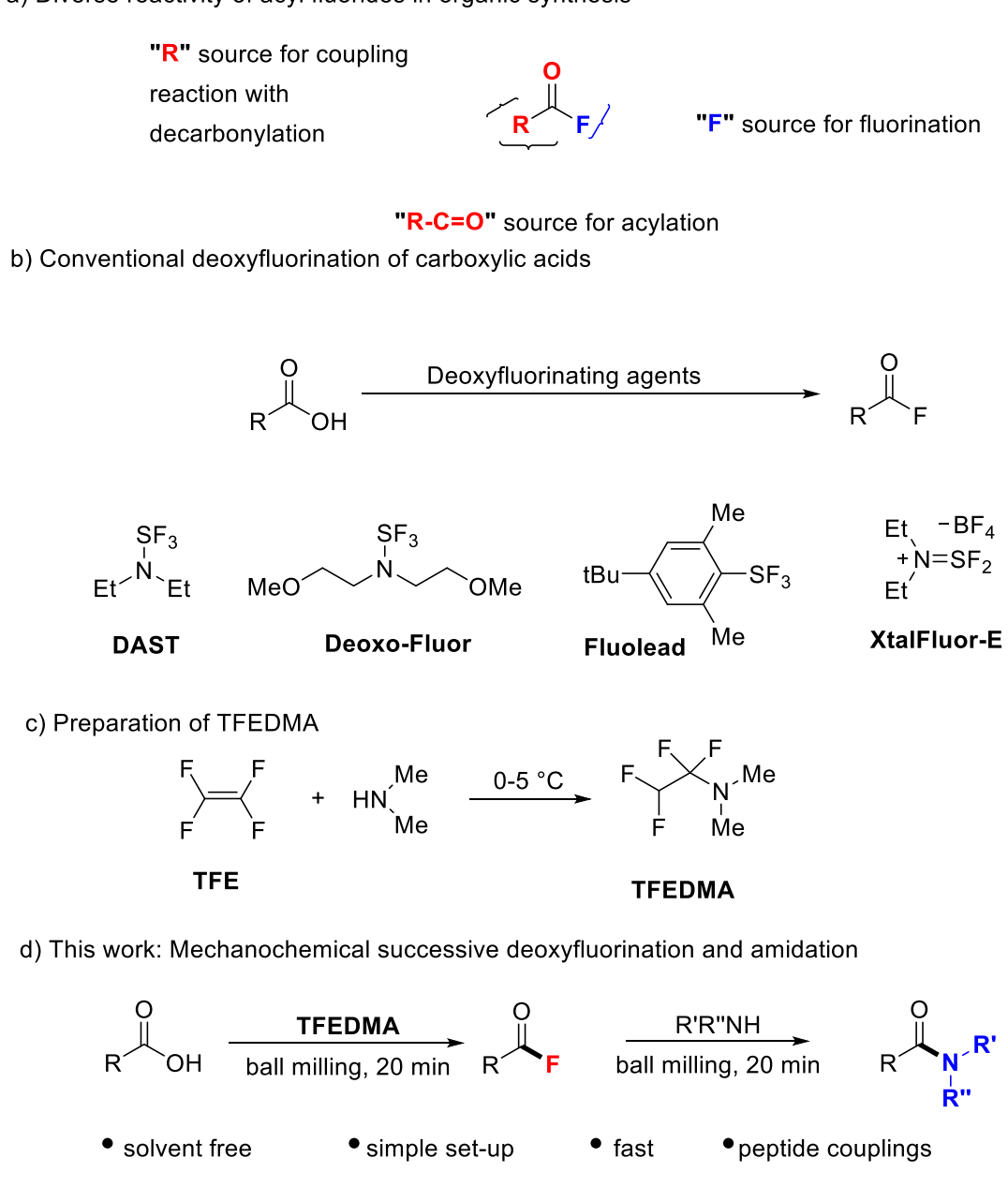
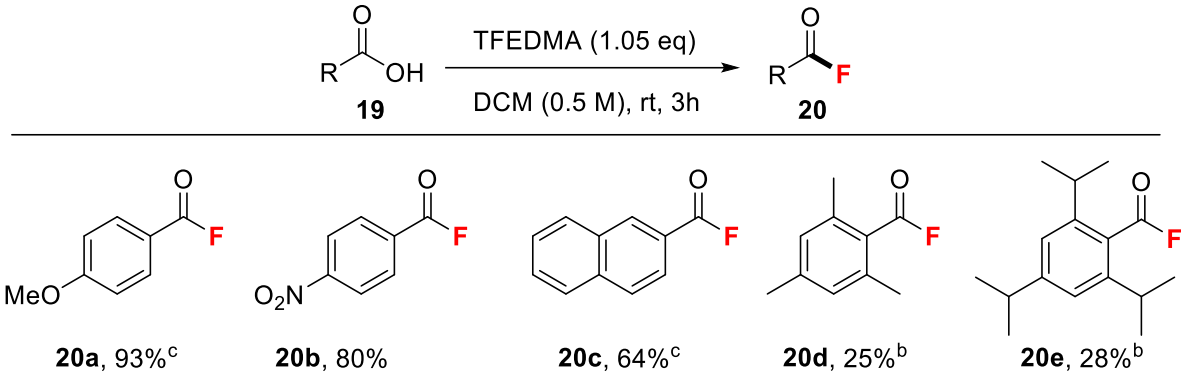


Scheme 6.1 Reactivity and Synthetic Pathway of Acyl fluorides

Results and discussion

Before investigating the mechanochemical fluorination reaction, we confirmed the feasibility of the deoxyfluorination of carboxylic acids mediated by TFEDMA in the batch solution system. Petrov showed a single example of deoxyfluorination mediated by TFEDMA using perfluoroalkyl acid, but did not explore the substrate scope of conventional carboxylic acids; however.[109] In our search for optimal reaction conditions in the batch solution syetem, we performed TFEDMA-mediated deoxyfluorination using 4-methoxybenzoic acid (**19a**) as a model substrate. By optimizing the reaction conditions (Table 6.1), we found that the reaction proceeded smoothly at room temperature for 3 h in DCM to afford the desired acyl fluoride 2a in 93% yield in the batch solution system. 4-Nitrobenzoic acid (**19b**) and 2-naphthoic acid (**19c**) were also converted into acid

fluorides **20b** and **20c** in 80% and 64% yields, respectively. However, the reactions of sterically demanding substrates **19d** and **19e** were extremely slow. Extending the reaction time to 6 h reduced the yields of **20d** and **20e** (25% and 28%, respectively) (Scheme 6.2). These results demonstrate the disadvantages of batch solution systems for sterically demanding carboxylic acids.

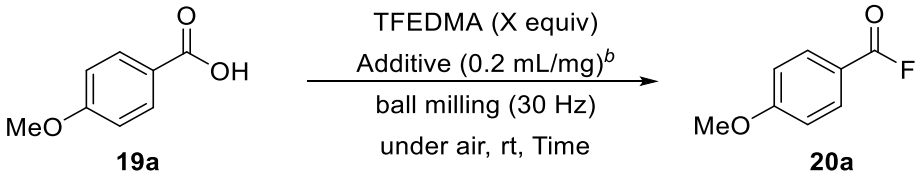


[a]Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale for 3 h; [b] The reaction lasted 6 h. [c]Reaction was conducted on a 0.1 mmol scale.

Scheme 6.2 Batch Reaction for Acyl Fluorides mediated by TFEDMA[a]

Based on the initial results of the batch, solution reactions shown in Scheme 6.2, the targeted mechanochemical deoxyfluorination of carboxylic acids using **19a** was investigated. The reactions were performed in a 1.5 mL stainless-steel grinding jar (Retsch MM400 ball mill) at 30 Hz using a 5 mm-diameter stainless-steel ball. The results of the optimization are presented in Table 6.1. Although the ball-milling reaction does not require the use of a solvent, the addition of a minimal solvent can reportedly improve or regulate reactivity, a process known as liquid-assisted grinding (LAG).[113] Thus, first, a slight excess of TFEDMA (1.05 equiv.) and the DCM additive (0.2 µL/mg) were used. The ball mill was shaken at room temperature for 10 min, affording benzoyl fluoride (**20a**) in 78% ^{19}F NMR yield (entry 1, Table 6.1). Extending the reaction time to 20 min slightly improved the yield (81%, entry 2); however, further extension did not change the yield (entries 3–4). Notably, the yield significantly improved to 92% (entry 5) when the reaction was performed without DCM, indicating that the addition of DCM as LAG did not improve the reaction. This result demonstrates that the use of an organic solvent such as LAG is not required for this mechanochemical reaction, which is a strong environmental benefit. This could be attributed to the liquid nature of TFEDMA, which may partially act as a solvent. The highest yield (entry 6) was obtained when 1.3 equiv. of TFEDMA was used.

Table 6.1 Optimization of the reaction conditions[a]



[113] (a) P. Ying, J. Yu, W. Su, Liquid-assisted grinding mechanochemistry in the synthesis of pharmaceuticals. *Adv. Synth. Catal.* **2021**, *363* (5), 1246-1271; (b) A. Kosimov, G. Yusibova, J. Aruväli, P. Paiste, M. Käärik, J. Leis, A. Kikas, V. Kisand, K. Šmits, N. Kongi, Liquid-assisted grinding/compression: a facile mechanosynthetic route for the production of high-performing Co–N–C electrocatalyst materials. *Green Chem.* **2022**, *24* (1), 305-314.

Entry	TFEDMA (X equiv)	Additive	Time (min)	^{19}F NMR yield (%)[c]
1	1.05	DCM	10	78
2	1.05	DCM	20	81
3	1.05	DCM	30	82
4	1.05	DCM	60	82
5	1.05	-	20	92
6	1.30	-	20	94
7	1.50	-	20	91

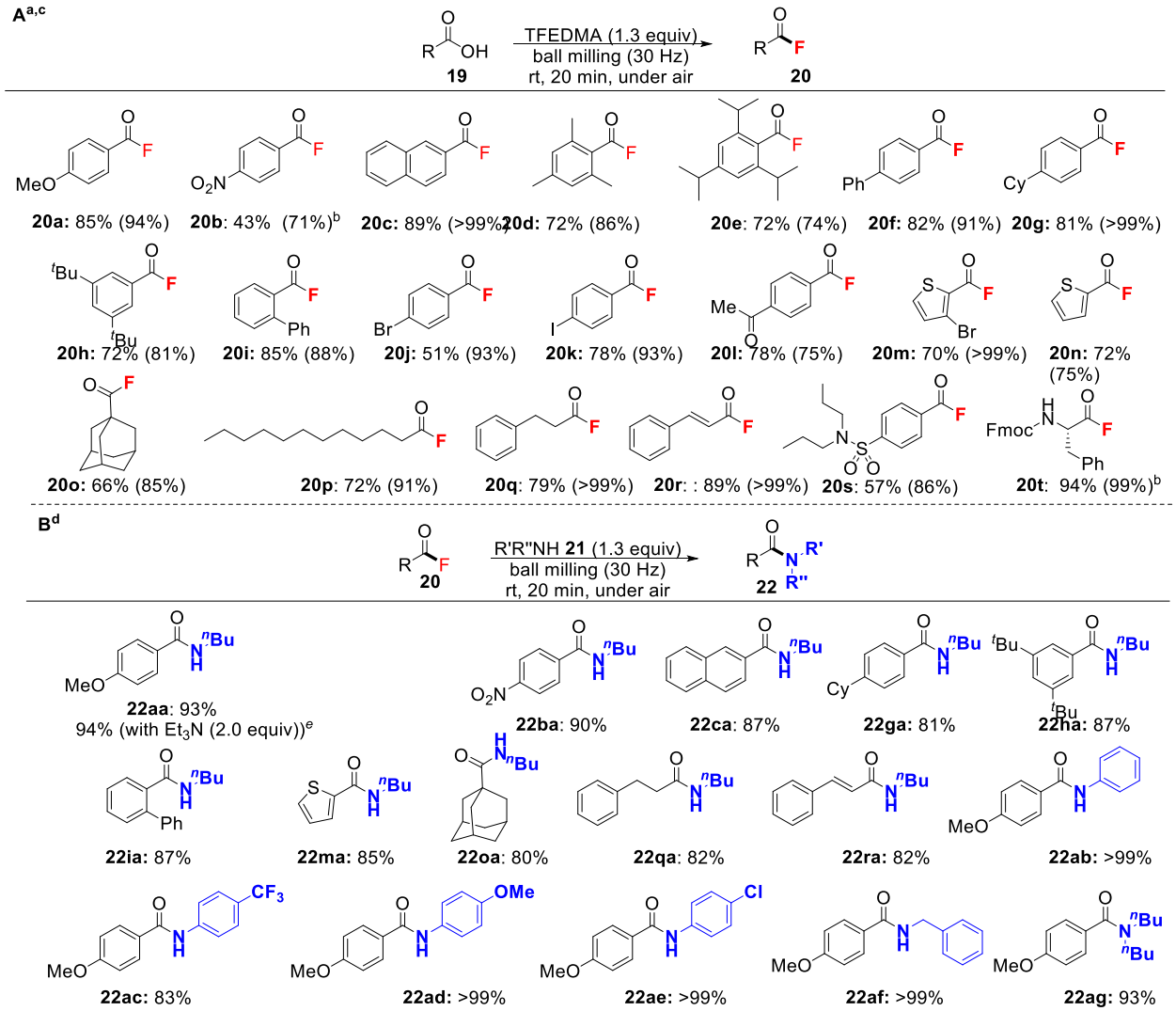
[a]Mechanochemical reactions were performed using a 1.5 mL stainless-steel grinding jar and a 5 mm stainless-steel ball. [b]Additive was added based on the total weight of **19a** and TFEDMA. [c] The ^{19}F NMR yield of the crude product was determined using fluorobenzene as the internal standard in chloroform-*d*.

Next, the substrate scope for ball-milling deoxyfluorination was investigated under the optimized reaction conditions (Scheme 6.3A). Aryl carboxylic acids with electron-donating groups (EDGs) [methoxy (**19a**), 2,4,6-trimethyl (**19d**), 2,4,6-triisopropyl (**19e**), cyclohexyl (**19g**), 3,5-dibutyl (**19h**)], electron-withdrawing groups (EWGs) [4-nitro (**19b**), 4-acetyl (**19l**)], π-conjugated aryl groups [naphthyl (**19c**), biphenyl (**19f**)], and halogens [4-bromo (**19j**), 4-iodo (**19k**)] afforded the corresponding products in excellent yields (71−99%). Furthermore, sterically hindered substrates **19d**, **19e**, and **19i** afforded **20d**, **20e**, and **20i** in high yields (86%, 74%, and 88%, respectively), whereas **20d** and **20e** were produced in low yields (25% and 28%, respectively) in batch reactions, even after extending the reaction time to 6 h (Scheme 6.2). In addition, heteroaryl (**19m** and **19n**) and aliphatic substrates (**19o–q**) afforded **20m−q** in high yields (75−99%). Moreover, cinnamic acid (**19r**), drug-like molecule **19s**, and *N*-Fmoc-phenylalanine (*N*-Fmoc-Phe) **19t** were converted into the corresponding acyl fluorides **20r–t** in high yields (86–99%).

Subsequently, we explored the mechanochemical coupling reactions between acyl fluorides and amines. The formation of amide bonds from the reaction of acyl halides and amines is one of the most atom-efficient pathways, and therefore produces minimal waste in relation to the method mediated by activators. Although acyl chlorides are the most common acyl halides for amidation reactions, the use of acyl fluorides has recently attracted attention because of their stability and facile operation.[97a-g] The reaction between acyl fluorides and amines is typically performed in the presence of a base in a solvent.[114] During the optimization of the conditions for the reaction of acyl fluoride **20a** and *n*-butyl amine (**21a**) to afford amide **22aa**, we observed that mechanochemical coupling proceeded smoothly to afford **22aa** in 93% yield without any base or solvent (Scheme 6.3B). The outcome was similar to that obtained in the presence of Et_3N (2.0 equiv.), yielding **22aa** in a 94% yield. Based on the successful observation of the reaction in the absence of a base, we hypothesized

[114] (a) T. Ueda, H. Konishi, K. Manabe, Palladium-catalyzed fluorocarbonylation using N-formylsaccharin as CO source: general access to carboxylic acid derivatives. *Org. Lett.* **2013**, *15* (20), 5370-5373; (b) M. E. Due-Hansen, S. K. Pandey, E. Christiansen, R. Andersen, S. V. F. Hansen, T. Ulven, A protocol for amide bond formation with electron deficient amines and sterically hindered substrates. *Org. Biomol. Chem.* **2016**, *14* (2), 430–433; (c) S. B. Munoz, H. Dang, X. Ispizua-Rodriguez, T. Mathew, G. S. Prakash, Direct access to acyl fluorides from carboxylic acids using a phosphine/fluoride deoxyfluorination reagent system. *Org. Lett.* **2019**, *21* (6), 1659-1663; (d) Y. Liang, Z. Zhao, N. Shibata, Pd-catalyzed fluoro-carbonylation of aryl, vinyl, and heteroaryl iodides using 2-(difluoromethoxy)-5-nitropyridine. *Commun. Chem.* **2020**, *3* (1), 59-67; (e) X. Wang, F. Wang, F. Huang, C. Ni, J. Hu, Deoxyfluorination of Carboxylic Acids with CpFluor: Access to Acyl Fluorides and Amides. *Org. Lett.* **2021**, *23* (5), 1764–1768; (f) C. Lee, B. J. Thomson, G. M. Sammis, Rapid and column-free syntheses of acyl fluorides and peptides using ex situ generated thionyl fluoride. *Chem. Sci.* **2022**, *13* (1), 188–194; (g) T. G. Bolduc, C. Lee, W. P. Chappell, G. M. Sammis, Thionyl Fluoride-Mediated One-Pot Substitutions and Reductions of Carboxylic Acids. *J. Org. Chem.* **2022**, *87* (11), 7308-7318; (h) S. Nagano, K. Maruoka, Synthesis of Acyl Fluorides from Carboxylic Acids with KI/$AgSCF_3$ for Efficient Amide and Peptide Synthesis. *Adv. Synth.Catal.* **2023**, *365* (3), 295-300; (i) E. M. Mahmoud, S. Mori, Y. Sumii, N. Shibata, Elemental Sulfur-Mediated Transformation of Carboxylic Acids to Acyl Fluorides by Electrophilic Fluorinating Reagent, Selectfluor. *Org. Lett.* **2023**, *25* (16), 2810-2814.

that the amide moiety in the products might be able to trap the HF generated during the reaction via its carbonyl oxygen. Supporting this notion is the fact that HF has a propensity to form stable 1:1–2:1 complexes with dimethylformamide (DMF).[115] Next, we explored the substrate scope of this reaction. The coupling reaction of amine **21a** with selected acyl fluorides bearing EDGs (**20a**, **20g**, **20h**), an EWG (**20b**), π-conjugated aryls (**20c**, **20i**), a heteroaryl group (**20m**), a sterically demanding group (**20i**), alkyls (**20o**, **20q**), and a cinnamyl group (**20r**) produced high yields of amides **22** within 20 min at room temperature independent of the steric and electronic character of the aryl moiety of acyl fluorides **20**. Furthermore, we investigated the coupling reaction of 4-methoxy benzoyl fluoride (**20a**) with different amines **21b–21g**. Under the applied mechanochemical conditions, the reaction of **20a** with aniline (**21b**) and aniline derivatives with an EWG (CF_3, **21c**), an EDG (OMe, **21d**), and a halogen (Cl, **21e**) afforded **22ab**–**22ae** in excellent yields (>83%). Next, we examined the coupling of **20a** with benzylamine (**21f**) and a secondary amine, n-dibutyl amine (**21g**), which generated the expected products (**22af** and **22ag**) in excellent yields (99% and 93% yields, respectively).



[115] (a) E. G. Tarakanova, G. V. Yukhnevich, Structure and stability of hydrogen fluoride complexes with *N*,*N*-dimethylformamide. *J Struct Chem* **2005**, *46*, 23–27; (b) C. Yoshimura, S. Utsumi, Dissolving properties of *N*, *N*'-dimethylform-amide and dimethyl sulfoxide-acid adducts. *Bunseki Kagaku* **1997**, *26* (11), 785-789.

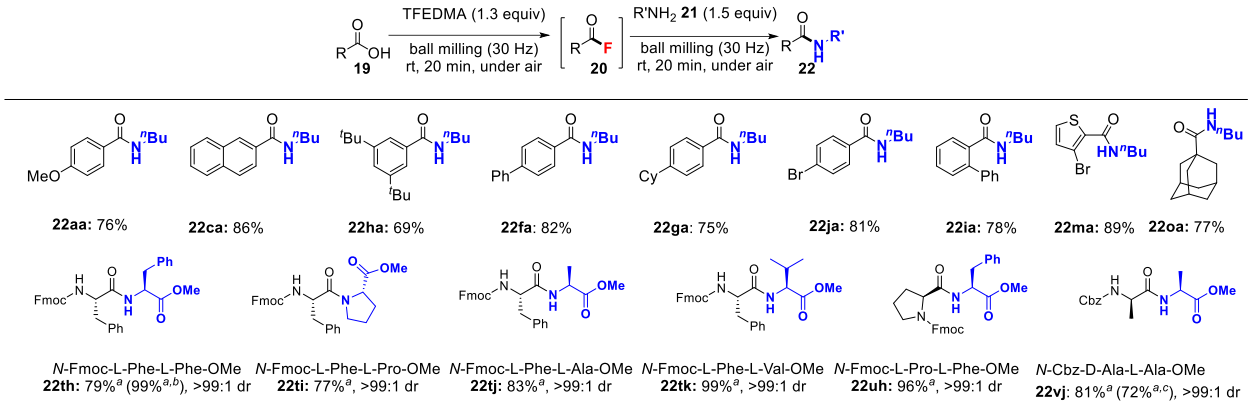
[a]For mechanochemical deoxyfluorination: Unless otherwise noted, all reactions were conducted on a 0.1 mmol scale. [b]The reaction was conducted on a 0.2 mmol scale. [c] Yields in parentheses were determined by ^{19}F NMR spectroscopy in chloroform-*d*. [d]For mechanochemical amidation: Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale. [e]Reaction was performed with Et_3N (2.0 equiv). [f]All mechanochemical reactions (A and B) were performed using a 1.5-mL stainless-steel grinding jar and a 5-mm stainless-steel ball.

Scheme 6.3 Substrate Scope for mechanochemical Deoxyfluorination and Amidation

Next, we demonstrated the direct mechanochemical coupling reaction between carboxylic acids **19** and amines **21** through a sequential one-pot deoxyfluorination/coupling pathway. The mechanochemical coupling reaction of carboxylic acids **19** and amines **21** has emerged as an attractive alternative to traditional solution-based reactions, especially for peptide synthesis.[116] However, these methods require additives, such as bases and activators. We optimized the reaction conditions for the reaction between benzoic acid **19a** and amine **21a** (Table S2) and observed that TFEDMA (1.3 equiv.), and **21a** (1.5 equiv.) for 20 min at room temperature afforded **22aa** with the highest yield (76%). Subsequently, the scope of different benzoic acid substrates **19** was explored (Scheme 6.4). The desired products **22** were obtained in good to high yields (69–86%) regardless of the substituents on the benzene moiety of the substrates (OMe, naphthyl, *t*Bu, Ph, cyclohexyl, and Br). Heteroaryl acid **19m** and aliphatic acid **19o** afforded **22ma** (89%) and **22oa** (77%), respectively. We then explored the peptide coupling reaction. The reactions of *N*-Fmoc-Phe (**19t**) with Phe methyl ester (Phe-OMe, **21h**), proline methyl ester (Pro-OMe, **21i**), alanine methyl ester (Ala-OMe, **21j**), and valine methyl ester (Val-OMe, **21k**) afforded the corresponding dipeptides **22th**–**22tk** without epimerization in comparable isolated yields (77–99%). The coupling of *N*-Fmoc-protected proline (*N*-Fmoc-Pro, **19u**) with Phe-OMe (**21h**) proceeded well, affording the corresponding dipeptide **22uh** in 96% yield. This transformation was not only compatible with *N*-Fmoc amino acids but also with *N*-Cbz-amino acids. The coupling reaction between *N*-Cbz-

[116] (a) C. Bolm, J. G. Hernández, From synthesis of amino acids and peptides to enzymatic catalysis: a bottom-up approach in mechanochemistry. *ChemSusChem* **2018**, *11* (9), 1410-1420; (b) L. Ferrazzano, M. Catani, A. Cavazzini, G. Martelli, D. Corbisiero, P. Cantelmi, T. Fantoni, A. Mattellone, S. De Luca, W. Cabri, A. Tolomelli, Sustainability in peptide chemistry: Current synthesis and purification technologies and future challenges. *Green Chem.* **2022**, **24** (3), 975-1020; (c) V. Declerck, P. Nun, J. Martinez, F. Lamaty, Solvent-free synthesis of peptides. *Angew. Chem. Int. Ed.* **2009**, *48* (49), 9318−9321; (d) J. G. Hernández, E. Juaristi, Green Synthesis of α, β-and β, β-Dipeptides under Solvent-Free Conditions. *J. Org. Chem.* **2010**, *75* (21), 7107−7111; (e) T. X. Métro, J. Bonnamour, T. Reidon, J. Sarpoulet, J. Martinez, F. Lamaty, Mechanosynthesis of amides in the total absence of organic solvent from reaction to product recovery. *Chem. Commun.* **2012**, *48* (96), 11781−11783; (f) J. Bonnamour, T. X. Métro, J. Martinez, F. Lamaty, Environmentally benign peptide synthesis using liquid-assisted ball-milling: application to the synthesis of Leu-enkephalin. *Green Chem.* **2013**, *15* (5), 1116−1120; (g) T. X. Métro, J. Bonnamour, T. Reidon, A. Duprez, J. Sarpoulet, J. Martinez, F. Lamaty, Comprehensive Study of the Organic-Solvent-Free CDI-Mediated Acylation of Various Nucleophiles by Mechanochemistry. *Chem. Eur. J.* **2015**, *21* (36), 12787–12796; (h) J. G. Hernández, K. J. Ardila-Fierro, D. Crawford, S. L. James, C. Bolm, Mechanoenzymatic peptide and amide bond formation. *Green Chem.* **2017**, *19* (11), 2620−2625; (i) O. Maurin, P. Verdié, G. Subra, F. Lamaty, J. Martinez, T. X. Métro, Peptide synthesis: ball-milling, in solution, or on solid support, what is the best strategy? *Beilstein J. Org. Chem.* **2017**, *13* (1), 2087−2093; (j) L. Gonnet, T. Tintillier, N. Venturini, L. Konnert, J. F. Hernandez, F. Lamaty, G. Laconde, J. Martinez, E. Colacino, N-Acyl benzotriazole derivatives for the synthesis of dipeptides and tripeptides and peptide biotinylation by mechanochemistry. *ACS Sustainable Chem. Eng.* **2017**, *5* (4), 2936−2941; (k) K. J. Ardila-Fierro, D. E. Crawford, A. Körner, S. L. James, C. Bolm, J. G. Hernández, Papain-catalysed mechanochemical synthesis of oligopeptides by milling and twin-screw extrusion: application in the Juliá–Colonna enantioselective epoxidation. *Green Chem.* **2018**, *20* (6), 1262−1269; (l) F. Casti, R. Mocci, A. Porcheddu, From amines to (form) amides: a simple and successful mechanochemical approach. *Beilstein J. Org. Chem.* **2022**, *18* (1), 1210–1216; (m) V. Štrukil, B. Bartolec, T. Portada, I. Đilović, I. Halasz, Margetić, D. One-pot mechanosynthesis of aromatic amides and dipeptides from carboxylic acids and amines. *Chem. Commun*. **2012**, *48* (99), 12100–12102; (n) C. Duangkamol, S. Jaita, S. Wangngae, W. Phakhodee, M. Pattarawarapan, An efficient mechanochemical synthesis of amides and dipeptides using 2, 4, 6-trichloro-1, 3, 5-triazine and PPh_3. *RSC Adv.* **2015**, *5* (65), 52624−52628; (o) V. Porte, M. Thioloy, T. Pigoux, T. X. Métro, J. Martinez, F. Lamaty, Peptide Mechanosynthesis by Direct Coupling of N-Protected α-Amino Acids with Amino Esters. *Eur. J. Org. Chem.* **2016**, *2016* (21), 3505–3508; (p) J. M. Landeros, E. Juaristi, Mechanochemical Synthesis of Dipeptides Using Mg-Al Hydrotalcite as Activating Agent under Solvent-Free Reaction Conditions. *Eur. J. Org. Chem.* **2017**, *2017* (3), 687–694; (q) Y. Yeboue, M. Jean, G. Subra, J. Martinez, F. Lamaty, T. X. Métro, Epimerization-free C-term activation of peptide fragments by ball milling. *Org. Lett.* **2021**, *23* (3), 631−635; (r) T. Dalidovich, K. A. Mishra, T. Shalima, M. Kudrjašova, D. G. Kananovich, Aav, R. Mechanochemical synthesis of amides with uronium-based coupling reagents: A method for hexa-amidation of biotin[6]uril. *ACS Sustainable Chem. Eng.* **2020**, *8* (41), 15703–15715.

protected alanine (N-Cbz-Ala, **19v**) and alanine-OMe (**21j**) resulted in the formation of *N*-Cbz-dipeptide **22vj** in 81% yield without any loss of the Cbz moiety. The Cbz group is stable under mild acidic conditions, but can be removed under strong acidic conditions, such as HF. Thus, the generated HF could be captured by the amide moiety of peptide.[117]



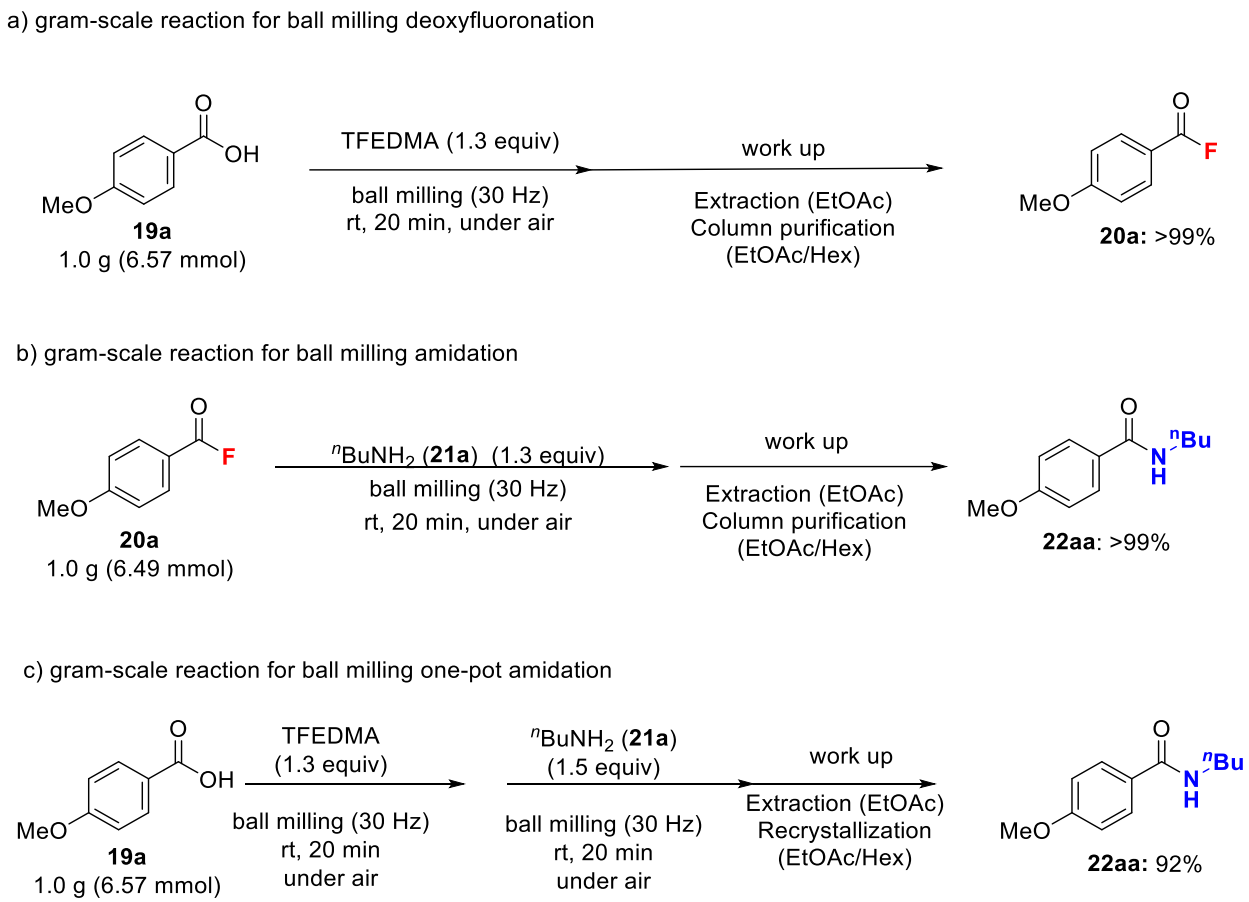
Mechanochemical reactions were performed using a 1.5-mL stainless-steel grinding jar and a 5-mm stainless-steel ball. Isolated product yields were on a 0.2-mmol scale. [a]2.0 equiv. of TFEDMA and amines were used. [b]Purified by extraction with EtOAc to provide a pure **22th**. [c] Purified by recrystallization instead of column chromatography.

Scheme 6.4 Substrate scope for one-pot ball-milling amidation

In addition to the amide synthesis shown in Scheme 6.3B, a one-pot approach can be used for both amide and peptide syntheses. This approach not only eliminates the need to isolate acyl fluoride but also maintains a high yield without significant reduction. While all products **22** in Scheme 6.4 were isolated by silica gel column chromatography, direct isolation was also attempted from a green chemistry point of view, for 4th (isolated by extraction with EtOAc; 99% yield) and 4vj (isolated by extraction with Hex/EtOAc and recrystallization; 72% yield) (note: All the amino esters utilized were in the form of hydrochloride salts).

To demonstrate the practicality and environmental benefits of our method, we conducted ball-milling deoxyfluorination, coupling reactions, and one-pot deoxyfluorination/coupling on a gram-scale (Scheme 6.5). The ball-milling deoxyfluorination of **19a** and the coupling reaction of **20a** with amine **21a** yielded the desired products in high yields within 20 min (**20a**: >99%, **22aa**: >99%) (Scheme 6.5a and 6.5b). Impressively, mechanochemical one-pot deoxyfluorination/coupling of carboxylic acid **19a** with amine **21a** delivered **22aa** in 92% yield within 40 min (Scheme 6.5c). Notably, DCM was not employed in the work-up during the gram-scale reaction. Furthermore, a one-pot deoxyfluorination/coupling product (**22aa**) was obtained through recrystallization, eliminating the need for column purification. These results not only emphasize the efficiency of our method but also highlight its eco-friendly attributes.

[117] (a) E. G. Tarakanova, G. V. Yukhnevich, Structure and stability of hydrogen fluoride complexes with *N*,*N*-dimethylformamide. *J Struct Chem* **2005**, *46*, 23–27. (b) C. Yoshimura, S. Utsumi, Dissolving properties of *N*, *N*'-dimethylform-amide and dimethyl sulfoxide-acid adducts. *Bunseki Kagaku* **1997**, *26* (11), 785-789.



[a]All ram-scale mechanochemical reactions were performed using a 5.0 mL stainless-steel grinding jar and a 7.0 mm stainless-steel ball.

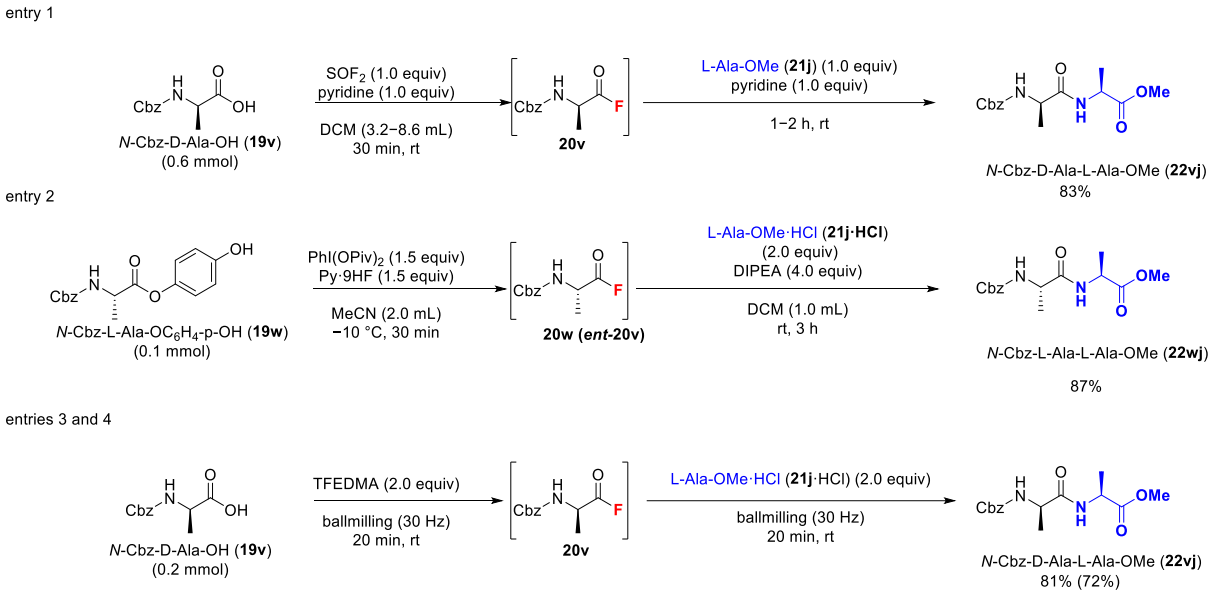
Scheme 6.5 Gram-scale ball-milling deoxyfluorination and one-pot amination[a]

Next, we conducted a comparative analysis of our ball-milling system with the reported batch reactions for the synthesis of the dipeptides **22vj** and **22wj** (Table 6.2), as described by Sammis et al.[114g] and Maruoka et al.[118] (entries 1 and 2). Notably, both batch reactions rely on the use of solvents, such as DCM and acetonitrile (MeCN), whereas our mechanochemical method operates without any solvent. Additionally, batch reactions were performed at room temperature, except for the initial step of the Maruoka method. In terms of the reaction time, the two batch reactions required 2–4 h for two-step conversion, whereas our mechanochemical reaction achieved complete conversion within 40 min, even on a gram scale (Scheme 6.5). Furthermore, we assessed various green markers, including atom economy, atom efficiency, carbon efficiency, reaction mass efficiency, and the E-factor[119] (Table 6.2). Among the batch methods, Sammis' approach (entry 1) yielded the most favorable results (54.0%, 44.9%, 49.8%, 44.9%, and 52.2). These outcomes were influenced by the low molecular weight of the fluorinating reagent used in the first step (MW of SOF_2 = 86.06) and the use of only one equivalent of the base for amidation. In contrast, Maruoka's approach (entry 2) displayed low values for all green markers (14.6%, 12.7%, 14.8%, 12.8%, and 114.3), primarily because of the utilization of ester as a raw material, the high molecular weight of the fluorinating reagent (MW of Py·HF = 258.15), and the excess of all reagents. Remarkably, our mechanochemical method (entries 3 and 4) demonstrated significantly lower E-

[118] H. J. Lee, X. Huang, S. Sakaki, K. Maruoka, Metal-free approach for hindered amide-bond formation with hypervalent iodine (iii) reagents: Application to hindered peptide synthesis. *Green Chem.* **2021**, *23* (2), 848–855.
[119] R. A. Sheldon, The E Factor: fifteen years on. *Green Chem.* **2007**, *9* (12), 1273–1283.

factor values (entry 3, 2.2; entry 4, 2.6), and other green marker values were slightly lower than those in entry 1 (entry 3, 38.9%, 31.5%, 45.0%, and 31.5%; entry 4, 38.9%, 28.0%, 40.0%, and 27.7%).

Table 6.2 Evaluation of green chemistry metrics for peptide synthesis and literature methods via acyl fluorides



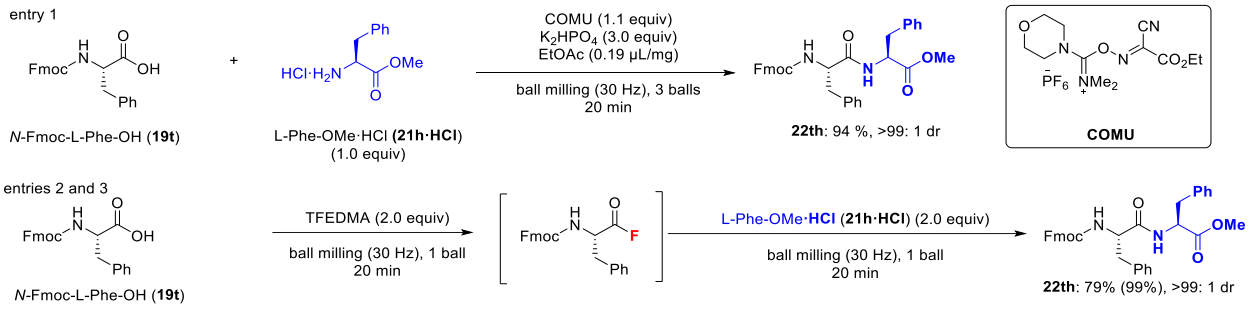
Entry	Solvent (Step 1/ Step 2)	Temperature (°C)	Time (h)	Yield (%)	Atom economy (%)[a]	Atom efficiency (%)[b]	Carbon efficiency (%)[c]	Reaction mass efficiency (%)[d]	E-factor[e]	Purification
1[f]	DCM / –	rt	2	83	54.0	44.9	49.8	44.9	52.2	filtration (DCM, step 1) extraction (DCM, step2)
2[g]	MeCN / DCM	−10 to rt	3.5	87	14.6	12.7	14.8	12.8	114.3	column (Hex/EtOAc, step2)
3	–	rt	0.67	81	38.9	31.5	45.0	31.5	2.2	column (Hex/EtOAc, step 2)
4	–	rt	0.67	72	38.9	28.0	40.0	27.7	2.6	extraction (Hex/EtOAc), recrystallization

[a]Atom economy (%) = (Mol. wt. of product) / (Mol. wt. of all reactants) × 100. [b]Atom efficiency (%) = (yield of product) × (atom economy) × 100. [c]Carbon efficiency (%) = [(moles of product) × (numbers of carbon in product) × 100] / [(moles of reactant 1) × (numbers of carbon in reactant 1) + (moles of reactant 2) × (numbers of carbon in reactant 2) + (moles of reactant 3) × (numbers of carbon in reactant 3)⋯]. [d]Reaction mass efficiency (%) = (mass of isolated product) / (mass of all reactants). [e]E-factor = [weight of total waste (mg)] / [weight of total product (mg)]. [f]*ref* 114f. [g] ref 116j.

Finally, our method for dipeptide synthesis was compared to previously reported works[116m-r] on the mechanochemical synthesis of peptides, focusing on enhancing the greenness of the method. Mechanochemical peptide synthesis has gained attention since the seminal work of 2009.[116] The early development of mechanochemical peptide synthesis requires activated carboxylic acid derivatives of N-protected amino acids,[116a-l] Métro and al. reported a one-pot, solvent-free, and base-free amidation process mediated by 1,1'-carbonyldiimidazole (CDI) from carboxylic acids, which exhibit broad substrate compatibility and rapid reaction times (usually within 10 min).[116g] While commonly utilized in peptide synthesis, the authors showcased the process's scalability through a 4-gram reaction, indicating its viability for larger-scale applications. However, the formation of stoichiometric amounts of carbon dioxide as a byproduct might be a matter of concern during the reaction. In addition, acylimidazole intermediates can lead to minor

racemization issues in peptide synthesis. A number of environmentally friendly methods for directly coupling N-protected amino acids have been recently developed.[116m-r] However, similar to conventional liquid approaches, the activation of acids using reagents such as *N*-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC),[116m] 2,4,6-trichloro-1,3,5-triazine (TCT),[116n] and oxyma/EDC[116o-q] is necessary for the mechanochemical coupling of amines with carboxylic acids. These reagents have low atom economy, which poses a significant drawback and some of these strategies requires the use of harmful additives like DMAP,[116m] HOBt,[116p] and PPh_3.[116n] Additionally, other than the case of the use of CDI, all reactions should be performed through the LAG approach using DCM, nitromethane, or ethyl acetate.[116m-r]

Table 6.3 Evaluation of green chemistry metrics for peptide synthesis compared to the reported mechanochemical direct coupling of *N*-Fmoc-Phe-OH (19t) and *L*-Phe-OMe (21h)



Entry	Solvent	Time (min)	Yield (%)	Atom economy (%)[a]	Atom efficiency (%)[b]	Carbon efficiency (%)[c]	Reaction mass efficiency (%)[d]	E-factor[e]	Purification
1[f]	EtOAc	20	94	34.5	32.3	67.7	32.2	2.6	Filtration (wash with water)
2	-	40	79	49.5	39.1	51.7	39.3	1.5	column (Hex/EtOAc, step 2)
3	-	40	>99	49.5	49.0	64.7	49.3	1.0	Extraction (EtOAc)

[a]Atom Economy (%) = (Mol. wt. of product) / (Mol. wt. of all reactants) × 100. [b]Atom efficiency (%) = (yield of product) × (atom economy) × 100. [c]Carbon Efficiency (%) = [(moles of product) × (numbers of carbon in product) ×100] / [(moles of reactant 1) × (numbers of carbon in reactant 1) + (moles of reactant 2) × (numbers of carbon in reactant 2) + (moles of reactant 3) × (numbers of carbon in reactant 3)]. [d]Reaction Mass Efficiency (%) = (mass of isolated product) / (mass of all reactants). [e]E-factor = [weigh of total waste (mg)] / [weight of total product (mg)]. [f]ref 116q.

In 2020, Kananovich, Aav, and co-workers[116r] developed an environmentally benign mechanochemical protocol for the direct synthesis of amides from carboxylic acids and amines by employing a uronium-type coupling reagent, (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate (COMU), and K_2HPO_4 as a base. The reaction protocols demonstrated high reaction rates and high yields, a simple isolation procedure for solid amide products, and no noticeable epimerization. To evaluate the environmental impact of our TFEDMA method, we compared our green chemistry metrics to those reported for the COMU method (Table 6.3). As depicted, both methods exhibit competitive green marker metrics, with our method (entries 2 and 3) offering even advantages concerning atom economy (34.5 vs 49.5), atom efficiency (32.3 vs 39.1/49.0), carbon efficiency (67.7 vs 51.7/64.7), reaction mass efficiency (32.2 vs 39.3/49.3), and E-factor (2.6 vs 1.5/1.0).

Conclusion

We have developed the first solvent-free mechanochemical method for the synthesis of acyl fluorides from carboxylic acids, mediated by the industrially useful fluorinating reagent TFEDMA. The ball-milling method tolerated different aryl and alkyl acyl fluorides. The reaction was complete in 20 min and afforded high yields even with sterically challenged substrates. Moreover, the amide bond formation reactions of acyl fluorides and amines via this mechanochemical method furnished the corresponding products in high yields and short reaction times without a base. We also demonstrated base-free, one-pot, two-step mechanochemical coupling between carboxylic acids and amines mediated by TFEDMA. Furthermore, we successfully applied the ball-milling deoxyfluorination method to peptide synthesis, demonstrating its efficiency and adherence to green chemistry principles. This technique is environmentally friendly because it eliminates the use of organic solvents, requires minimal reaction time, and employs a fluorinating reagent, TFEDMA, which is thermally stable, nonexplosive, industrially scalable, and suitable for mechanochemical reactions. Given that highly toxic HF is formed during the reaction and TFEDMA can also produce HF upon exposure to moisture or water, this imposes limitations on this protocol. Therefore, implementing suitable protective measures is essential to prevent potential hazards.

Summary

We have pioneered an innovative and transformative reaction protocol centered around silyl boronate-mediated C-F bond cleavage activated by frustrated radical pairs (FRPs). This groundbreaking methodology represents a significant leap forward in the field of chemical synthesis, enabling the formation of various bonds, notably including C-Si, C-C, and C-N, all achieved under remarkably mild reaction conditions. This protocol stands out as a trailblazer, being the inaugural approach to C-F bond activation that facilitates multiple bond transformations, marking a milestone in the realm of chemical reactivity.

One of the most distinctive and promising aspects of our developed protocol is its exceptional versatility and broad substrate scope. It demonstrates an unparalleled ability to engage with a diverse range of substrates, showcasing remarkable adaptability across a spectrum of chemical structures. Notably, the protocol's capability extends to the synthesis of compounds bearing resemblance to drug-like molecules, signifying its potential significance in medicinal chemistry. This versatility and potential to synthesize drug-related molecules hold promise for the development and exploration of new therapeutic agents, offering a new avenue in drug discovery and synthesis.

What distinguishes our protocol is not solely its capacity for enabling multiple bond transformations but also its ability to achieve these transformations under mild reaction conditions. This aspect is pivotal, as it mitigates the necessity for harsh reaction environments or intricate setups, thereby streamlining the process and enhancing its utility across various settings. The protocol's efficiency in facilitating these transformations under mild conditions underscores its practicality and accessibility for chemists across different disciplines.

Beyond its immediate applications, the impact of this protocol transcends its practical utility. Its emergence serves as a beacon of inspiration and guidance for future researchers venturing into the realm of C-F bond activation. The innovative methodology and the vast possibilities it unlocks are poised to inspire and direct upcoming researchers in their pursuit of exploring new frontiers in chemical synthesis and reactivity.

In addition, a solvent-free mechanochemical deoxyfluorination of carboxylic acids to acyl fluorides has been achieved through mediation by 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA) using a ball mill. This approach resulted in high product yields within shorter reaction times, even for sterically challenged carboxylic acids. The mechanochemical coupling of acyl fluorides and amines, along with TFEDMA-mediated direct mechanochemical coupling reactions of carboxylic acids with amines via a sequential one-pot deoxyfluorination/coupling pathway, was also observed. Furthermore, the application of this protocol has been extended to peptide synthesis. The efficiency of the protocol, characterized by its speed, solvent-free nature, and favorable E-factor, is in accordance with current environmental policies.

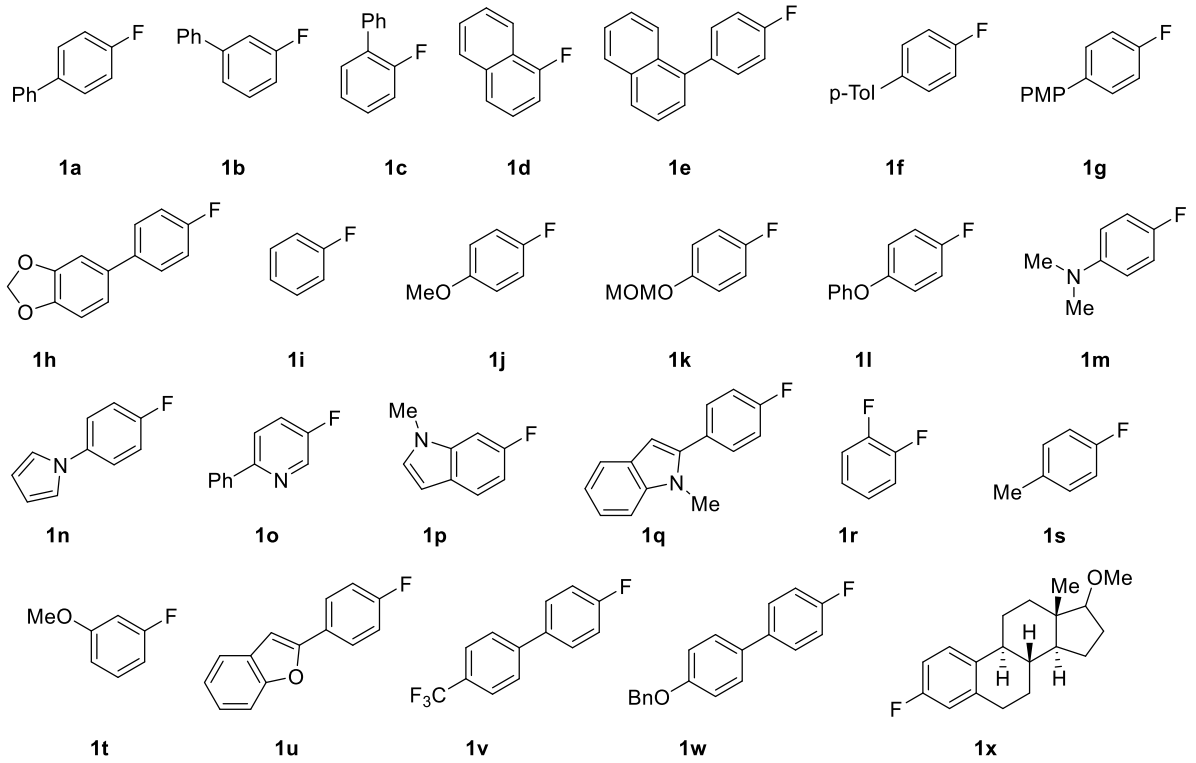
In summary, our research group's development of the silyl boronate-mediated C-F bond activation protocol and mechanical force promoted C-F bond cleavage represent a paradigm shift in chemical innovation. Its capability to forge diverse bonds, synthesize drug-like molecules, and operate under mild conditions not only expands the boundaries of synthetic chemistry but also holds immense promise in advancing medicinal chemistry. Crucially, there is an anticipation that it has the potential to achieve additional bond formations, which we will keep exploring.

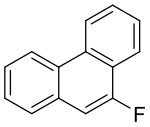
Experimental Section

All reagents were used as received from commercial sources, unless specified otherwise. All reactions were performed in oven-dried glassware or FEP tube under a positive pressure of nitrogen. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel (60-F_{254}). The TLC plates were visualized with UV light (254 nm), potassium permanganate and *p*-Anisaldehyde in ethanol/heat. Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 63–210 μm. Unless otherwise specified, the ^{1}H-NMR (300 MHz), ^{1}H-NMR (500 MHz), ^{19}F-NMR (282 MHz) and ^{13}C-NMR (126 MHz) spectra for solution in $CDCl_3$ were recorded on a Buruker Avance 500, Varian Mercury 300. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (δH = 0.00 ppm) or chloroform (δC = 77.00 ppm) or hexafluorobenzene (δF = −162.20 ppm). Mass spectra were recorded on a SHIMADZU LCMS-2020EV (ESI-MS) system and a JEOL JMS-Q1050GC Master-Quad GC/MS (EI) system. High resolution mass spectrometry (HRMS) was recorded on a Waters Synapt G2 HDMS (ESI-MS) and a SHIMADZU GCMS-QP5050A (EI-MS). The wave numbers (ν) of recorded IR-signals are quoted in cm^{-1} on a JASCO FT/IR-4100 spectrometer. The melting point was recorded on a BUCHI M-565. All solvents were dried and distilled before use.

Synthetic methods for fluoroarenes 1

Fluoroarenes **1a**, **1c**, **1d**, **1i**, **1j**, **1r**, **1s**, **1t**, **1zb**, **1zc**, **1zd** were purchased from TCI or Sigma Aldrich. **1b**, **1e**, **1f**, **1g**, **1h**, **1k**, **1l**, **1m**, **1n**, **1o**, **1p**, **1q**, **1u**, **1v**, **1w**, **1x**, **1y**, **1z**, **1za**, **1ze**, **1zf**, **1zg**, **1zh**, **1zi**, **1zj**, **1zk**, **1zl**, **1zm**, **1zp**, **1zq**, **1zzd**, **1zze**, **1zzf**, **1zzg**, **1zzh**, and **1zzi** were used prepared according to known methods.[37,49,96] **1zn**, **1zo**, **1zr**, **1zs**, **1zt**, **1zu**, **1zv**, **1zw**, **1zx**, **1zy**, **1zz**, **1zza**, **1zzb**, **1zzc** were prepared with following methods. Silylboronates **2a**, **2b**, and **2c** were used prepared according to previous methods.[37]





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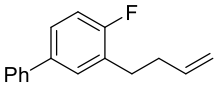

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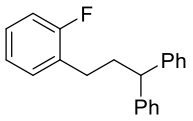

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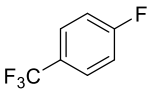

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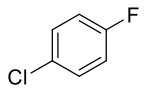

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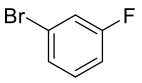

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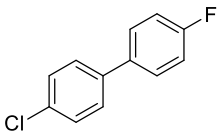

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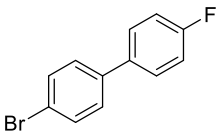

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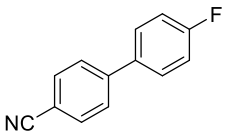

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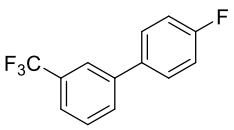

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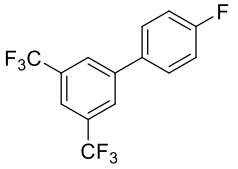

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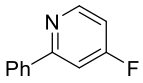

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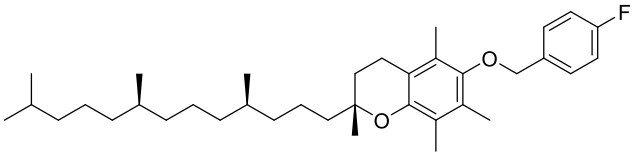

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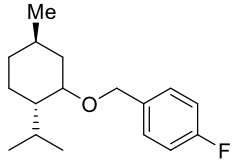

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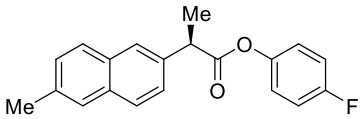

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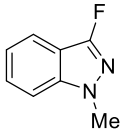

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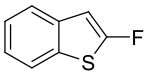

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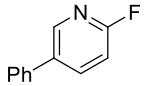

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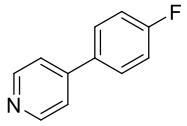

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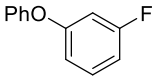

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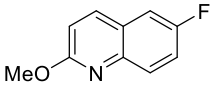

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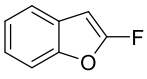

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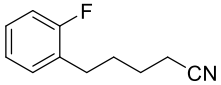

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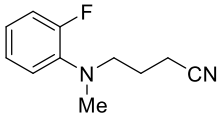

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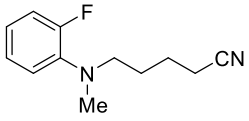

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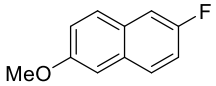

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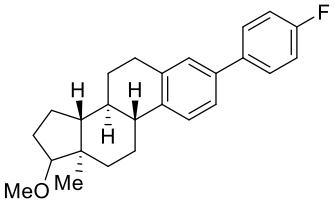

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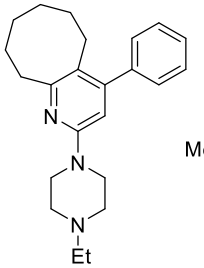

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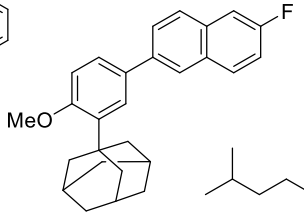
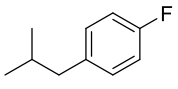
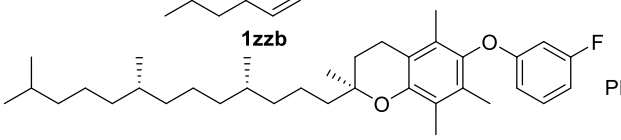


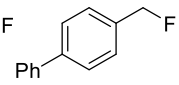
1zza



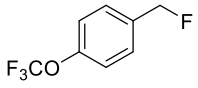
1zzb



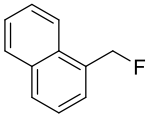
1zzc



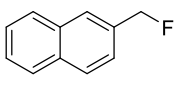
1zzd



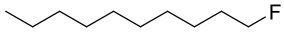
1zze



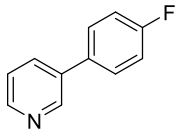
1zzf



1zzg



1zzh



1zzi

3-fluoro-1-methyl-1*H*-indazole (1zn)

To a flask with a magnetic stirring bar were added 1-methyl-1*H*-indazole-3-carboxylic acid (528.5 mg, 3.0 mmol), Selectfluor® (2.13 g, 6.0 mmol), KF (700 mg, 12.0 mmol). Then AcOEt (10 mL) and water (5 mL) were added. The reaction mixture was heated to 70 ºC and stirred for 15 h. The reaction mixture was diluted with water, followed by extracting with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/AcOEt 3/1) to give the title product as yellow oil (67.1 mg, 15%yield).

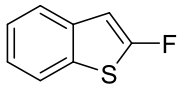
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.3 – 7.28 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 3.93 (d, *J* = 1.2 Hz, 3H).

^{19}F NMR (282 MHz, $CDCl_3$) δ -118.74 (s, 1F).

HRMS (ESI) [$C_8H_8N_2F$] $[M+H]^+$ calculated: 151.0672, found: 151.0675.

The chemical shifts were consistent with those reported in the literature. [120]

2-fluorobenzo[*b*]thiophene (1zo)



Under inert conditions, benzo[*b*]-thiophene (670 mg, 5.0 mmol) was dissolved in dry tetrahydrofuran (THF) (40 mL) and stirred for 20 min at −78 °C. *n*BuLi (6.3 mL, 1.59 M in hexane) was added dropwise, and the resulting mixture was stirred for 1 hr at −78 °C. N-Fluorobenzenesulfonimide (7.0 g, 11.5 mmol) was added portionwise. The reaction mixture was further stirred for 2 hr at −78 °C and then overnight at room temperature. After the completion of the reaction, the solvents were removed in reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane) to title product as colorless oil (484.3 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.37 – 7.25 (m, 2H), 6.70 (d, *J* = 2.8 Hz, 1H).

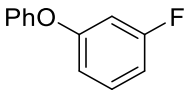
^{19}F NMR (282 MHz, $CDCl_3$) δ -126.03 (d, *J* = 3.0 Hz, 1F).

MS (EI) *m*/*z* $[M]^+$: 152.

[120] X. Yuan, J. Yao, Z. Tang, Decarboxylative Fluorination of Electron-Rich Heteroaromatic Carboxylic Acids with Selectfluor, *Org. Lett.* **2017**, 19, 1410–1413.

The chemical shifts were consistent with those reported in the literature.[121]

1-fluoro-3-phenoxybenzene (1zr)



Under a nitrogen atmosphere, K_3PO_4 (4.2 g, 20.0 mmol), phenol (1.9 g, 20.0 mmol), 3,4,7,8-tetramethylphenanthroline (236.3 mg, 1.0 mmol) and CuI (190 mg, 1.0 mmol) were successively added into a dry flask, dry DMSO (10 mL) was added followed by addition of 1-bromo-3-fluorobenzene (1.1 mL, 10 mmol). Keep the reaction mixture under an inert atmosphere stirring the reaction mixture at 110 °C for 24 h. Upon completion of the reaction, the mixture was cooled to room temperature, dilute the mixture by the addition of AcOEt, Filter the crude product through silica gel using AcOEt as eluent, the resulting solution was furtherly extracted with AcOEt for three times, The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EA 10/1) to give the title product as yellow oil (1.32 g, 75%yield).

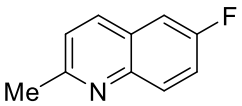
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.29 – 7.21 (m, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.03 (d, J = 7.6 Hz, 2H), 6.81 – 6.74 (m, 2H), 6.72 – 6.67 (m, 1H).

^{19}F NMR (282 MHz, $CDCl_3$) δ -111.02 (q, *J* = 8.4 Hz, 1F).

MS (EI) *m/z* $[M]^+$: 188.

The chemical shifts were consistent with those reported in the literature.[122]

6-fluoro-2-methylquinoline (1zs)



A mixture of 4-fluroroaniline (489 μL, 5.0 mmol) and ethyl vinyl ether (1.1 g, 15.0 mmol) in glacial acetic acid (5 mL) was stirred at 25 ºC for 4 h. After 4-fluoroaniline was completely consumed (monitored by TLC), the reaction mixture was refluxed for 4 h. After the intermediate spot was disappeared (monitored by TLC), then the reaction mixture was poured into water (15 mL), neutralized with $NaHCO_3$ and extracted with ethyl acetate three times. The Organic layer was washed with water, then with brine, dried over anhydrous Na_2SO_4, concentrated, and was purified by column chromatography on silica gel (*n*-hexane/AcOEt, 4/1), then recrystallized from hexane to give title product as white solid. (185.1 mg, 23 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.94 (m, 2H), 7.45 (td, *J* = 8.3, 2.4 Hz, 1H), 7.37 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.73 (s, 3H).

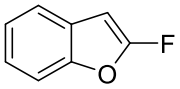
^{19}F NMR (282 MHz, $CDCl_3$) δ -114.98 (m, 1F).

[121] M. Feofanov, V. Akhmetov, R. Takayama, K. Y. Amsharov, Facile Synthesis of Thienoacenes via Transition-Metal-Free Ladderization, *J. Org. Chem.* **2021**, 86, 14759–14766.
[122] B. Xing, C. Ni, J. Hu, Hypervalent Iodine(III)-Catalyzed Balz–Schiemann Fluorination under Mild Conditions, *Angew. Chem. Int. Ed.* **2018**, *57*, 9896–9900.

MS (EI) *m/z* $[M]^+$: 161**.**

The chemical shifts were consistent with those reported in the literature.[123]

2-fluorobenzofuran (1zt)



To a flask with a magnetic stirring bar were added benzofuran-2-carboxylic acid (0.97 g, 6.0 mmol), Selectfluor® (4.26 g, 12.0 mmol), KF (1.39 g, 24.0 mmol). Then DCE (20 mL) and water (10 mL) were added. The reaction mixture was heated to 70 ºC and stirred for 15 hours. The reaction mixture was diluted with water, followed by extracting with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-Pentane/Et_2O 15/1) to give the title product as a yellow oil (273.3 mg, 33%).

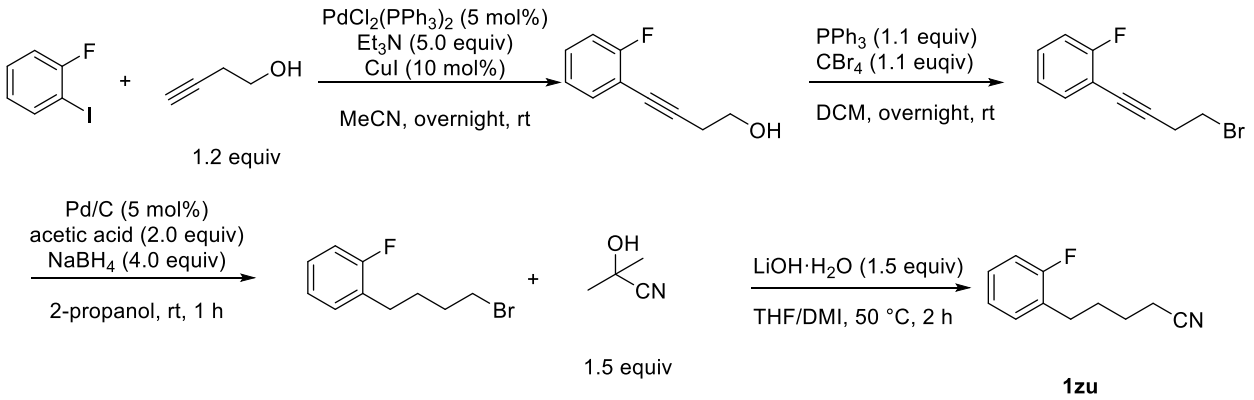
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 1H), 7.42 – 7.36 (m, 1H), 7.27 – 7.21 (m, 2H), 5.86 (dd, *J* = 6.5, 0.8 Hz, 1H).

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.3 (d, *J* = 6.6 Hz).

MS (EI) *m/z* $[M]^+$: 136.

The chemical shifts were consistent with those reported in the literature.[120]

5-(2-fluorophenyl)pentanenitrile (1zu)[8]



To a mixture of a 1-fluoro-2-iodobenzene (2.3 mL, 20.0 mmol) in MeCN (120 mL) was added Et_3N (14.6 mL, 5.0 equiv), $Pd(PPh_3)_4$ (701 mg, 1 mmol) and CuI (381 mg, 2 mmol), stir the mixture for 20 minutes at room temperature, but-3-yn-1-ol was added. The mixture was furtherly reacted for 12 h at rt. After the completion of the reaction, the mixture was filtered over celite washing with AcOEt, the resulted filtrate was concentrated under reduced pressure, The residue was purified by column chromatography on silica gel (eluent:

[123] M. Kojima, M. Kanai, Tris(pentafluorophenyl)borane-Catalyzed Acceptorless Dehydrogenation of N-Heterocycles, *Angew. Chem. Int. Ed.* **2016**, *55*, 12224–12227.

n-hexane/AcOEt 3/1) to give 4-(2-fluorophenyl)but-3-yn-1-ol as yellow oil (2.9 g, 90%).

To a mixture of 4-(2-fluorophenyl)but-3-yn-1-ol in DCM (54 mL) was added CBr_4 (6.5 g, 19.8 mmol), stir the reaction mixture for 5 minutes at rt, PPh_3 (5.2 g, 19.8 mmol) dissolved in minimum amount of DCM was drop wised into the mixture, then stir the mixture overnight at rt, quench the reaction with sat. aq. $NaHCO_3$. The resulting mixture was extracted with DCM for three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: n-hexane) to give 1-(4-bromobut-1-yn-1-yl)-2-fluorobenzene as paleyellow oil (3.0 g, 72%).

To a stirring mixture with Pd/C catalyst (5 mol%), 1-(4-bromobut-1-yn-1-yl)-2-fluorobenzene (13 mmol) in isopropyl alcohol (50 mL) were added acetic acid (1.5 mL, 26 mmol), Powdered $NaBH_4$ (1.9 g, 52 mmol) was added in a single portion directly to the stirring heterogeneous solution The contents of the reaction flask are left to stir in open air at room temperature for 1 h. Quench the reaction mixture with 0.1 M HCl until no hydrogen evolution is observed. The solution is then adjusted to a pH of approximately 10 using NaOH and filtered to remove the Pd/C catalyst, iPrOH was removed under reduced pressure, the residue was extracted with ether for 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane) to give 1-(4-bromobutyl)-2-fluorobenzene as a colorless oil (2.81 g, 94%)

To a solution of 2-hydroxy-2-methylpropanenitrile (1.16 g, 5 mmol) in THF/DMI (15 mL: 5 mL, v/v, 3/1) was added $LiOH{\cdot}H_2O$ (315 mg, 7.5 mmol), The reaction mixture was heated to 50 ºC and stirred for 1 h, 1-(4-bromobutyl)-2-fluorobenzene was added and stir the mixture for more 3 h. After the completion of the reaction, dilute the mixture with water and extract with AcOEt for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EA 10/1) to give the final product as a colorless oil (837 mg, 95%).

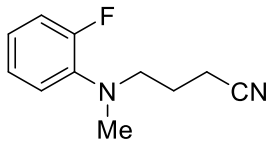
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 2H), 7.08 – 7.05 (m, 1H), 7.03 – 6.99 (m, 1H), 2.69 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.0 Hz, 2H), 1.81 – 1.75 (m, 2H), 1.72 – 1.68 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.10 (d), 130.59 (d), 128.03 (d), 127.89 (d), 124.12, 124.09, 119.63, 115.33 (d), 29.11, 28.11 (d), 24.85, 17.03.

^{19}F NMR (282 MHz, $CDCl_3$) δ -118.85 – -118.93 (m, 1F).

HRMS (ESI) $[C_{11}H_{13}NF]$ $[M+H]^+$ calculated: 178.1032, found: 178.1036.

4-((2-fluorophenyl)(methyl)amino)butanenitrile (1zv)



To a mixture of a 2-fluoro-*N*-methylaniline (568 μL, 5.0 mmol) and K_2CO_3 (2.4 g, 3.5 equiv) in MeCN (10 mL) was added 4-bromobutanenitrile (596 μL, 1.2 equiv), reflux the mixture for 24 h, dilute the mixture with water and extract with DCM for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography

on silica gel (eluent: *n*-hexane/EA 5/1) to give the title product as colorless oil (218 mg, 23% yield).

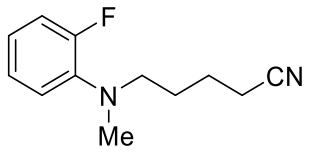
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 – 6.99 (m, 2H), 6.95 (ddd, *J* = 9.5, 8.1, 1.7 Hz, 1H), 6.92 – 6.87 (m, 1H), 3.20 (t, *J* = 6.8 Hz, 2H), 2.81 (s, 3H), 2.46 (t, *J* = 7.3 Hz, 2H), 1.94 (p, *J* = 7.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.43 (d), 139.71 (d), 124.42 (d), 121.91 (d), 119.81, 119.50 (d), 116.34 (d Hz), 53.69 (d), 39.80, 23.63, 14.55.

^{19}F NMR (282 MHz, $CDCl_3$) δ -123.51 (m, 1F).

HRMS (ESI) $[C_{11}H_{13}N_2NaF]$ $[M+Na]^+$ calculated: 215.0960, found: 215.0957.

5-((2-fluorophenyl)(methyl)amino)pentanenitrile (1zw)



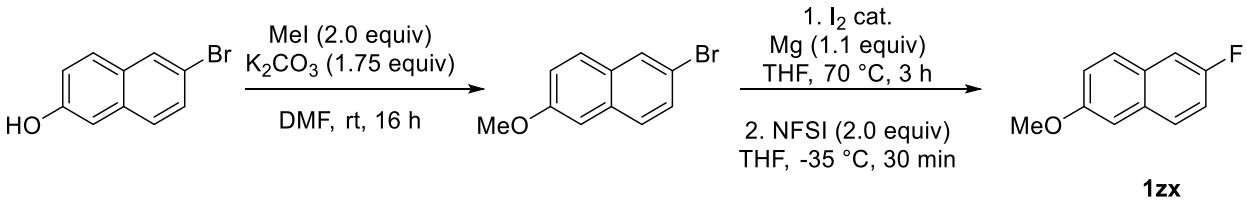
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 – 6.98 (m, 2H), 6.94 – 6.90 (m, 1H), 6.89 – 6.85 (m, 1H), 3.16 – 3.13 (m, 2H), 2.81 (s, 3H), 2.40 – 2.37 (m, 2H), 1.74 – 1.71 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.25 (d), 139.99 (d), 124.37 (d), 121.34 (d), 119.71, 119.24 (d), 116.23 (d), 54.24 (d), 39.57, 26.31, 22.93, 17.09.

^{19}F NMR (282 MHz, $CDCl_3$) δ -123.31 (m, 1F).

HRMS (ESI) $[C_{12}H_{15}N_2F]$ $[M+H]^+$ calculated: 207.1298, found: 207.1299.

2-fluoro-6-methoxynaphthalene (1zx)



1zx

A suspension of 6-bromo-2-naphthol (8.9 g, 40.0 mmol), K_2CO_3 (9.7 g, 70 mmol), and MeI (5.0 mL, 80 mmol) was stirred for 16 h in DMF (50 mL). dilute with addition of Et_2O, thorough washing with H_2O for three times, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. Recrystallized from hexane to give 2-bromo-6-methoxynaphthalene as white solid (9.7 g, quantitative).

Preparation of Grignard reagent: Charge flask equipped with a reflux condenser tube with magnesium turnings (158 mg, 6.6 mmol), a little iodine under nitrogen atmosphere. Dissolve 2-bromo-6-methoxynaphthalene (1.4 g, 6.0 mmol) in dry THF (8 mL), which then was introduced slowly to flask while stirring at room temperature. Stir the mixture at 70 °C for 3 h and cool for the next step.

To a solution of N-Fluorobenzenesulfonimide (3.8 g, 12 mmol) in dry THF (10 mL) under nitrogen

atmosphere at -35 °C was dropwised slowly the Grignard reagent, stir the mixture for 30 min, quench with MeOH, warm the mixture to room temperature, extract with Et_2O for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) to give the title product as white solid (328 mg, 31%).

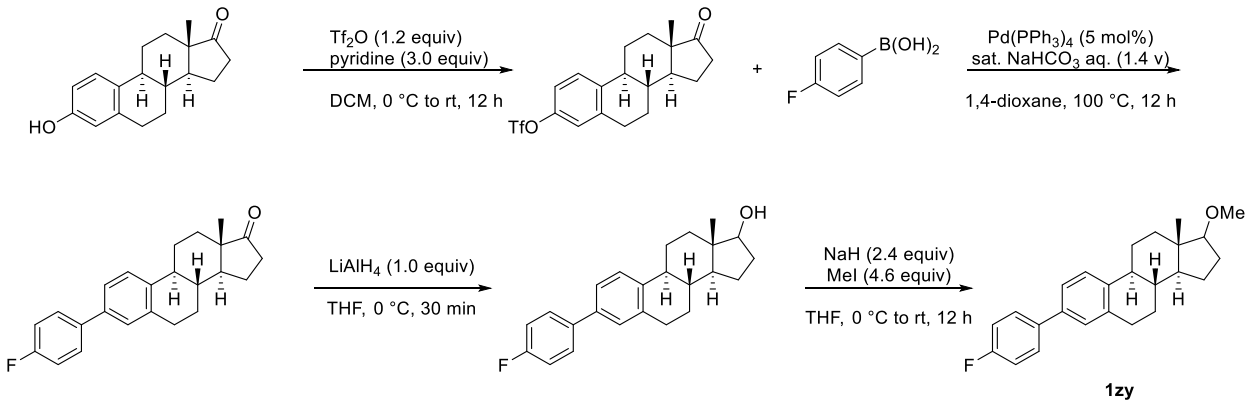
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 9.0, 5.5 Hz, 1H), 7.67 (d, *J* = 8.9 Hz, 1H), 7.39 (dd, *J* = 9.8, 2.7 Hz, 1H), 7.22 (td, *J* = 8.7, 2.6 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.33 (d), 157.07 (d), 131.42, 129.30 (d), 128.77 (d), 128.63 (d), 119.81, 116.53 (d), 110.86 (d), 105.88, 55.35.

^{19}F NMR (282 MHz, $CDCl_3$) δ -118.48 (s, 1F).

HRMS (ESI) $[C_{11}H_{10}FO]$ $[M+H]^+$ calculated: 177.0715, found: 177.0718.

(8*R*, 9*S*, 13*S*, 14*S*)-3-(4-fluorophenyl)-17-methoxy-13-methyl-7, 8, 9, 11, 12, 13, 14, 15, 16, 17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (1zy)



To an oven dried 100 mL round-bottomed flask was added estrone (2.0 g, 7.5 mmol) and dry dichloromethane (20 mL) under an argon atmosphere. reaction mixture was cooled to 0 ℃. After that, pyridine (1.8 mL, 3.0 equiv.) was added dropwise at 0 ℃. The mixture was stirred at 0 ℃ for 30 minutes. Then, trifluoromethanesulfonic anhydride (1.5 mL, 1.2 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and furtherly stirred for 12 hours. water was added and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. After filtered, the filtrate was were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 4/1) to give (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7, 8, 9, 11, 12, 13, 14, 15, 16, 17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate as white solid (2.94 g, yield: 97%).

A 100 mL flask was charged with 4-fluorophenylboronic acid (840 mg, 6.0 mmol), $Pd(PPh_3)_4$ (289 mg, 0.25 mmol), 1,4-dioxane (15 mL). stir the reaction mixture for 20 min at rt, (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7, 8, 9, 11, 12, 13, 14, 15, 16, 17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate (2.0 g, 5.0 mmol), sat. $NaHCO_3$ aq. (7 mL) were added successively. Heat the mixture to 100 ℃ for 12 h. After the reaction completed, the resulted mixture was filtered through a short pad of celite, then the filtrate was concentrated under reduced pressure to give the residue, which was diluted with EtOAc, then wash it with water and brine, after dried over Na_2SO_4, filtered, and concentrated the solution under reduced pressure. The

residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc/DCM 9/1/2) to give (8*R*,9*S*,13*S*,14*S*)-3-(4-fluorophenyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one as white solid (1.66 g, yield: 95%).

To an oven dried 50 mL round-bottomed flask was added (8*R*,9*S*,13*S*,14*S*)-3-(4-fluorophenyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (1.0 g, 3.0 mmol) and dry THF (15 mL) under an argon atmosphere. Cool the solution to 0 ℃ followed by the addition of $LiAlH_4$ (114 mg, 3.0 mmol) portion-wise, after the addition, stir the mixture for 30 min at 0 ℃, quench the reaction with 1N HCl, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure, the obtained crude product was recrystallized from DCM/*n*-hexane to give (8*R*,9*S*,13*S*,14*S*)-3-(4-fluorophenyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol as white solid (950 mg, yield: 91%).

To an oven dried 30 mL round-bottomed flask was added (8*R*,9*S*,13*S*,14*S*)-3-(4-fluorophenyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (350 mg, 1.0 mmol) and dry THF (8 mL) under an argon atmosphere. Cool the reaction mixture to 0 ℃ followed by the addition of NaH (60 % in mineral oil, 96 mg, 2.4 mmol), after the addition, stir the mixture for 15 min at 0 ℃, MeI (286 μL, 4.6 mmol) was added, the reation mixture was furtherly stirred for 12 h. quench the reaction with H_2O, the resulted mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure, the residue was recrystallized from Et_2O/MeOH to give the title product as white solid (303 mg, yield: 83%).

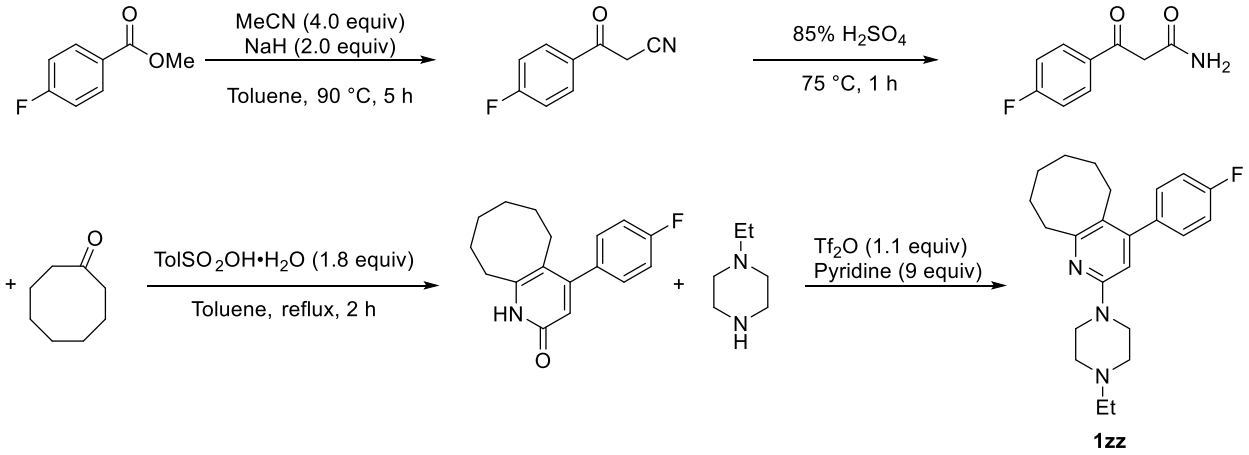
m. p. = 112.3 – 112.9 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 7.37 – 7.31 (m, 2H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.11 – 7.08 (m, 2H), 3.39 (s, 3H), 3.34 – 3.31 (m, 1H), 2.38 – 2.33 (m, 2H), 2.30 – 2.25 (m, 1H), 2.30 – 2.25 (m, 1H), 2.12 – 2.04 (m, 2H), 1.95 – 19.0 (m, 1H), 1.74 – 1.68 (m, 1H), 1.61 – 1.45 (m, 3H), 1.46 – 1.42 (m, 1H), 1.41 – 1.33 (m, 2H), 1.26 – 1.20 (m, 1H), 0.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.31 (d), 139.64, 137.58, 137.27, 137.24, 128.51 (d), 127.60, 125.95, 124.29, 115.53 (d), 90.78, 57.96, 50.42, 44.33, 43.24, 38.43, 38.08, 29.71, 27.78, 27.23, 26.30, 23.09, 11.58.

HRMS (ESI) $[C_{25}H_{29}ONaF]$ $[M+Na]^+$ calculated: 387.2100, found: 387.2097.

2-(4-ethylpiperazin-1-yl)-4-(4-fluorophenyl)-5, 6, 7, 8, 9, 10-hexahydrocycloocta[*b*]pyridine (1zz)



To a stirring solution of acetonitrile (20.0 mmol) in dry toluene (10 mL) was added NaH (60 % in mineral oil, 20.0 mmol) at room temperture. Then dropwise the solution of methyl 4-fluorobenzoate (1.5 g, 10 mmol) in dry toluene (5 mL) to the reaction. The reaction mixture was heated to 90 °C for 2 h, after the rest 20 mmol acetonitrile was added, the reaction mixture was furtherly stirred for 5 h at 90 °C. when the reaction completed, toluene was removed followed by addition of ice water and 3N HCl to adjust the PH to 5~6. And the mixture was extracted with DCM for 3 times. The combined organic layer was dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The given residue was recrystallized from DCM/*n*-hexane to give 3-(4-fluorophenyl)-3-oxopropanenitrile as pale-yellow solid (1.4 g, 86%).

To a dried flask charged with 85% H_2SO_4 was added portion-wise 3-(4-fluorophenyl)-3-oxopropanenitrile while stirring at 60 °C, after the addition. The reaction temperature was raised to 75 °C for 1 h. The reaction mixture was poured into ice-water and stirred for 10 min until the yellow solid was fully participated. The resulting solid was filtered off and washed with water to afford pale-yellow solid, which was dried in vacuo to give 3-(4-fluorophenyl)-3-oxopropanamide as pale-yellow solid (1.34 g, 86%).

A dried flask was charged with 4-methylbenzenesulfonic acid monohydrate (2.55 g, 13.4 mmol), which was dehydried by keep stirring under 110 °C for 1 h. Then cooled to 65 °C before a solution of 3-(4-fluorophenyl)-3-oxopropaneamide (1.34 g, 7.4 mmol) and cyclooctanone (0.94 g, 7.4 mmol) in toluene (20 mL) were added, followed by equipped with a Deanstock device. The mixture was refluxed for 2 h and monitored by TLC until the reaction completed. Toluene was removed followed by addition of DCM and water. The reaction mixture was neutralized (pH = 7～8) by adding saturated $NaHSO_4$ solution. Stir the mixture for 2 h while maintaining the reaction temperature at 10 ℃. The resulting solid was filtered and washed with cold toluene and water. The obtained solid was dried in vacuo to give pyridin-2(1*H*)-one as white solid (0.96 g, yield: 48%).

An oven-dried test-tube was charged with pyridin-2(1*H*)-one (271 mg, 1.0 mmol) and pyridine (725 μL, 9.0 mmol). Then trifluoromethanesulfonic anhydride (185 μL, 1.1 mmol) was added dropwise and stir for 1.5 h at room temperature. Then, 1-ethylpiperazine (525 μL, 4.0 mmol) was added, the reaction mixture was heated to 100 °C stirring for 4 h until the reaction completed. To the reaction mixture was added ice water (2 mL), and stir for 10 min. Then extracted by DCM for 3 times, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the residue, which was purified by silica gel column chromatography (DCM/MeOH: 10/1) to afford the title product which further recrystallized from *n*-hexane in a refrigerator to give pure Blonanserin (213 mg, yield: 58%) as white solid.

m. p. = 122.6 – 123.3 ℃

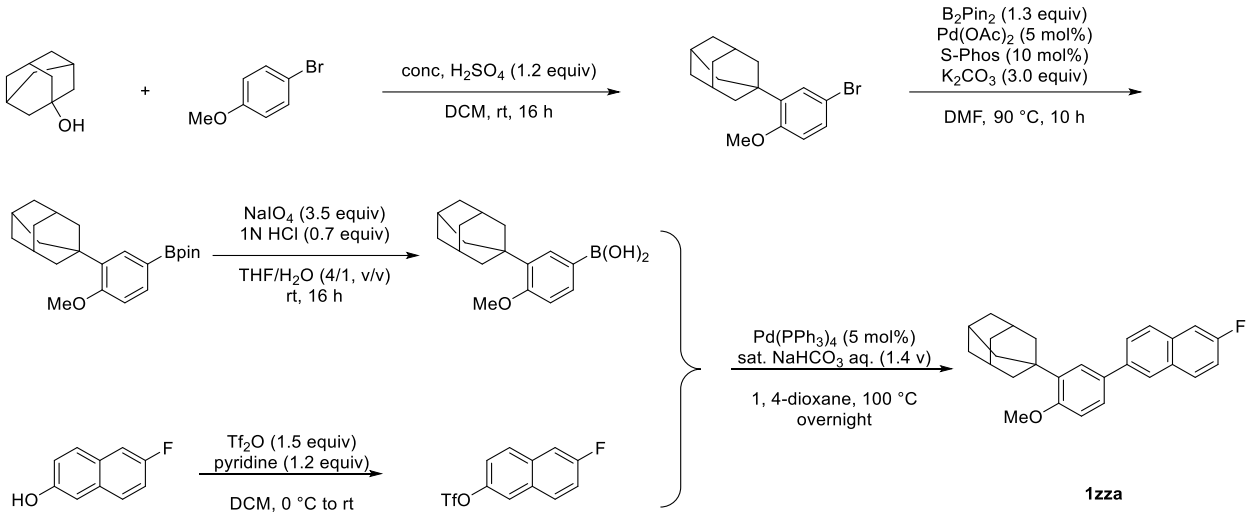
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.20 (m, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 6.30 (s, 1H), 3.54 – 3.52 (m, 4H), 2.89 – 2.87 (m, 2H), 2.58 – 2.55 (m, 6H), 2.46 (q, *J* = 7.2 Hz, 2H), 1.81 – 1.76 (m, 2H), 1.46 – 1.39(m, 2H), 1.38 – 1.33 (m, 4H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.09 (d), 159.95, 157.29, 150.38, 137.42 (d), 130.10 (d), 122.92, 114.90 (d), 105.95, 52.79, 52.50, 45.54, 35.58, 31.50, 30.62, 26.59, 26.46, 25.81, 12.03.

^{19}F NMR (282 MHz, $CDCl_3$) δ -115.45 (s, 1F).

HRMS (ESI) [$C_{27}H_{27}ONaF$] $[M+Na]^+$ calculated: 409.1944, found: 409.1933.

1-(5-(6-fluoronaphthalen-2-yl)-2-methoxyphenyl)adamantane (1zd)



To a round-bottle reaction flask were added 1-adamantol (3.0 g, 20 mmol), 4-bromoanisole (3.0 mL, 24 mmol), and DCM (15 mL) at room temperature. Then conc. H_2SO_4 (1.27 mL, 24 mmol) was added dropwise to the mixture. After the addition, keep stirring for 4 h at room temperature, then H_2O (12 mL) was added to the mixture slowly. Furtherly stir the mixture for 10 min, the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, concentrate the solution. The residue was recrystallized from *n*-hexane under 0 ℃ to give 1-(5-bromo-2-methoxyphenyl)adamantane as white solid (4.82 g, yield: 75%).

A flame-dried flask was charged with 1-(5-bromo-2-methoxyphenyl)adamantane (3.2 g, 10.0 mmol), $Pd(OAc)_2$ (113 mg, 0.5 mmol), S-Phos (410 mg, 1.0 mmol), and B_2Pin_2 (3.3 g, 13.0 mmol), then sealed the flask. After the flask was evacuated and backfilled with N_2 for 3 times, dry DMF was added to the flask. The mixture was allowed to stir for 30 min at room temperature, K_2CO_3 (4.4 g, 30.0 mmol) was added followed by rise the reaction temperature to 90 ℃ for 10 h. After the reaction completed, cool to rt, the resulted mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and filtered through a short pad of silica. The solvent was removed and the solid was recrystallized under 0 ℃ to give 2-(3-(adamantan-1-yl)-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as white solid (2.72 g, yield: 74%).

To a round-bottle reaction flask, 2-(3-(adamantan-1-yl)-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.72 g, 7.4 mmol) were suspended in a mixed solvent of THF/H_2O (50 mL, 4/1, v/v), then $NaIO_4$ (4.7 g, 22.2 mmol) was added while stirring. The reaction mixture was kept stirring for 1 h at room temperature, aqueous 1N HCl (5.2 mL, 5.2 mmol) was added, stir the mixture for another16 h. After the reaction completed, dilute the mixture with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the residue, which was recrystallized from MeOH to give (3-(adamantan-1-yl)-4-methoxyphenyl)boronic acid as white solid (1.92 g, yield: 91 %).

To a round-bottle reaction flask was added 6-fluoronaphthalen-2-ol (0.81 g, 5.0 mmol), pyridine (0.48 mL, 6.0 mmol), and dry DCM (20 mL), then sealed and cooled to 0 ℃. followed by the dropwise addition of Tf_2O (1.23 mL, 7.5 mmol), then slowly warm up to room temperature, and keep stirring overnight. The reaction was quenched with saturated $NaHCO_3$, extracted with DCM, washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the residue, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) to give aryl triflate as a colorless oil (1.16 g, yield: 79 %).

A 20 mL flask was charged with aryl boronic acid (343 mg, 1.2 mmol), $Pd(PPh_3)_4$ (60 mg, 0.05 mmol), 1,4-

dioxane (3 mL). stir the reaction mixture for 20 min at rt, aryl triflate (189 μL, 1.0 mmol), sat. $NaHCO_3$ aq. (1.4 mL) were added successively. Heat the mixture to 100 ℃ overnight. After the reaction completed, the resulted mixture was filtered through a short pad of celite, washed with hot toluene, then the filtrate was extracted with hot toluene and hot water, after dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was recrystallized from hot toluene to give adapalene derivative as white solid (194.4 mg, yield: 50%).

m. p. = 204.8 – 205.7 ℃

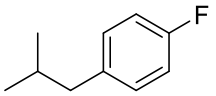
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.87 (dd, *J* = 9.0, 5.5 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.76 – 7.74 (m, 1H), 7.57 (d, *J* = 2.3 Hz, 1H), 7.50 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.46 (dd, *J* = 9.8, 2.6 Hz, 1H), 7.29 – 7.24 (m, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 2.18 (s, 6H), 2.10 (s, 3H), 1.80 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.45 (d), 158.60, 138.93, 138.39, 138.36, 132.90, 130.79, 130.42, 130.35, 127.63, 127.59, 126.79, 125.86, 125.54, 125.01, 116.54 (d), 112.09, 110.69 (d), 55.19, 40.62, 37.20, 37.15, 29.13.

^{19}F NMR (282 MHz, $CDCl_3$) δ -115.31 – -115.22 (m, 1F).

HRMS (ESI) [$C_{27}H_{27}ONaF$] $[M+Na]^+$ calculated: 409.1944, found: 409.1933.

1-fluoro-4-isobutylbenzene (1zzb)



Isopropyl-triphenylphosphonium bromide (5.1 g, 1.2 equiv) was suspended in 30 ml dry THF, then potassium tert-butoxide (1.3 g, 1.2 equiv) was added protionwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. After the phosphonium ylide was formed, 4-fluorobenzaldehyde (1.0 mL, 10.0 mmol) was dissolved in 10 ml dry THF and it was added drop wise to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water, then the THF was evaporated at reduced pressure. The residue was extracted with Et_2O for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: n-hexane) to give 1-fluoro-4-(2-methylprop-1-en-1-yl)benzene as colorless oil (712 mg, 47%).

To a mixture of 1-fluoro-4-(2-methylprop-1-en-1-yl)benzene (712 mg, 4.7 mmol) in methanol (10 mL) was added Pd/C (25 mg, 5 mol%), Stir vigorously under 1 atmosphere H_2 (balloon) at room temperature for 2 h, After the completion of the reaction, extracted the mixture with Et_2O for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane) to give the title product as colorless oil (614 mg, 86%).

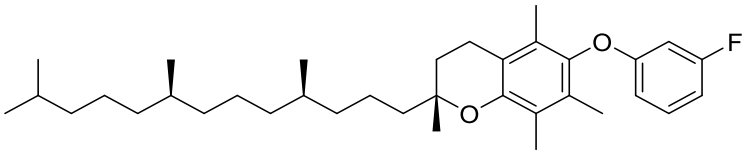
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 – 7.07 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 2.44 (d, *J* = 7.2 Hz, 2H), 1.82 (dp, *J* = 13.5, 6.5 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.22 (d), 137.26 (d), 130.36 (d), 114.79 (d), 44.58, 30.35, 22.26.

^{19}F NMR (282 MHz, $CDCl_3$) δ -118.74 (m, 1F).

HRMS (ESI) [$C_{10}H_{14}F$] $[M+H]^+$ calculated: 153.1079, found: 153.1080.

(*R*)-6-(3-fluorophenoxy)-2, 5, 7, 8-tetramethyl-2-((4*R*,8*R*)-4, 8, 12-trimethyltridecyl)chromane (1zzc)



An oven-dried flask was charged with $Pd(OAc)_2$ (45 mg, 0.2 mmol), Johnphos (90 mg, 0.3 mmol), K_3PO_4 (2.07 g, 10.0 mmol), 1-bromo-3-fluorobenzene (820 μL, 7.5 mmol), α-Tocopherol (2.15 g, 5.0 mmol) and Toluene (25 mL) successively, stir the reaction at 120 ℃ for 24 h, after the reaction completed, cool it to rt, then dilute with EtOAc, filter through a pad of celite, the filtrate was concentrated under reduced pressure, the obtained residue was purified by column chromatography on silica gel (eluent: *n*-hexane) to give the title product as colorless viscous oil (386 mg, yield: 15%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (td, *J* = 8.3, 6.7 Hz, 1H), 6.62 (td, *J* = 8.3, 2.5 Hz, 1H), 6.57 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.42 (dt, *J* = 10.8, 2.3 Hz, 1H), 2.60 (t, *J* = 6.8 Hz, 2H), 2.12 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.87 – 1.76 (m, 2H), 1.66 – 1.55 (m, 2H), 1.54 – 1.47 (m, 2H), 1.45 – 1.37 (m, 3H), 1.36 – 1.19 (m, 12H), 1.15 – 1.11 (m, 3H), 1.09 – 1.04 (m, 2H), 0.87 – 0.84 (m, 12H).

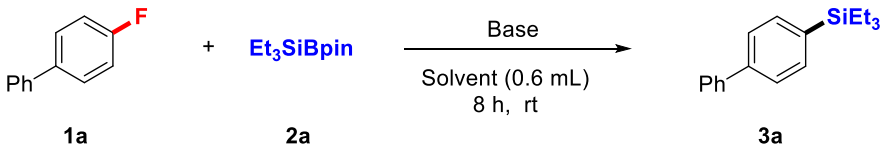
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.86 (d), 160.36 (d), 149.00, 143.15, 130.28 (d), 128.04, 126.15, 123.48, 117.98, 110.69 (d), 107.73 (d), 102.43 (d), 75.11, 40.02, 39.44, 37.62, 37.54, 37.46, 37.42, 37.36, 32.86 (d), 31.27 (d), 28.05, 24.89, 24.52, 23.92, 22.80, 22.70, 21.11, 20.68, 19.75 (t), 12.87, 12.00, 11.89.

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.42 – -112.33 (m, 1F).

HRMS (ESI) [$C_{35}H_{53}O_2NaF$] $[M+Na]^+$ calculated: 547.3927, found: 547.3925.

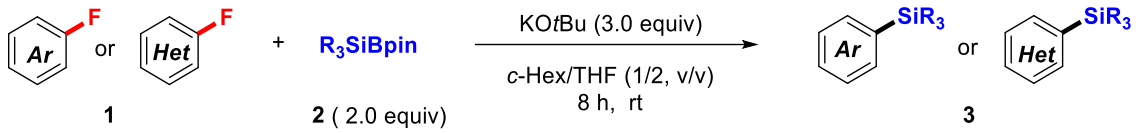
Chapter 1. Silylboronate-mediated Defluorosilylation of Aryl Fluorides with or without Ni-catalyst

1.1 General procedure for the optimization of defluorosilylation reactions



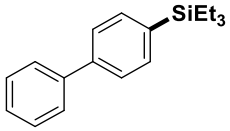
In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added Aryl fluorides **1a** (0.10 mmol, 1.0 equiv), with or without $Ni(cod)_2$ (10 mol %), indicated amount of Silyl boronates **2a**, base and solvent (0.6 mL) sequentially. The tube then was sealed and removed from the glovebox. The solution was stirred at room temperature for 8h. The reaction tube was added *n*-Hexane (5 mL), then subject to filter through a short silica pad, and washed with Et_2O, concentrated under vacuum, followed by 3-Fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After NMR analysis was conducted. The mixture was then concentrated again to give the residue, which was purified by column chromatography on silica gel to give the corresponding arylsilanes **3a**.

1.2 General procedure for the defluorosilylation of aryl fluorides



In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added Aryl fluorides **1** (0.20 mmol, 1.0 equiv), Silyl boronates **2** (0.4 mmol, 2.0 equiv), with or without $Ni(cod)_2$ (10 mol %), KOtBu (67 mg, 0.6 mmol, 3.0 equiv) and cyclohexane/THF (1.2 mL, 1/2, v/v) sequentially. The tube then was sealed and removed from the glovebox. The solution was stirred at room temperature for 8h. The reaction tube was added n-Hexane (5 mL), then subject to filter through a short silica pad, and washed with Et_2O, concentrated under vacuum, followed by 3-Fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After NMR analysis was conducted. The mixture was then concentrated again to give the residue, which was purified by column chromatography on silica gel to give the corresponding arylsilanes **3**.

Biphenyl-4-yltriethylsilane (3a)

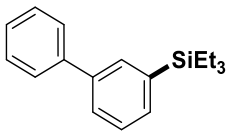


Compound **3a** was obtained as a colorless oil (without Nickel catalysis: 31.8 mg, Yield: 59%; with Nickel catalysis: 46.1 mg, Yield: 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.55 (m, 5H), 7.51 – 7.41 (m, 3H), 7.39 – 7.32 (m, 1H), 1.01 (t, *J* = 7.7 Hz, 9H), 0.83 (q, *J* = 8.9, 8.3 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 268.

The chemical shifts were consistent with those reported in the literature.[37]

Biphenyl-3-yltriethylsilane (3b)

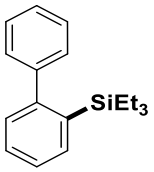


Compound **3b** was obtained as a colorless oil (without Nickel catalysis: 27.4 mg, Yield: 51%; with Nickel catalysis: 44 mg, Yield: 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.64 – 7.56 (m, 3H), 7.54 – 7.42 (m, 4H), 7.38 (d, *J* = 7.1 Hz, 1H), 1.02 (t, *J* = 7.5 Hz, 9H), 0.92 – 0.82 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 268.

The chemical shifts were consistent with those reported in the literature.[37]

Biphenyl-2-yltriethylsilane (3c)

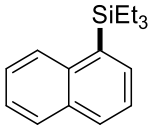


Compound **3c** was obtained as a colorless oil (without Nickel catalysis: 14 mg, Yield: 26%; with Nickel catalysis: 40 mg, Yield: 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.64 – 7.55 (m, 3H), 7.46 (t, *J* = 7.4 Hz, 3H), 7.39 – 7.33 (m, 2H), 1.01 (t, *J* = 7.6 Hz, 9H), 0.92 – 0.80 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 268.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(naphthalen-1-yl)silane (3d)

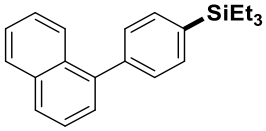


Compound **3d** was obtained as a colorless oil (without Nickel catalysis: 38.7 mg, Yield: 40%; with Nickel catalysis: 67.8 mg, Yield: 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 – 8.06 (m, 1H), 7.96 – 7.79 (m, 2H), 7.69 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.55 – 7.42 (m, 3H), 1.13 – 0.89 (m, 15H). **MS** (EI) *m*/*z* $[M]^+$: 242.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(4-(naphthalen-1-yl)phenyl)silane (3e)



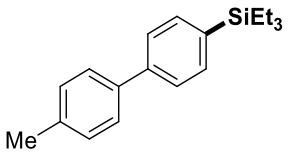
Compound **3e** was obtained as a colorless oil (without Nickel catalysis: 35.1 mg, Yield: 55%; with Nickel catalysis: 50 mg, Yield: 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.67 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.51 – 7.43 (m, 3H), 7.35 (dt, *J* = 4.5, 1.1 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.22 – 7.09 (m, 2H), 0.93 – 0.73 (m, 9H), 0.50 (q, *J* = 7.8 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 318.

The chemical shifts were consistent with those reported in the literature.[124]

Triethyl(4'-methylbiphenyl-4-yl)silane (3f)

[124] J. Zhang, Y. Zhang, S. Geng, S. Chen, Z. Liu, X. Zeng, Y. He, Z. Feng, C–O Bond Silylation Catalyzed by Iron: A General Method for the Construction of Csp^2–Si Bonds, *Org. Lett.* **2020**, *22*, 2669–2674.

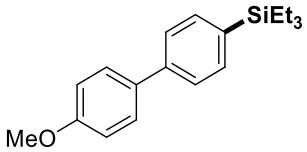


Compound **3f** was obtained as a white solid (26 mg, Yield: 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.46 (m, 6H), 7.26 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H), 1.00 (t, *J* = 7.7 Hz, 9H), 0.90 – 0.66 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 282.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(4'-methoxybiphenyl]-4-yl)silane (3g)

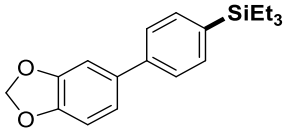


Compound **3g** was obtained as a white solid (26.8 mg, Yield: 45%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.40 (m, 6H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 1.01 (t, *J* = 7.8 Hz, 9H), 0.93 – 0.68 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 298.

The chemical shifts were consistent with those reported in the literature.[37]

(4-(Benzo[*d*][1,3]dioxol-5-yl)phenyl)triethylsilane (3h)

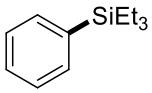


Compound **3h** was obtained as a white solid (24.4 mg, Yield: 39%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.37 (m, 4H), 7.10 – 7.03 (m, 2H), 6.94 – 6.83 (m, 1H), 6.00 (s, 2H), 0.99 (t, *J* = 7.7 Hz, 9H), 0.81 (q, *J* = 7.7 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 312.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(phenyl)silane (3i)

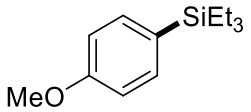


Compound **3i** was obtained as a colorless oil (36.5 mg, Yield: 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.37 (dd, *J* = 3.9, 2.4 Hz, 3H), 0.99 (t, *J* = 7.7 Hz, 9H), 0.82 (q, *J* = 7.3, 6.8 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 192.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(4-methoxyphenyl)silane (3j)

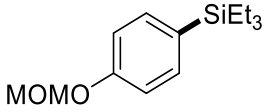


Compound **3j** was obtained as a colorless oil (28 mg, Yield: 32%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.21 (m, 2H), 7.12 – 6.83 (m, 2H), 3.82 (s, 3H), 1.04 – 0.89 (m, 9H), 0.85 – 0.71 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 222.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(4-(methoxymethoxy)phenyl)silane (3k)

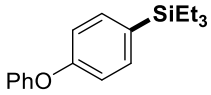


Compound **3k** was obtained as a colorless oil (12.6 mg, Yield: 25%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 5.19 (s, 2H), 3.48 (s, 3H), 1.05 – 0.86 (m, 9H), 0.82 – 0.67 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 252.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(4-phenoxyphenyl)silane (3l)

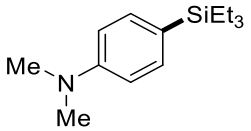


Compound **3l** was obtained as a colorless oil (23.3 mg, Yield: 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.8 Hz, 2H), 7.33 (q, *J* = 6.4, 5.2 Hz, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.06 – 6.94 (m, 4H), 0.96 (t, *J* = 7.7 Hz, 9H), 0.78 (q, *J* = 8.7, 7.8 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 284.

The chemical shifts were consistent with those reported in the literature.[37]

***N*,*N*-Dimethyl-4-(triethylsilyl)aniline (3m)**

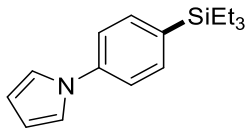


Compound **3m** was obtained as a colorless oil (19.3 mg, Yield: 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 1H), 6.92 – 6.82 (m, 2H), 6.82 – 6.69 (m, 1H), 2.96 (s, 6H), 0.99 (t, *J* = 7.7 Hz, 9H), 0.80 (q, *J* = 7.5 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 235.

The chemical shifts were consistent with those reported in the literature.[37]

1-(4-(Triethylsilyl)phenyl)-1*H*-pyrrole (3n)

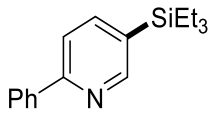


Compound **3n** was obtained as a colorless oil (23.8 mg, Yield: 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.12 (t, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.2 Hz, 2H), 1.03 – 0.92 (m, 9H), 0.88 – 0.76 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 257.

The chemical shifts were consistent with those reported in the literature.[37]

2-Phenyl-5-(triethylsilyl)pyridine (3o)

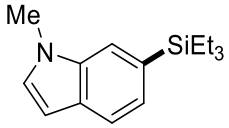


Compound **3o** was obtained as a colorless oil (22.8 mg, Yield: 43%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.91 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.68 (dd, *J* = 4.1, 1.5 Hz, 1H), 7.56 – 7.33 (m, 4H), 1.10 – 0.78 (m, 15H). **MS** (EI) *m*/*z* $[M]^+$: 269.

The chemical shifts were consistent with those reported in the literature.[125]

1-Methyl-6-(triethylsilyl)-1*H*-indole (3pa)



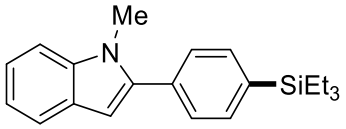
Compound **3p** was obtained as a colorless oil (18.2 mg, Yield: 37%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 6.47 (d, *J* = 3.2 Hz, 1H), 3.82 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 9H), 0.90 – 0.79 (m, 6H). **MS** (EI) *m*/*z* $[M]^+$: 245.

The chemical shifts were consistent with those reported in the literature.[37]

1-Methyl-2-(4-(triethylsilyl)phenyl)-1*H*-indole (3q)

[125] Z. Xu, L. Chai, Z. Q. Liu, Free-Radical-Promoted Site-Selective C–H Silylation of Arenes by Using Hydrosilanes, *Org. Lett.* **2017**, *19*, 5573–5576.

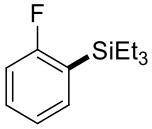


Compound **3q** was obtained as a colorless oil (30 mg, Yield: 42%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 15.4, 7.8 Hz, 3H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.57 (s, 1H), 3.76 (s, 3H), 1.01 (t, *J* = 7.7 Hz, 9H), 0.84 (q, *J* = 7.2 Hz, 6H). **MS** (EI) *m*/*z* $[M]^+$: 321.

The chemical shifts were consistent with those reported in the literature.[37]

Triethyl(2-fluorophenyl)silane (3r)

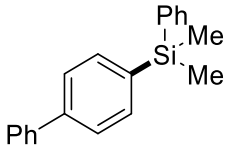


Compound **3a** was obtained as a colorless oil (52.1 mg, Yield: 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 2H), 7.13 (tt, *J* = 7.3, 1.0 Hz, 1H), 7.05 – 6.93 (m, 1H), 0.97 (t, *J* = 7.6 Hz, 9H), 0.90 – 0.80 (m, 6H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -99.99 (q, *J* = 6.7 Hz). **MS** (EI) *m*/*z* $[M]^+$: 210.

The chemical shifts were consistent with those reported in the literature.[37]

Biphenyl-4-yldimethyl(phenyl)silane (3s)

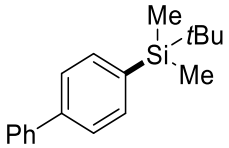


Compound **3s** was obtained as a colorless oil (21 mg, Yield: 36%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 8H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.42 – 7.34 (m, 4H), 0.60 (s, 6H). **MS** (EI) *m*/*z* $[M]^+$: 288.

The chemical shifts were consistent with those reported in the literature.[37]

Biphenyl-4-yl(*tert*-butyl)dimethylsilane (3t)



Compound **3t** was obtained as a colorless oil (without Nickel catalysis: 27.5 mg, Yield: 51%; with Nickel

catalysis: 41.8 mg, Yield: 78%).

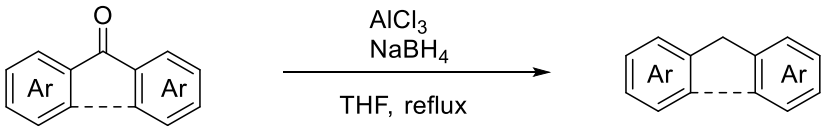
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 5H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 0.92 (s, 9H), 0.31 (s, 6H). **MS** (EI) *m/z* $[M]^+$: 268.

The chemical shifts were consistent with those reported in the literature.[126]

Chapter 3. Synthesis of triarylmethanes by silyl radical-mediated cross-coupling of aryl fluorides and arylmethanes

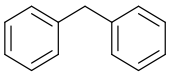
3.1 Synthesis of benzylic compounds and 9*H*-fluorene

Annulated diarylmethane derivatives 9,10-dihydroanthracene (**4h)**, 9*H*-xanthene (**4i)**, and 1,1-diphenylethane (**4j)**, cumene (**4m)**, ethylbenzene (**4n)**, butylbenzene (**4o)**, 4-phenyl-1-butene (**4p)**, allylbenzene (**4q)** were purchased from TCI or Sigma Aldrich. A typical known experimental procedure for the preparation of diarylmethanes **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4k**, **4l**, **4s**, **4t**, **4u** and **5zzc'** were described below.



General procedure A: The diarylmethanes was synthesized according to the known procedures with modifies.[7] A dried flask was charged with benzophenones, sodium borohydride, and anhydrous aluminum chloride in anhydrous THF. The mixture was stirred under reflux for 2 h and the reaction progress was monitored by TLC. After the ketones were fully consumed, the mixture was cooled to room temperature. To this mixture was slowly added water 10 mL, and then extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude, which was purified by column chromatography on silica gel (*n*-hexane) to give corresponding diarylmethanes **2** or **9*H*-fluorene**.

Diphenylmethane (4a)



According to **General Procedure A**, benzophenone (1.82 g, 10 mmol), sodium borohydride (1.90 g, 50 mmol), anhydrous aluminum chloride (4.0 g, 30 mmol), and anhydrous THF (50 mL) were used. The title product **4a** was isolated as a white solid after flash chromatography (1.66 g, yield: 99%).

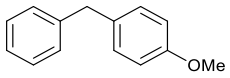
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 6.99 (m, 10H), 4.03 (s, 2H).

MS(EI): *m/z* 168 $[M]^+$.

[126] A. Streitwieser, L. Xie, P. Wang, S. M. Bachrach, Carbon acidity. 77. Ion pair carbon acidities of some silanes in tetrahydrofuran, *J. Org. Chem.* **1993**, *58*, 1778–1784.

The chemical shifts were consistent with those reported in the literature.[127]

4-Methoxydiphenylmethane (4b)



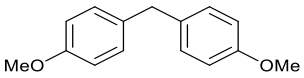
According to **General Procedure A**, 4-methoxybenzophenone (3.18 g, 15 mmol), sodium borohydride (2.85 g, 75 mmol), anhydrous aluminum chloride (6.00 g, 45 mmol), and anhydrous THF (60 mL) were used. The title product **4b** was isolated as a white solid after flash chromatography (2.64 g, yield: 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.88 – 6.79 (m, 2H), 3.92 (s, 2H), 3.77 (s, 3H).

MS(EI): *m/z* 198 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[128]

Dianisylmethan (4c)



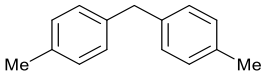
According to **General Procedure A**, 4,4'-diMethoxybenzophenone (0.97 g, 4 mmol), sodium borohydride (0.76 g, 20 mmol), anhydrous aluminum chloride (1.60 g, 12 mmol), and anhydrous THF (20 mL) were used. The title product **4c** was isolated as a white solid after flash chromatography (1.96 g, yield: 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.2 Hz, 4H), 6.86 (d, *J* = 8.5 Hz, 4H), 3.90 (s, 2H), 3.81 (s, 6H).

MS(EI): *m/z* 228 $[M]^+$.

The chemical shifts *were* consistent with those reported in the literature.[129]

Di-*p*-tolylmethane (4d)



According to **General Procedure A**, 4,4'-dimethylbenzophenone (1.05 g, 5 mmol), sodium borohydride (0.95 g, 25 mmol), anhydrous aluminum chloride (2.00 g, 15 mmol), and anhydrous THF (25 mL) were used. The title product **4d** was isolated as a white solid after flash chromatography (1.90 g, yield: 97%).

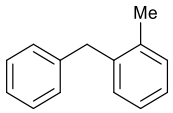
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 8H), 3.88 (s, 2H), 2.29 (s, 6H).

[127] A. Ono, N. Suzuki, J. Kamimura, Hydrogenolysis of Diaryl and Aryl Alkyl Ketones and Carbinols by Sodium Borohydride and Anhydrous Aluminum(III) Chloride, *Synthesis* **1987**, *8*, 736–738.
[128] I. Abdiaj, A. Fontana, M. V. Gomez, A. de la Hoz, J. Alcázar, Visible-Light-Induced Nickel-Catalyzed Negishi Cross-Couplings by Exogenous-Photosensitizer-Free Photocatalysis, *Angew. Chem., Int. Ed.* 2018, **57**, 8473–8477.
[129] K. Endo, T. Ishioka, T. Ohkubo, T. Shibata, One-Pot Synthesis of Symmetrical and Unsymmetrical Diarylmethanes via Diborylmethane, *J. Org. Chem.* **2012**, *77*, 7223–7231.

MS(EI): *m/z* 196 $[M]^+$.

The chemical shifts *were* consistent with those reported in the literature.[129]

1-Benzyl-2-methylbenzene (4e)



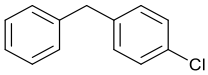
According to **General Procedure A**, 2-methylbenzophenone (1.96 g, 10 mmol), sodium borohydride (1.90 g, 50 mmol), anhydrous aluminum chloride (4.00 g, 30 mmol), and anhydrous THF (50 mL) were used. The title product **4e** was isolated as a white solid after flash chromatography (1.50 g, yield: 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 6.73 (m, 9H), 3.98 (s, 2H), 2.23 (s, 3H).

MS(EI): *m/z* 182 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[130]

1-Benzyl-4-chlorobenzene (4f)



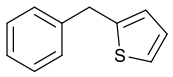
According to **General Procedure A**, 4-chlorobenzophenone (2.16 g, 10 mmol), sodium borohydride (1.90 g, 50 mmol), anhydrous aluminum chloride (4.00 g, 30 mmol), and anhydrous THF (50 mL) were used. The title product **4f** was isolated as a white solid after flash chromatography (1.47 g, yield: 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 4H), 7.23 – 7.14 (m, 5H), 3.98 (s, 2H).

MS(EI): *m/z* 202 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[131]

2-Benzylthiophene (4g)



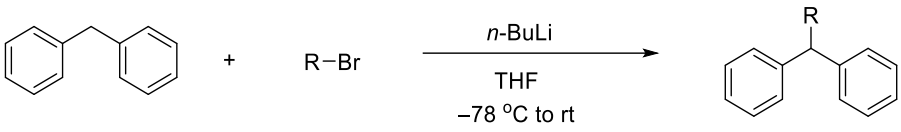
According to **General Procedure A**, 2-benzoylthiophene (1.88 g, 10 mmol), sodium borohydride (1.90 g, 50 mmol), anhydrous aluminum chloride (4.00 g, 30 mmol), and anhydrous THF (50 mL) were used. The title product **4g** was isolated as a colorless oil after flash chromatography (1.60 g, yield: 91%).

[130] F. Chahdoura, C. Pradel, M. Gómez, Palladium Nanoparticles in Glycerol: A Versatile Catalytic System for C□X Bond Formation and Hydrogenation Processes, *Adv. Synth. Catal.* **2013**, *355*, 3648–3660.
[131] E. Alacid, C. Nájera, First Cross-Coupling Reaction of Potassium Aryltrifluoroborates with Organic Chlorides in Aqueous Media Catalyzed by an Oxime-Derived Palladacycle, *Org. Lett.* **2008**, *10*, 5011–5014.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, 5H), 7.08 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.78 – 6.73 (m, 1H), 4.10 (s, 2H).

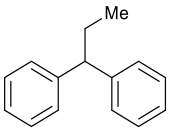
MS(EI): *m/z* 174 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[132]



General procedure B: The diarylmethane derivatives was synthesized according to the known procedures with modifies.[14] A dried flask was charged with diphenylmethane and anhydrous THF. The mixture was stirred under –78 ℃, and then *n*-butyllithium (1.6 M in *n*-hexane) was added dropwise, after addition finished, the mixture was allowed to warm up to 0 ℃ and keep stirring for 1 h. Then alkyl bromide in THF (1.0 M) was added dropwise and keep stirring for another 1 h under 0 ℃ followed by stirring at room temperature for 24 h. To this mixture was slowly added water, and then extracted with EtOAc. The combined organic layer was washed with brine, and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude, which was purified by column chromatography on silica gel (*n*-hexane) to give corresponding diarylmethane derivatives **4j** and 4**k**.

Propane-1,1-diyldibenzene (4j)



According to **General Procedure B**, diphenylmethane (1.68 g, 10 mmol), *n*-butyllithium (12.5 mL, 20 mmol), anhydrous ethyl bromide (1.11 mL, 15 mmol), and anhydrous THF (20 mL) were used. The title product **4j** was isolated as a white solid after flash chromatography (1.55 g, yield: 79%).

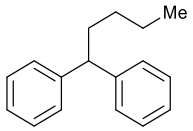
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.03 (m, 10H), 3.79 (t, *J* = 7.8 Hz, 1H), 2.08 (p, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

MS(EI): *m/z* 196 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[133]

Pentane-1,1-diyldibenzene (4k)

[132] M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal, R. J. K. Tayor, Simple palladium(II) precatalyst for Suzuki-Miyaura couplings: Efficient reactions of benzylic, aryl, heteroaryl, and vinyl coupling partners, *Org. Lett.* **2007**, *9*, 5397–5400.
[133] M. L. Czyz, M. S. Tayor, T. H. Horgren, A. Polyzos, Reductive Activation and Hydrofunctionalization of Olefins by Multiphoton Tandem Photoredox Catalysis, *ACS Catal.* **2021**, *11*, 5472–5480.



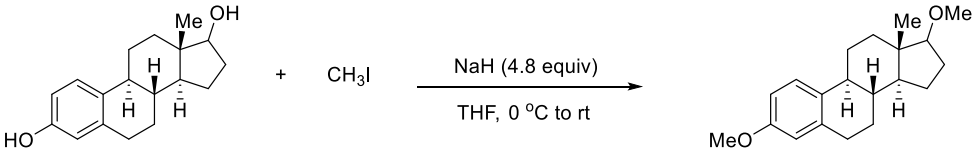
According to **General Procedure B**, diphenylmethane (1.68 g, 10 mmol), *n*-butyllithium (12.5 mL, 20 mmol), anhydrous butyl bromide (1.60 mL, 15 mmol), and anhydrous THF (20 mL) were used. The title product **4k** was isolated as a white solid after flash chromatography (2.0 g, yield: 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 10H), 3.88 (t, *J* = 7.8 Hz, 1H), 2.04 (q, *J* = 7.7 Hz, 2H), 1.44 – 1.14 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H).

MS(EI): *m/z* 224 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[134]

(8*R*,9*S*,13*S*,14*S*)-3,17-Dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (4s)



2s: 86%

To a flame dried flask, NaH (0.23 g, 9.6 mmol, 60% in mineral oil) was added to a solution of α-estradiol (0.544 g, 2.0 mmol) in THF (25 mL) under 0℃, and the mixture kept stirring for 30 min. A solution of iodomethane (1.16 mL, 18.6 mmol) in THF (5 mL) was added dropwise and then stirred at room temperature overnight. After the reaction finished ice water was added, quenched with saturated ammonium chloride solution and the mixture was extracted with EtOAc. The organic layer was combined and washed with brine, then dried over Na_2SO_4. Filtered and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 20/1) to give titled compound as a white solid (0.52 g, yield: 86%).

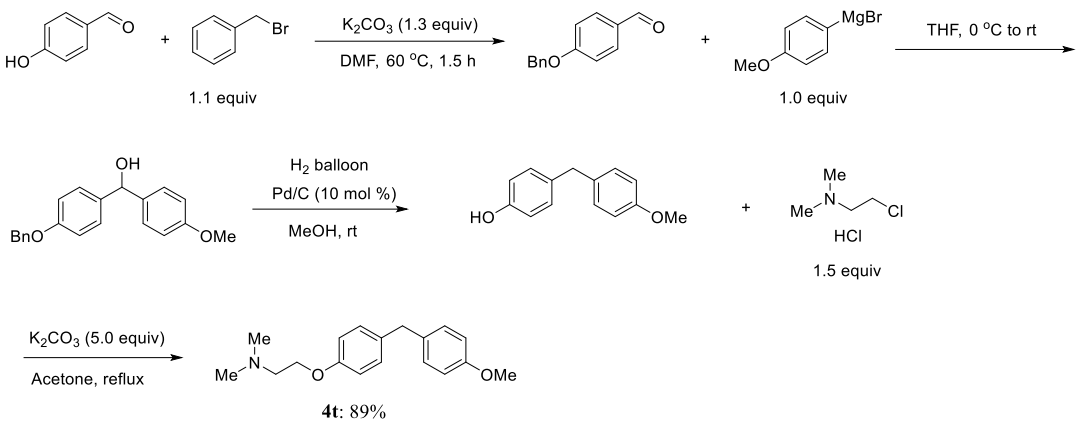
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 3.39 (s, 3H), 3.32 (t, *J* = 8.3 Hz, 1H), 2.95 – 2.74 (m, 2H), 2.37 – 2.13 (m, 2H), 2.10 – 1.99 (m, 2H), 1.93 – 1.82 (m, 1H), 1.76 – 1.60 (m, 1H), 1.59 – 1.18 (m, 7H), 0.79 (s, 3H).

MS(EI): *m/z* 300 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[135]

2-(4-(4-Methoxybenzyl)phenoxy)-*N*,*N*-dimethylethan-1-amine (4t)

[134] Z. Jia, Q. Liu, X. Peng, H. N. Wong, Iron-catalysed cross-coupling of organolithium compounds with organic halides, *Nat. Commun*. **2016**, *7*, 10614–10621.
[135] B. Wang, L. Qin, K. D. Neumann, S. Uppaluri, R. L. Cerny, S. G. Dimagno, Improved arene fluorination methodology for I(III) salts, *Org. Lett.*, **2010**, *12*, 3352–3355.



The diarylmethane derivative **4t** was synthesized according to the known procedures with modifies.[136]

To a flame dried flask were added 4-hydroxybenzaldehyde (1.22 g, 10.0 mmol), benzyl bromide (1.3 mL, 11.0 mmol), K_2CO_3 (1.8 g, 13.0 mmol) and DMF (5 mL). Seal and stir the mixture at 60 ℃ for 1.5 h. Then quench the reaction with saturated ammonium chloride solution after cooling to room temperature. Extracted with CH_2Cl_2, and dry the combined organic extracts over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 20/1) to give 4-(benzyloxy)benzaldehyde as a white solid (1.70 g, 80%).

To a flame dried flask was added 4-(benzyloxy)benzaldehyde (1.65 g, 7.75 mmol) and THF (10 mL) at room temperature under N_2 atmosphere, and the mixture was slowly added freshly prepared 4-methoxyphenylmagnesium bromide solution (7.8 mL, 7.8 mmol, approximately 1.0 M in THF) at 0 ℃, and then warm up to room temperature while keep stirring overnight. After the reaction finished, quenched with saturated ammonium chloride solution, and the mixture was extracted with EtOAc. The organic layer was combined and washed with brine, then dried over Na_2SO_4. Filtered and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10/1) to give (4-(benzyloxy)phenyl)(4-methoxyphenyl)methanol as a white solid (1.80 g, 73%).

To a flame dried flask was added (4-(benzyloxy)phenyl)(4-methoxyphenyl)methanol (1.28 g, 4.0 mmol), methanol (30 mL), and then Pd/C (40 mg). The mixture was stirred under hydrogen atmosphere at room temperature for 3 h. After the catalyst was removed, filtrate was evaporated in vacuo to give 4-(4-methoxybenzyl)phenol as a white solid (0.66 g, 77%).

To a flame dried flask was added 4-(4-methoxybenzyl)phenol (0.428 g, 2.0 mmol), 2-chloro-*N*,*N*-dimethylethanamine hydrochloride (0.432 g, 3 mmol), anhydrous acetone (30 mL), and then K_2CO_3 (1.38 g, 10 mmol). The mixture was stirred while refluxing overnight. After the reaction finished, the mixture was filtered through a short pad of silica gel, washed with EtOAc, the filtrate was evaporated in vacuo give the crude, which was purified by column chromatography on silica gel (EtOAc) to give the titled compound as a white solid (0.60 g, yield: 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.6, 3.6 Hz, 4H), 6.84 (dd, *J* = 8.6, 6.4 Hz, 4H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.87 (s, 2H), 3.78 (s, 3H), 2.72 (t, *J* = 5.8 Hz, 2H), 2.34 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 157.3, 133.9, 133.8, 129.8, 129.7, 114.6, 113.9, 66.1, 58.5, 55.3, 46.0,

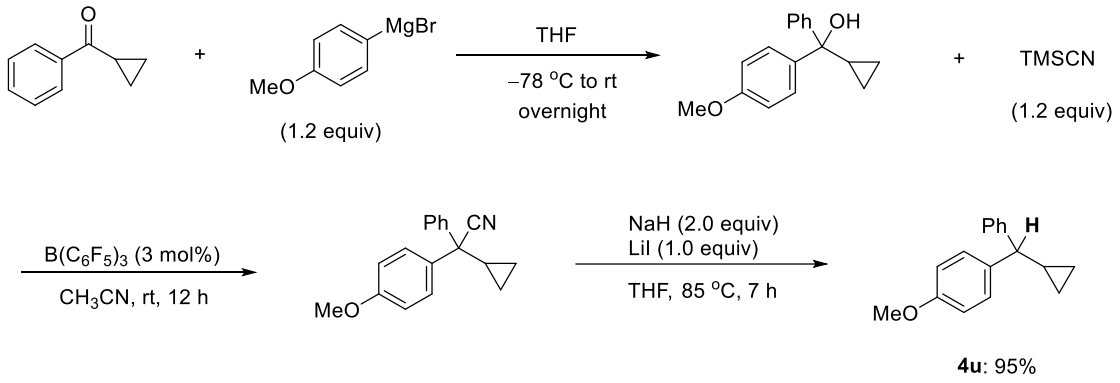
[136] G. Panda, M. K. Parai, S. K. Das, Shagufta, M. Sinha, V. Chaturvedi, A. K. Srivastava, Y. K. Manju, A. Gaikwad, S. Sinha, Effect of substituents on diarylmethanes for antitubercular activity, *Eur. J. Med. Chem.* **2007**, *42*, 410–419.

40.2.

MS(EI): *m/z* 285 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[136]

1-(Cyclopropyl(phenyl)methyl)-4-methoxybenzene (4u)



The cyclopropyl-containing diarylmethane derivative **4u** was synthesized according to the known procedures with modifies.[137]

To a solution of cyclopropyl(phenyl)methanone (1.46 g, 10.0 mmol) in anhydrous THF (10 mL) was added (4-methoxyphenyl)magnesium bromide (freshly prepared from 1-bromo-4- methoxybenzene (2.24 g, 12.0 mmol) and Mg (0.37 g, 15.0 mmol) in 10 mL of THF) dropwise at –78 °C. The reaction was then allowed to warm up to room temperature and stirred for 2 h. After completion, the reaction was quenched with aqueous HCl (1 N) at 0 °C and the organic materials were extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Then the obtained residue was purified over silica gel flash column chromatography (*n*-hexane/EtOAc: 4/1) to give cyclopropyl(4-methoxyphenyl)(phenyl)methanol as a white solid (2.33 g, 91%).

To a stirred solution of cyclopropyl(4-methoxyphenyl)(phenyl)methanol (1.27 g, 5.0 mmol) and $B(C_6F_5)_3$ (77 mg, 0.15 mmol) in CH_3CN (5 mL) was added dropwise trimethylsilyl cyanide (0.6 g, 6.0 mmol). The reaction mixture was stirred at room temperature for 12 h. Volatile materials were removed in vacuo and the crude residue was purified by silica gel flash column chromatography (*n*-hexane/EtOAc: 8/1) to give 2-cyclopropyl-2-(4-methoxyphenyl)-2-phenylacetonitrile as a colorless oil (1.04 g, 79%).

To a mixture of NaH (60% dispersion in mineral oil; 240 mg, 6.0 mmol) and LiI (402 mg, 3.0 mmol) in an oven-dried flask was added a solution of 2-cyclopropyl-2-(4-methoxyphenyl)-2-phenylacetonitrile (0.79 g, 3.0 mmol) in THF (10 mL). The reaction mixture was stirred at 85 °C overnight. After cooling to room temperature, the reaction was then quenched with water at 0 °C and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. Concentrated and the crude residue was purified by silica gel flash column chromatography (*n*-hexane/EtOAc: 20/1) to give titled compound as a colorless oil (680 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 4H), 7.21 – 7.13 (m, 3H), 6.90 – 6.74 (m, 2H), 3.76 (s, 3H),

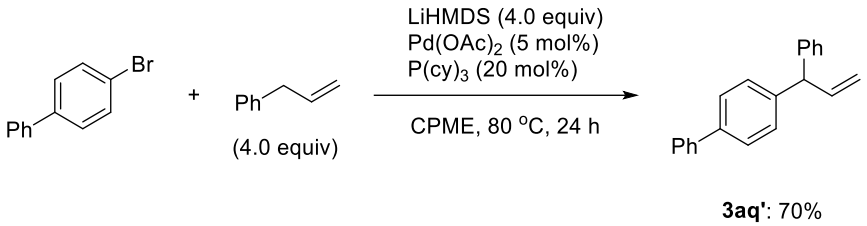
[137] P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, Hydride Reduction by a Sodium Hydride–Iodide Composite, *Angew. Chem. Int. Ed.* **2016**, *55*, 3719–3723.

3.16 (d, *J* = 9.5 Hz, 1H), 1.42 – 1.25 (m, 1H), 0.73 – 0.53 (m, 2H), 0.34 – 0.17 (m, 2H).

MS(EI): *m/z* 238 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[137]

4-(1-Phenylallyl)biphenyl (5zzc')



The title compound **5zzc'** was synthesized according to the known procedures with modifies.[138]

In a nitrogen filled glovebox, to an oven-dried flask was charged with $LiN(SiMe_3)_2$ (3.34 g, 20 mmol), $Pd(OAc)_2$ (57 mg, 0.25 mmol) and PCy_3 (280 mg, 1.0 mmol), then dry CPME (25 mL) was added to the mixture. After stirring for 5 min at room temperature, allylbenzene (2.7 mL, 20 mmol) was added to the reaction mixture followed by biphenyl bromide (1.17 g, 5 mmol). The reaction mixture was stirred in an oil-bath for 24 h at 80 °C, cooled, quenched with few drops of H_2O, diluted with 10 mL of EtOAc, and filtered over a pad of silica. The pad was washed with EtOAc, and the solution was concentrated in vacuo. The crude was purified by silica gel flash column chromatography (*n*-hexane/EtOAc: 50/1) to give titled compound as a colorless oil (0.95 g, 70%).

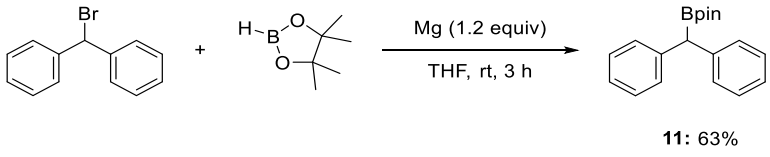
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.47 (m, 4H), 7.46 – 7.36 (m, 2H), 7.36 – 7.14 (m, 8H), 6.44 – 6.21 (m, 1H), 5.24 (d, *J* = 9.2 Hz, 1H), 5.03 (d, *J* = 17.0 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 142.5, 141.0, 140.6, 139.4, 129.1, 128.9, 128.7, 128.6, 127.3, 127.2, 126.6, 116.6, 54.8.

IR (KBr): 3082, 3058, 3028, 2977, 2885, 1636, 1600, 1489, 1449, 1407, 1269, 1072, 1008, 994, 917, 849, 762, 697 cm^{-1}.

HRMS (EI) $[C_{21}H_{18}]$ $[M]^+$ calculated: 270.1409, found: 270.1412.

2-Benzhydryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11)



The synthetic procedure of **11** was followed by the reported procedures.[139]

[138] N. Hussain, G. Frensch, J. Zhang, P. J. Walsh, Chemo- and Regioselective C(sp3)□H Arylation of Unactivated Allylarenes by Deprotonative Cross-Coupling, *Angew. Chem. Int. Ed.* **2014**, *53*, 3693–3697.

An oven-dried flask was charged with magnesium turnings (290 mg, 12 mmol), which was activated by addition of iodine crystals and warming until iodine sublimed. The flask was cooled to room temperature and was protected by Ar balloon. Dry THF (25 mL) was added to the flask, followed by the addition of neat pinacolborane (1.2 mL, 12 mmol). bromodiphenylmethane (2.46 g, 10 mmol) diluted in dry THF (5 mL) was then added dropwise over 10 min at room temperature. After stirring for 3 h, the reaction mixture was cooled to 0 °C and acidified with aqueous HCl (15 mL, 3 N) (**Caution!** H_2 gas evolution). After stirring for 10 min, the reaction mixture was warmed to room temperature and keep stirring for an additional 30 min. The reaction mixture was then extracted with diethyl ether, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Then the obtained residue was purified over silica gel flash column chromatography (*n*-hexane/EtOAc: 40/1) to give the titled compound as a white solid (1.06 g, 63%).

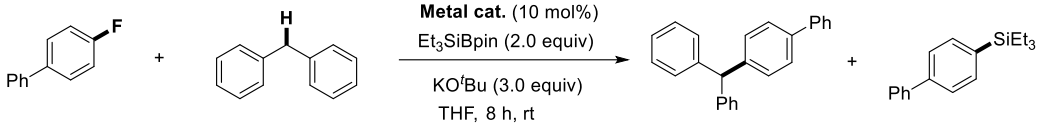
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.10 (m, 10H), 3.87 (s, 1H), 1.23 (s, 12H).

MS(EI): *m*/*z* 294 $[M]^+$.

The chemical shifts were consistent with previous reported data.[140]

3.2 Optimization Studies

Table S1. Screening for proper metal catalysts[a]



1a **4a** **5a** **3a**

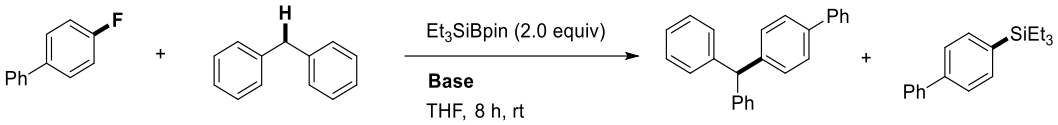
Entry	**4a** (equiv)	**Metal Cat.**	Yield of 5**a**[b]	**3a**
1	2.0	$Ni(COD)_2$	37%	+
2	2.0	$NiBr_2$·Diglyme	24%	+
3	2.0	$NiCl_2(PPh_3)_2$	33%	+
4	2.0	CuI	41%	+
5	2.0	$CoCl_2$	38%	+
6	**2.0**	**--**	**47%**	+

[a] Reactions were attempted under indicated reagents and conditions: **1a** (17.2 mg, 0.1 mmol), **4a** (33.6 mg, 0.2 mmol), metal catalyst (10 mol%), $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO^{t}Bu (33.6 mg, 0.3 mmol) in dry THF (1.0 mL) were reacted at room temperature for 8 h. [b] Determined by ^{19}F NMR and ^1H NMR spectroscopy using 3-fluoropyridine as an internal standard.

Table S2. Screening for proper base[a]

[139] J. W. Clary, T. J. Rettenmaier, R. Snelling, W. Bryks, J. Banwell, W. T. Wipke, B. Singaram, Hydride as a Leaving Group in the Reaction of Pinacolborane with Halides under Ambient Grignard and Barbier Conditions. One-Pot Synthesis of Alkyl, Aryl, Heteroaryl, Vinyl, and Allyl Pinacolboronic Esters, *J. Org. Chem.*, **2011**, *76*, 9602–9610.

[140] S. Roesner, C. A. Brown, M. Mohiti, A. P. Pulis, R. Rasappan, D. J. Blair, S. Essafi, D. Leonori, V. K. Aggarwal, Stereospecific conversion of alcohols into pinacol boronic esters using lithiation–borylation methodology with pinacolborane, *Chem. Commun.* **2014**, *50*, 4053–4055.

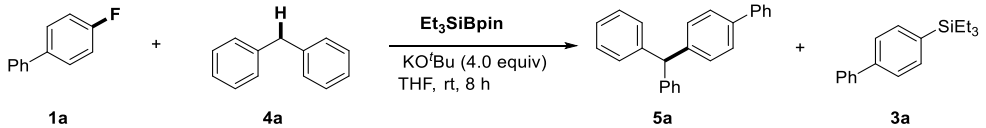


1a **4a** **5a** **3a**

Entry	**4a** (equiv)	Base (equiv)	Yield of 5**a**[b]	**3a**
1	2.0	KO^{t}Bu (3.0)	47%	+
2	2.0	K_2CO_3 (3.0)	--	--
3	2.0	NaO^{t}Bu (3.0)	28%	+
4	2.0	KHMDS (3.0)	30%	+
5	2.0	Cs_2CO_3 (3.0)	--	--
6	**2.0**	**KO^{t}Bu (4.0)**	**49%**	+
7	2.0	--	--	--

[a] Reactions were attempted under indicated reagents and conditions: **1a** (17.2 mg, 0.1 mmol), **4a** (33.6 mg, 0.2 mmol), $Et_3SiBpin$ (48.4 mg, 0.2 mmol), base in dry THF (1.0 mL) were reacted at room temperature for 8 h. [b] Determined by ^{19}F NMR and ^1H NMR spectroscopy using 3-fluoropyridine as an internal standard.

Table S3. Screening for the equivalent of $Et_3SiBpin$[a]

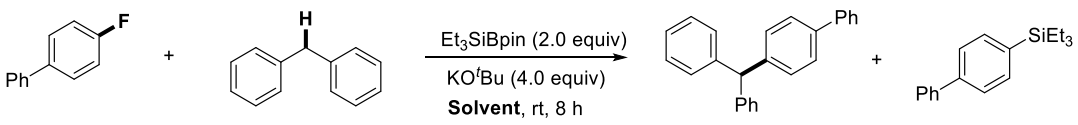


1a **4a** **5a** **3a**

Entry	**4a** (equiv)	**Et$_3$SiBpin** (equiv)	Yield of 5**a**[b]	**3a**
1	2.0	1.0	14%	+
2	2.0	2.0	49%	+
3	2.0	3.0	76%	+
4	2.0	--	--	--

[a] Reactions were attempted under indicated reagents and conditions: **1a** (17.2 mg, 0.1 mmol), **3a** (33.6 mg, 0.2 mmol), $Et_3SiBpin$, KO^{t}Bu (45 mg, 0.4 mmol) in dry THF (1.0 mL) were reacted at room temperature for 8 h. [b] Determined by ^{19}F NMR and ^1H NMR spectroscopy using 3-fluoropyridine as an internal standard.

Table S4. Screening for suitable solvent[a]



1a **4a** **5a** **3a**

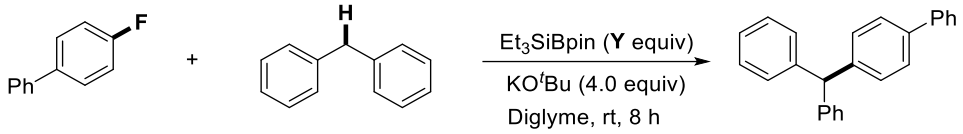
Entry	**4a** (equiv)	**solvent**	Yield of 5**a**[b]	**3a**
1	2.0	Cyclohexane/THF (8/1, *v/v*)	34%	+

2	2.0	Cyclohexane	9%	+
3	2.0	Toluene	11%	+
4	2.0	Dioxane	trace	+
5	2.0	DME	36%	+
6	2.0	CPME	18%	+
7	2.0	MTBE	12%	+
8	2.0	DTBT	trace	+
9	**2.0**	**diglyme**	**95%**	**--**
10	2.0	triglyme	64%	--

[a] Reactions were attempted under indicated reagents and conditions: **1a** (17.2 mg, 0.1 mmol), **4a** (33.6 mg, 0.2 mmol), $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO^{t}Bu (45 mg, 0.4 mmol) in corresponding solvent (1.0 mL) were reacted at room temperature for 8 h.

[b] Determined by ^{19}F NMR and ^1H NMR spectroscopy using 3-fluoropyridine as an internal standard.

Table S5. Screening for proper combination of diphenylmethane and $Et_3SiBpin$[a]



1a **4a** (**X** equiv) **5a**

Entry	**4a** (**X** equiv)	**$Et_3SiBpin$** (**Y** equiv)	Yield of **5a**[b]
1	2.0	2.0	95%
2	1.5	2.0	91%
3	1.2	2.0	83%
4	1.5	3.0	95%
5[c]	2.0	2.0	96%(93%)

[a] Reactions were attempted under indicated reagents and conditions: **1a** (17.2 mg, 0.1 mmol), **4a**, $Et_3SiBpin$, KO^{t}Bu (45 mg, 0.4 mmol) in dry diglyme (1.0 mL) were reacted at room temperature for 8 h. [b] Determined by ^{19}F NMR and ^1H NMR spectroscopy using 3-fluoropyridine as an internal standard. The number in parentheses referred to the isolated yield. [c] 0.2 mmol scale were performed.

3.3 General Procedures for the Cross-Coupling Reaction of Aryl Fluorides and Arylalkanes

3.3.1 General procedure for the optimization of cross-coupling reaction

General procedure C: In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added 4-fluorobiphenyl **1a** (17.2 mg, 0.1 mmol, 1.0 equiv), silyl boronates, metal catalysts (10 mol %) or without metal catalysts, diphenylmethane **4a**, base and solvent (1.0 mL) sequentially. The tube then was sealed and removed from the glovebox. The solution was stirred at room temperature for 8 h. The reaction was diluted with Et_2O (5 mL), quenched with H_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After

NMR analysis. The mixture was then concentrated again to give the crude, which was purified by column chromatography on silica gel to give the 4-benzhydrylbiphenyl **5a**.

3.3.2 General procedure for the cross-coupling reaction of aryl fluorides and benzylic C–H bonds

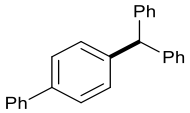
General procedure D: In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added aryl fluorides **1** (0.2 mmol, 1.0 equiv), silyl boronates $Et_3SiBpin$ (0.4 mmol, 2.0 equiv), arylalkanes **4** (0.4 mmol, 2.0 equiv), KO*t*Bu (89.6 mg, 0.8 mmol, 4.0 equiv) and dry diglyme (2.0 mL) sequentially. The tube then was sealed and removed from the glovebox. The solution was stirred at room temperature for 8 h. The reaction was diluted with Et_2O (5 mL), quenched with H_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After NMR analysis was conducted. The mixture was then concentrated again to give the crude, which was purified by column chromatography on silica gel to give the corresponding triarylalkanes or diarylalkanes **5**.

3.3.3 General procedure for the scale-up reaction

General procedure E: In a N_2 filled glovebox, to a flame-dried flask was added 4-fluorobiphenyl **1a** (0.688 g, 4.0 mmol, 1.0 equiv), KOtBu (1.80 g, 16.0 mmol, 4.0 equiv), dry diglyme (40 mL), and diphenylmethane **4a** (1.33 mL, 8.0 mmol, 2.0 equiv), sequentially. Then a solution of $Et_3SiBpin$ (1.94 g, 8.0 mmol, 2.0 equiv) in 5.0 mL dry diglyme was added to the flask slowly over 30 minutes after the flask was sealed and moved out from the glovebox. The solution was stirred at room temperature for 8 h. The reaction mixture was diluted with Et_2O (100.0 mL), quenched with saturated NH_4Cl solution, then extracted with Et_2O, washed with water and brine, dried over Na_2SO_4, then concentrated under vacuum to give the crude, which was purified by column chromatography on silica gel to give the corresponding triarylmethane **5a** (1.09 g, 85% yield).

3.4 Characterization Data of Cross-Coupling Products

4-Benzhydrylbiphenyl (5a)



Compound **5a** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (59.5 mg, yield: 93%).

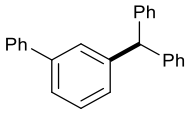
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.49 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.00 (m, 13H), 5.61 (s, 1H).

MS(EI): *m/z* 320 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[141]

3-Benzhydrylbiphenyl (5b)

[141] Z. Zhang, H. Wang, N. Qiu, Y. Kong, W. Zeng, Y. Zhang, J. Zhao, Synthesis of Triarylmethanes via Palladium-Catalyzed Suzuki Coupling of Trimethylammonium Salts and Arylboronic Acids, *J. Org. Chem.* **2018**, *83*, 8710–8715.



Compound **5b** was prepared according to the general procedure **D** start from 3-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (57.0 mg, yield: 89%).

m.p. = 79.1 – 79.9 ℃.

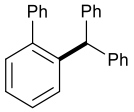
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.51 – 7.46 (m, 1H), 7.46 – 7.35 (m, 4H), 7.37 – 7.29 (m, 5H), 7.29 – 7.22 (m, 2H), 7.23 – 7.17 (m, 4H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.65 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 143.9, 141.33, 141.28, 129.6, 128.9, 128.8, 128.6, 128.49, 128.47, 127.4, 127.3, 126.5, 125.3, 57.1.

IR (KBr): 3056, 3027, 1597, 1495, 1449, 1077, 1030, 796, 756, 698, 607 cm^{-1}.

HRMS (EI) [$C_{25}H_{20}$] $[M]^+$ calculated: 320.1565, found: 320.1577.

2-Benzhydrylbiphenyl (5c)



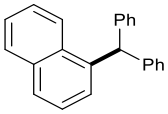
Compound **5c** was prepared according to the general procedure **D** start from 2-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (29.4 mg, yield: 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 12H), 7.21 – 7.11 (m, 3H), 7.08 – 6.96 (m, 4H), 5.62 (s, 1H).

MS(EI): *m/z* 320 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[142]

1-Benzhydrylnaphthalene (5d)



Compound **5d** was prepared according to the general procedure **D** start from 1-fluoronaphthalene (26.0 μL, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (44.1 mg, yield: 75%).

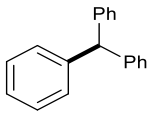
[142] J. Yu, and R. Kuwano, Suzuki-Miyaura Coupling of Diarylmethyl Carbonates with Arylboronic Acids: A New Access to Triarylmethanes, *Org. Lett.* **2008**, *10*, 973–976.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.90 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.41 – 7.24 (m, 7H), 7.21 – 7.11 (m, 4H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.33 (s, 1H).

MS(EI): *m/z* 274 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[60]

Triphenylmethane (5e)



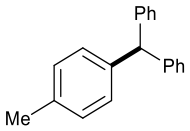
Compound **5e** was prepared according to the general procedure **D** start from fluorobenzene (38.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (69.1 mg, yield: 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 6.95 (m, 15H), 5.59 (s, 1H).

MS(EI): *m/z* 244 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[143]

1-Benzhydryl-4-methylbenzene (5f)



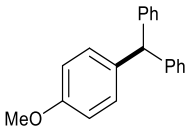
Compound **5f** was prepared according to the general procedure **D** start from 4-fluorotoluene (44.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (64.5 mg, yield: 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 6H), 7.20 – 7.08 (m, 6H), 7.08 – 7.00 (m, 2H), 5.55 (s, 1H), 2.35 (s, 3H).

MS(EI): *m/z* 258 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[144]

4-Benzhydrylanisole (5g)



[143] S. Podder, S. Roy, Efficient and selective alkylation of arenes and heteroarenes with benzyl and allyl ethers using a Ir/Sn bimetallic catalyst, *Tetrahedron* **2007**, *63*, 9146–9152.
[144] G. Pallikonda, M. Chakravarty, Benzylic Phosphates in Friedel–Crafts Reactions with Activated and Unactivated Arenes: Access to Polyarylated Alkanes, *J. Org. Chem.*, **2016**, *81*, 2135–2142.

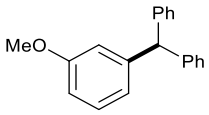
Compound **5g** was prepared according to the general procedure **D** start from 4-fluoroanisole (45.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (46.5 mg, yield: 42%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 4H), 7.27 (dd, *J* = 6.9, 2.0 Hz, 2H), 7.20 – 7.14 (m, 4H), 7.12 – 7.03 (m, 2H), 6.88 (dd, *J* = 8.7, 2.0 Hz, 2H), 5.56 (s, 1H), 3.82 (s, 3H).

MS(EI): *m/z* 274 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[145]

3-Benzhydrylanisole (5h)



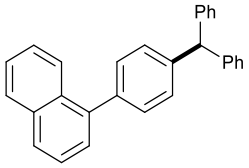
Compound **5h** was prepared according to the general procedure **D** start from 3-fluoroanisole (45.5 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 6/1) as a white solid (50.4 mg, yield: 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 4H), 7.28 – 7.16 (m, 3H), 7.19 – 7.09 (m, 4H), 6.82 – 6.65 (m, 3H), 5.53 (s, 1H), 3.75 (s, 3H).

MS(EI): *m/z* 274 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[145]

1-(4-Benzhydrylphenyl)naphthalene (5i)



Compound **5i** was prepared according to the general procedure **D** start from 1-(4-fluorophenyl)naphthalene (44.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 8/1) as a white solid (42.3 mg, yield: 57%).

m.p. = 148.0 – 149.3 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.94 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.50 – 7.44 (m, 4H), 7.42 – 7.35 (m, 4H), 7.33 – 7.25 (m, 8H), 5.70 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 143.0, 140.1, 138.8, 133.9, 131.7, 130.1, 129.6, 129.4, 128.5, 128.4,

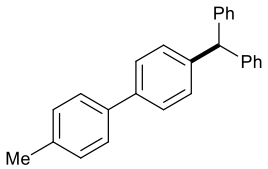
[145] J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, Palladium-Catalyzed C(sp3)–H Arylation of Diarylmethanes at Room Temperature: Synthesis of Triarylmethanes via Deprotonative-Cross-Coupling Processes, *J. Am. Chem. Soc.*, **2012**, *134*, 13765–13772.

127.7, 127.1, 126.5, 126.2, 126.1, 125.9, 125.5, 56.8.

IR (KBr): 3057, 3026, 1599, 1496, 1450, 1395, 1109, 1033, 964, 842, 798, 781, 754, 703, 614 cm^{-1}.

HRMS (EI) [$C_{29}H_{22}$] $[M]^+$ calculated: 370.1722, found: 370.1714.

4-Benzhydryl-4'-methylbiphenyl (5j)



Compound **5j** was prepared according to the general procedure **D** start from 4'-fluoro-4-methylbiphenyl (37.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (48.9 mg, yield: 73%).

m.p. = 122.1 – 123.3 ℃.

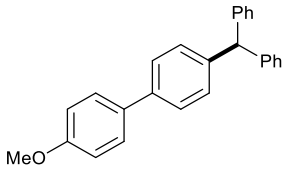
^{1}H NMR (500 MHz, $CDCl_3$) δ7.52 – 7.45 (m, 4H), 7.29 (dd, *J* = 8.1, 6.8 Hz, 4H), 7.24 – 7.19 (m, 4H), 7.18 – 7.13 (m, 6H), 5.58 (s, 1H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 142.8, 139.2, 138.1, 137.0, 129.9, 129.6, 128.5, 127.0, 126.95, 126.5, 56.7, 21.2.

IR (KBr): 3026, 2916, 1606, 1597, 1492, 1445, 1399, 1254, 1130, 1032, 800, 741, 702, 606 cm^{-1}.

HRMS (EI) [$C_{26}H_{22}$] $[M]^+$ calculated: 334.1722, found: 334.1732.

4-Benzhydryl-4'-methoxybiphenyl (5k)



Compound **5k** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 8/1) as a white solid (47.6 mg, yield: 68%).

m.p. = 112.4 – 114.1 ℃.

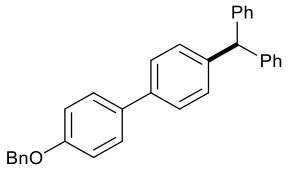
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 4H), 7.16 – 7.09 (m, 2H), 7.10 – 7.04 (m, 6H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.48 (s, 1H), 3.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 144.0, 142.5, 138.9, 133.5, 129.9, 129.6, 128.5, 128.1, 126.7, 126.5, 114.3, 56.6, 55.4.

IR (KBr): 3056, 3024, 2839, 1606, 1497, 1447, 1274, 1250, 1180, 1036, 826, 806, 757, 743, 700, 605 cm^{-1}.

HRMS (EI) [$C_{26}H_{22}O$] $[M]^+$ calculated: 350.1671, found: 350.1661.

4-Benzhydryl-4'-(benzyloxy)-biphenyl (5l)



Compound **5l** was prepared according to the general procedure **D** start from 4-(benzyloxy)-4'-fluorobiphenyl (55.6 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 6/1) as a white solid (34.1 mg, yield: 40%).

m.p. = 143.7 – 144.5 ℃.

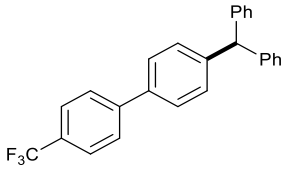
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.54 – 7.48 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.32 (m, 5H), 7.28 (d, *J* = 6.1 Hz, 2H), 7.24 – 7.18 (m, 6H), 7.08 (d, *J* = 8.8 Hz, 2H), 5.63 (s, 1H), 5.15 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 144.0, 142.6, 138.9, 137.1, 133.8, 129.9, 129.6, 128.8, 128.5, 128.2, 128.1, 127.6, 126.7, 126.5, 115.2, 70.2, 56.6.

IR (KBr): 3060, 3028, 2881, 1606, 1497, 1450, 1384, 1273, 1250, 1176, 1042, 843, 807, 762, 743, 713, 606 cm^{-1}.

HRMS (EI) [$C_{32}H_{26}O$] $[M]^+$ calculated: 426.1984, found: 426.1971.

4-Benzhydryl-4'-(trifluoromethyl)biphenyl (5m)



Compound **5m** was prepared according to the general procedure **D** start from 4-fluoro-4'-(trifluoromethyl)biphenyl (38.0 μL, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a light-yellow oil (34.9 mg, yield: 45%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 4H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.27 (m, 4H), 7.28 – 7.18 (m, 4H), 7.15 (d, *J* = 7.2 Hz, 4H), 5.60 (s, 1H).

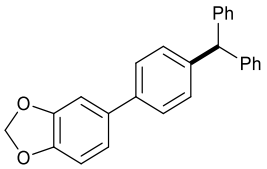
^{13}C NMR (176 MHz, $CDCl_3$) δ 144.5, 144.3, 143.7, 137.8, 130.2, 129.6, 128.6, 127.4, 127.3, 126.6, 125.8 (q, *J* = 3.9 Hz), 124.5 (q, *J* = 271.7 Hz), 56.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.88 (s, 3F).

IR (KBr): 3056, 2974, 2912, 1617, 1495, 1326, 1166, 1126, 1071, 1007, 835, 700 cm^{-1}.

HRMS (EI) [$C_{26}H_{19}F_3$] $[M]^+$ calculated: 388.1439, found: 388.1474.

5-(4-Benzhydrylphenyl)benzo[*d*][1,3]dioxole (5n)



Compound **5n** was prepared according to the general procedure **D** start from 5-(4-fluorophenyl)benzo[*d*][1,3]dioxole (43.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (34.3 mg, yield: 47%).

m.p. = 127.4 – 128.2 ℃.

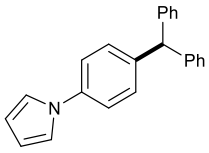
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.29 (m, 4H), 7.26 – 7.22 (m, 2H), 7.18 – 7.15 (m, 6H), 7.08 – 7.04 (m, 2H), 6.87 (d, *J* = 7.9 Hz, 1H), 5.99 (s, 2H), 5.59 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 147.1, 144.0, 142.8, 139.0, 135.4, 129.9, 129.6, 128.5, 126.9, 126.5, 120.6, 108.7, 107.7, 101.2, 56.6.

IR (KBr): 3056, 3026, 2877, 1599, 1501, 1481, 1341, 1265, 1225, 1040, 800, 738, 701, 625 cm^{-1}.

HRMS (EI) [$C_{26}H_{20}O_2$] $[M]^+$ calculated: 364.1463, found: 364.1474.

1-(4-Benzhydrylphenyl)-1*H*-pyrrole (5o)



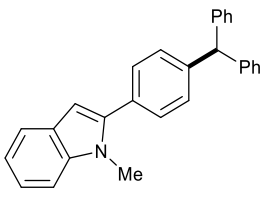
Compound **5o** was prepared according to the general procedure **D** start from 1-(4-fluorophenyl)-1*H*-pyrrole (32.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (53.2 mg, yield: 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 6H), 7.30 – 7.26 (m, 2H), 7.23 – 7.14 (m, 6H), 7.10 (t, *J* = 2.2 Hz, 2H), 6.37 (t, *J* = 2.2 Hz, 2H), 5.61 (s, 1H).

MS(EI): *m/z* 309 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[60]

2-(4-Benzhydrylphenyl)-1-methyl-1*H*-indole (5p)



Compound **5p** was prepared according to the general procedure **D** start from 2-(4-fluorophenyl)-1-methyl-1*H*-indole (45.0 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 8/1) as a white solid (54.5 mg, yield: 73%).

m.p. = 168.3 – 169.4 ℃.

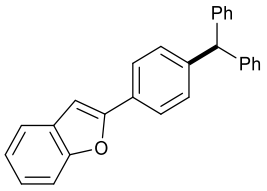
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.41 – 7.31 (m, 5H), 7.31 – 7.22 (m, 5H), 7.24 – 7.18 (m, 4H), 7.20 – 7.13 (m, 1H), 6.58 (d, *J* = 0.9 Hz, 1H), 5.64 (s, 1H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 143.78, 141.5, 138.5, 130.9, 129.7, 129.6, 129.4, 128.6, 128.1, 126.6, 121.7, 120.6, 120.0, 109.7, 101.7, 56.8, 31.4.

IR (KBr): 3057, 3023, 2935, 1599, 1493, 1465, 1432, 1337, 1316, 1110, 1032, 842, 777, 749, 702 cm^{-1}.

HRMS (EI) $[C_{28}H_{23}N]$ $[M]^+$ calculated: 373.1830, found: 373.1841.

2-(4-Benzhydrylphenyl)benzofuran (5q)



Compound **5q** was prepared according to the general procedure **D** start from 2-(4-fluorophenyl)benzofuran (42.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (28.2 mg, yield: 39%).

m.p. = 147.7 – 148.7 ºC.

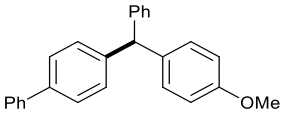
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.28 – 7.20 (m, 6H), 7.16 (d, *J* = 7.6 Hz, 4H), 6.99 (s, 1H), 5.60 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 155.0, 144.7, 143.7, 130.0, 129.6, 129.4, 128.7, 128.6, 126.6, 125.1, 124.3, 123.0, 121.0, 111.3, 101.2, 56.8.

IR (KBr): 3080, 3024, 2854, 1598, 1493, 1452, 1257, 1172, 1033, 796, 738, 699, 603 cm^{-1}.

HRMS (EI) $[C_{27}H_{20}O]$ $[M]^+$ calculated: 360.1514, found: 360.1516.

4-((4-Methoxyphenyl)(phenyl)methyl)biphenyl (5r)



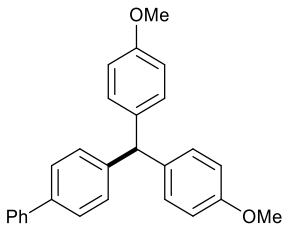
Compound **5r** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 6/1) as a white solid (53.9 mg, yield: 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 18.9, 7.6 Hz, 4H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.40 – 7.02 (m, 10H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.59 (s, 1H), 3.82 (s, 3H).

MS(EI): *m/z* 350 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[146]

4-(Bis(4-methoxyphenyl)methyl)biphenyl (5s)



Compound **5s** prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (39.6 mg, yield: 52%).

m.p. = 108.4 – 110.3 ℃.

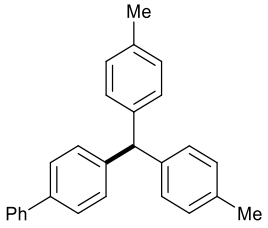
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.48 – 7.42 (m, 2H), 7.39 – 7.32 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.14 – 7.05 (m, 4H), 6.92 – 6.83 (m, 4H), 5.52 (s, 1H), 3.81 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 143.9, 141.0, 139.1, 136.5, 130.4, 129.8, 128.8, 127.2, 127.1, 127.1, 113.8, 55.4, 55.0.

IR (KBr): 3056, 3028, 2834, 1607, 1582, 1505, 1487, 1303, 1241, 1175, 1031, 824, 806, 739, 698, 580 cm^{-1}.

HRMS (EI) $[C_{27}H_{24}O_2]$ $[M]^+$ calculated: 380.1776, found: 380.1759.

4-(Di-*p*-tolylmethyl)biphenyl (5t)



Compound **5t** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (49.4 mg, yield: 71%).

[146] M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, Retention or Inversion in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst, *J. Am. Chem. Soc.* **2013**, *135*, 3303–3306.

m.p. = 117.3 – 118.5 ℃.

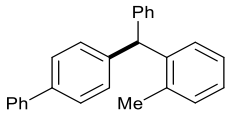
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.56 – 7.50 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.31 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 4H), 7.07 (d, *J* = 8.2 Hz, 4H), 5.54 (s, 1H), 2.36 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 141.2, 141.1, 139.1, 135.9, 129.9, 129.4, 129.2, 128.8, 127.2, 127.15, 127.1, 55.9, 21.2.

IR (KBr): 3049, 3026, 2918, 1599, 1510, 1487, 1447, 1021, 809, 755, 739, 697, 575 cm^{-1}.

HRMS (EI) $[C_{27}H_{24}]$ $[M]^+$ calculated: 348.1878, found: 348.1886.

4-(Phenyl(*o*-tolyl)methyl)biphenyl (5u)



Compound **5u** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (38.0 mg, yield: 57%).

m.p. = 112.8 – 114.2 ℃.

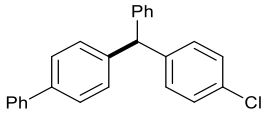
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.35 – 7.25 (m, 3H), 7.25 – 7.19 (m, 1H), 7.20 – 7.06 (m, 7H), 6.86 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.70 (s, 1H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 142.7, 142.4, 141.0, 139.2, 136.8, 130.6, 130.1, 129.8, 129.6, 128.9, 128.5, 127.3, 127.1, 126.6, 126.5, 125.9, 53.3, 20.1.

IR (KBr): 3059, 3026, 1599, 1487, 1450, 1380, 1289, 1076, 1029, 1009, 812, 760, 736, 655, 610 cm^{-1}.

HRMS (EI) $[C_{26}H_{22}]$ $[M]^+$ calculated: 334.1722, found: 334.1718.

4-((4-Chlorophenyl)(phenyl)methyl)biphenyl (5v)



Compound **5v** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (43.2 mg, yield: 61%).

m.p. = 98.9 – 100.3 ℃.

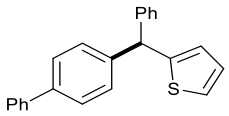
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.41 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.34 – 7.28 (m, 3H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.17 – 7.10 (m, 4H), 7.10 – 7.05 (m, 2H), 5.54 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 142.6, 142.5, 140.8, 139.5, 132.4, 130.9, 129.9, 129.5, 128.9, 128.6, 127.4, 127.3, 127.1, 126.7, 56.0.

IR (KBr): 3059, 3026, 1599, 1487, 1450, 1380, 1289, 1076, 1029, 1009, 812, 760, 736, 655, 610 cm^{-1}.

HRMS (EI) $[C_{25}H_{19}Cl]$ $[M]^+$ calculated: 354.1175, found: 354.1181.

2-(Biphenyl-4-yl(phenyl)methyl)thiophene (5w)



Compound **5w** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (54.5 mg, yield: 84%).

m.p. = 99.2 – 99.8 ℃.

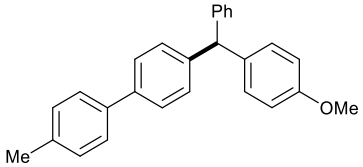
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.54 – 7.50 (m, 2H), 7.43 – 7.37 (m, 2H), 7.34 – 7.21 (m, 8H), 7.22 – 7.19 (m, 1H), 6.93 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.72 (dt, *J* = 3.5, 1.2 Hz, 1H), 5.71 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 143.9, 143.0, 140.9, 139.7, 129.3, 129.0, 128.9, 128.6, 127.3, 127.2, 127.2, 126.9, 126.8, 126.6, 124.7, 51.9.

IR (KBr): 3060, 3028, 1601, 1486, 1452, 1408, 1265, 1113, 846, 762, 740, 698, 623 cm^{-1}.

HRMS (EI) $[C_{23}H_{18}S]$ $[M]^+$ calculated: 326.1129, found: 326.1130.

4-((4-Methoxyphenyl)(phenyl)methyl)-4'-methylbiphenyl (5x)



Compound **5x** was prepared according to the general procedure **D** start from 4'-fluoro-4-methylbiphenyl (37.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a light-yellow oil (39.7 mg, yield: 55%).

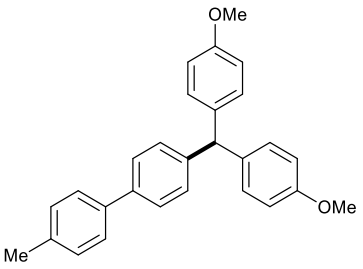
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 10.3, 7.9 Hz, 4H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 3H), 7.25 – 7.19 (m, 4H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.59 (s, 1H), 3.84 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 144.4, 143.2, 139.1, 138.1, 137.0, 136.2, 130.5, 129.8, 129.6, 129.5, 128.5, 127.0, 126.9, 126.4, 113.8, 55.8, 55.4, 21.2.

IR (KBr): 3051, 3025, 2835, 1608, 1581, 1505, 1450, 1302, 1244, 1176, 1031, 807, 739, 699, 583 cm^{-1}.

HRMS (EI) $[C_{27}H_{24}O]$ $[M]^+$ calculated: 364.1827, found: 364.1833.

4-(Bis(4-methoxyphenyl)methyl)-4'-methylbiphenyl (5y)



Compound **5y** was prepared according to the general procedure **D** start from 4'-fluoro-4-methylbiphenyl (37.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a light-yellow oil (51.1 mg, yield: 65%).

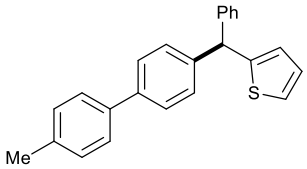
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 4H), 7.22 (d, *J* = 7.3 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 4H), 6.83 (d, *J* = 8.7 Hz, 4H), 5.48 (s, 1H), 3.78 (s, 6H), 2.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 143.5, 139.0, 138.1, 137.0, 136.5, 130.4, 129.8, 129.6, 127.0, 126.9, 113.8, 55.4, 55.0, 21.2.

IR (KBr): 3025, 2952, 2834, 1609, 1582, 1505, 1463, 1301, 1253, 1177, 1037, 809, 577 cm^{-1}.

HRMS (EI) $[C_{28}H_{26}O_2]$ $[M]^+$ calculated: 394.1933, found: 394.1939.

2-((4'-Methyl-biphenyl]-4-yl)(phenyl)methyl)thiophene (5z)



Compound **5z** was prepared according to the general procedure **D** start from 4'-fluoro-4-methylbiphenyl (37.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (50.2 mg, yield: 74%).

m.p. = 96.5 – 97.0 ℃.

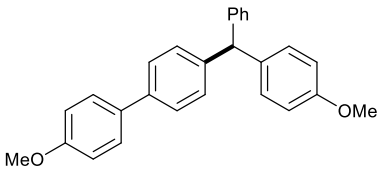
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.28 – 7.17 (m, 8H), 6.93 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.72 (dt, *J* = 3.5, 1.2 Hz, 1H), 5.70 (s, 1H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 143.9, 142.7, 139.6, 138.0, 137.1, 129.6, 129.3, 129.0, 128.6, 127.03, 127.0, 126.9, 126.7, 126.5, 124.7, 51.9, 21.2.

IR (KBr): 3056, 3025, 2918, 1599, 1496, 1451, 1264, 1229, 1006, 858, 808, 736, 700, 600 cm^{-1}.

HRMS (EI) $[C_{24}H_{20}S]$ $[M]^+$ calculated: 340.1286, found: 340.1300.

4-Methoxy-4'-((4-methoxyphenyl)(phenyl)methyl)biphenyl (5za)



Compound **5za** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a light yellow solid (50.1 mg, yield: 66%).

m.p. = 111.9 – 112.1 ºC.

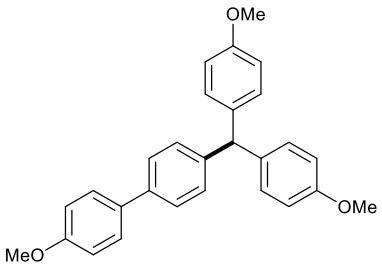
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 4H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 158.2, 144.4, 142.9, 138.8, 136.2, 133.6, 130.5, 130.0, 129.5, 128.4, 128.1, 126.7, 126.4, 114.3, 113.8, 55.8, 55.5, 55.4.

IR (KBr): 3084, 3028, 2928, 2873, 1609, 1510, 1464, 1251, 1207, 1178, 1038, 1000, 837, 698, 621 cm^{-1}.

HRMS (EI) $[C_{27}H_{24}O_2]$ $[M]^+$ calculated: 380.1776, found: 380.1783.

4-(Bis(4-methoxyphenyl)methyl)-4'-methoxybiphenyl (5zb)



Compound **5zb** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 4/1) as a light-yellow oil (70.2 mg, yield: 86%).

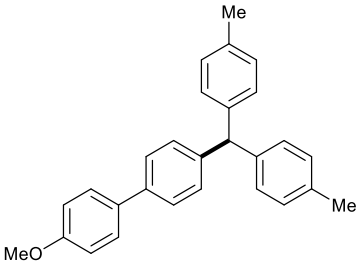
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.50 – 7.43 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.10 – 7.04 (m, 4H), 7.00 – 6.93 (m, 2H), 6.89 – 6.80 (m, 4H), 5.49 (s, 1H), 3.85 (s, 3H), 3.80 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.1, 143.2, 138.7, 136.6, 133.6, 130.4, 129.8, 128.1, 126.7, 114.3, 113.8, 55.5, 55.4, 55.0.

IR (KBr): 3068, 3026, 2834, 1614, 1506, 1259, 1179, 1112, 1040, 823, 774, 737 cm^{-1}.

HRMS (EI) $[C_{28}H_{26}O_3]$ $[M]^+$ calculated: 410.1882, found: 410.1897.

4-(Di-*p*-tolylmethyl)-4'-methoxybiphenyl (5zc)



Compound **5zc** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 6/1) as a light-yellow oil (58.7 mg, yield: 78%).

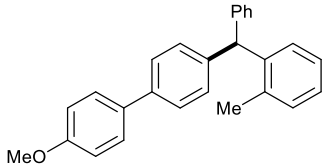
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 4H), 7.10 (d, *J* = 8.2 Hz, 4H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.56 (s, 1H), 3.88 (s, 3H), 2.38 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 142.9, 141.3, 138.7, 135.9, 133.6, 129.8, 129.4, 129.1, 128.1, 126.6, 114.3, 55.9, 55.4, 21.2.

IR (KBr): 3088, 3028, 3005, 2917, 2833, 1608, 1510, 1496, 1274, 1249, 1180, 1037, 1020, 838, 814, 776, 723 cm^{-1}.

HRMS (EI) $[C_{28}H_{26}O]$ $[M]^+$ calculated: 378.1984, found: 378.1991.

4-Methoxy-4'-(phenyl(*o*-tolyl)methyl)biphenyl (5zd)



Compound **5zd** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (24.0 mg, yield: 33%).

m.p. = 103.1 – 103.8 ℃.

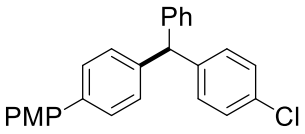
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.9 Hz, 2H), 7.50 – 7.46 (m, 2H), 7.31 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.21 – 7.16 (m, 2H), 7.16 – 7.09 (m, 5H), 7.01 – 6.95 (m, 2H), 6.89 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.72 (s, 1H), 3.85 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 143.5, 142.5, 143.0, 138.8, 136.8, 133.5, 130.6, 130.1, 129.7, 129.6, 128.5, 128.1, 126.7, 126.5, 126.4, 125.9, 114.3, 55.5, 53.3, 20.1.

IR (KBr): 3060, 3023, 2960, 2839, 1606, 1496, 1462, 1401, 1254, 1182, 1120, 1036, 814, 744, 700 cm^{-1}.

HRMS (EI) $[C_{27}H_{24}O]$ $[M]^+$ calculated: 364.1827, found: 364.1844.

4-((4-Chlorophenyl)(phenyl)methyl)-4'-methoxybiphenyl (5ze)



Compound **5ze** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 7/1) as a white solid (43.8 mg, yield: 57%).

m.p. = 82.6 – 83.6 ℃.

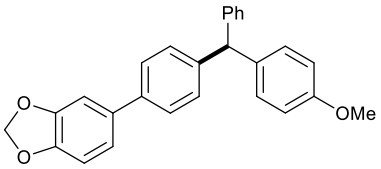
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.19 (m, 5H), 7.12 (d, *J* = 8.4 Hz, 4H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.52 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 143.5, 142.6, 141.9, 139.1, 133.4, 132.3, 130.9, 129.8, 129.5, 128.6, 128.1, 126.8, 126.7, 114.3, 56.0, 55.4.

IR (KBr): 3057, 2997, 2932, 2840, 1608, 1527, 1459, 1325, 1250, 1180, 1115, 1037, 838, 769, 701, 631 cm^{-1}.

HRMS (EI) [$C_{26}H_{21}ClO$] $[M]^+$ calculated: 384.1281, found: 384.1286.

5-(4-((4-Methoxyphenyl)(phenyl)methyl)phenyl)benzo[*d*][1,3]dioxole (5zf)



Compound **5zf** was prepared according to the general procedure **D** start from 5-(4-fluorophenyl)benzo[*d*][1,3]dioxole (43.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc = 20/1) as a light-yellow solid (53.6 mg, yield: 68%).

m.p. = 96.1 – 97.4 ℃.

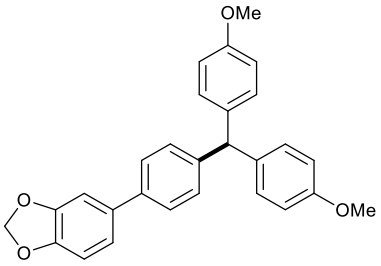
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.35 – 7.30 (m, 2H), 7.28 – 7.22 (m, 1H), 7.21 – 7.15 (m, 4H), 7.12 – 7.05 (m, 4H), 6.91 – 6.85 (m, 3H), 6.00 (s, 2H), 5.55 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 148.2, 147.1, 144.3, 143.2, 138.9, 136.1, 135.4, 130.5, 129.8, 129.5, 128.4, 126.8, 126.4, 120.6, 113.8, 108.7, 107.7, 101.2, 55.8, 55.3.

IR (KBr): 3027, 2952, 2907, 2835, 1610, 1481, 1414, 1250, 1111, 1040, 935, 842, 701, 568 cm^{-1}.

HRMS (EI) [$C_{27}H_{22}O_3$] $[M]^+$ calculated: 394.1569, found: 394.1581.

5-(4-(Bis(4-methoxyphenyl)methyl)phenyl)benzo[*d*][1,3]dioxole (5zg)



Compound **5zg** was prepared according to the general procedure **D** start from 5-(4-fluorophenyl)benzo[*d*][1,3]dioxole (43.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 4/1) as a light-yellow solid (47.5 mg, yield: 56%).

m.p. = 136.1 – 136.8 ℃.

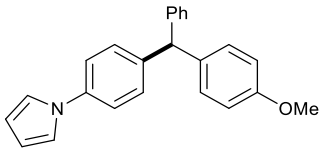
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.09 – 7.01 (m, 6H), 6.93 – 6.75 (m, 5H), 5.99 (s, 2H), 5.48 (s, 1H), 3.80 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 148.2, 147.0, 143.5, 138.8, 136.5, 135.4, 130.4, 129.8, 126.8, 120.6, 113.8, 108.7, 107.6, 101.2, 55.4, 54.9.

IR (KBr): 3008, 2967, 2932, 2892, 2834, 1609, 1509, 1481, 1438, 1293, 1245, 1175, 1028, 929, 802, 771 cm^{-1}.

HRMS (EI) $[C_{28}H_{24}O_4]$ $[M]^+$ calculated: 424.1765, found: 424.1761.

(4-((4-Methoxyphenyl)(phenyl)methyl)phenyl)-1*H*-pyrrole (5zh)



Compound **5zh** was prepared according to the general procedure **D** start from 1-(4-fluorophenyl)-1*H*-pyrrole (32.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc = 40/1) as a light-yellow oil (42.0 mg, yield: 62%).

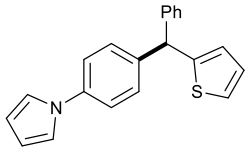
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.16 (m, 4H), 7.14 – 7.06 (m, 4H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.38 (t, *J* = 2.2 Hz, 2H), 5.57 (s, 1H), 3.84 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 144.1, 141.9, 139.1, 135.9, 130.5, 130.4, 129.4, 128.5, 126.5, 120.5, 119.4, 113.9, 110.4, 55.5, 55.4.

IR (KBr): 3058, 2905, 2833, 1611, 1510, 1483, 1330, 1248, 1176, 1070, 1035, 923, 823, 725, 572 cm^{-1}.

HRMS (EI) $[C_{24}H_{21}NO]$ $[M]^+$ calculated: 339.1623, found: 339.1635.

1-(4-(Phenyl(thiophen-2-yl)methyl)phenyl)-1*H*-pyrrole (5zi)



Compound **5zi** was prepared according to the general procedure **D** start from 1-(4-fluorophenyl)-1*H*-pyrrole (32.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 20/1) as a white solid (50.4 mg, yield: 80%).

m.p. = 90.1 – 90.9 ℃.

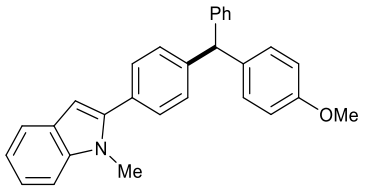
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 10H), 7.06 (s, 2H), 6.95 (t, *J* = 4.4 Hz, 1H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.33 (s, 2H), 5.69 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 143.6, 141.4, 139.5, 130.0, 128.9, 128.6, 127.0, 126.8, 126.6, 124.8, 120.5, 119.4, 110.5, 51.6.

IR (KBr): 3061, 2908, 2830, 1611, 1519, 1474, 1427, 1325, 1227, 1120, 1066, 1019, 923, 855, 794, 702, 617 cm^{-1}.

HRMS (EI) $[C_{21}H_{17}NS]$ $[M]^+$ calculated: 315.1082, found: 315.1082.

2-(4-((4-Methoxyphenyl)(phenyl)methyl)phenyl)-1-methyl-1*H*-indole (5zj)



Compound **5zj** was prepared according to the general procedure **D** start from 2-(4-fluorophenyl)-1-methyl-1*H*-indole (45.0 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (36.2 mg, yield: 45%).

m.p. = 157.9 – 159.2 ℃.

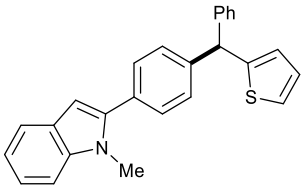
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.36 – 7.32 (m, 2H), 7.29 – 7.26 (m, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.19 (m, 2H), 7.19 – 7.15 (m, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.58 (s, 1H), 5.59 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 144.2, 144.1, 141.5, 138.5, 135.9, 130.8, 130.5, 129.6, 129.5, 129.3, 128.5, 128.1, 126.5, 121.7, 120.5, 119.9, 113.9, 109.7, 101.7, 56.0, 55.4, 31.4.

IR (KBr): 3058, 3023, 2908, 2836, 1610, 1509, 1464, 1317, 1250, 1111, 1036, 1005, 825, 742, 700, 620 cm^{-1}.

HRMS (EI) $[C_{29}H_{25}NO]$ $[M]^+$ calculated: 403.1936, found: 403.1939.

1-Methyl-2-(4-(phenyl(thiophen-2-yl)methyl)phenyl)-1*H*-indole (5zk)



Compound **5zk** was prepared according to the general procedure **D** start from 2-(4-fluorophenyl)-1-methyl-1*H*-indole (45.0 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (31.2 mg, yield: 41%).

m.p. = 138.0 – 139.4 ºC.

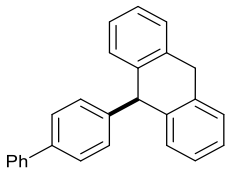
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.38 – 7.28 (m, 5H), 7.30 – 7.24 (m, 3H), 7.26 – 7.20 (m, 2H), 7.17 – 7.09 (m, 1H), 6.96 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.75 (dt, *J* = 3.5, 1.1 Hz, 1H), 6.55 (d, *J* = 0.9 Hz, 1H), 5.74 (s, 1H), 3.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 143.7, 141.4, 138.5, 131.3, 129.5, 129.1, 129.0, 128.7, 128.1, 127.0, 126.8, 126.6, 124.8, 121.8, 120.6, 120.0, 109.7, 101.8, 52.1, 31.4.

IR (KBr): 3058, 3025, 3026, 2867, 1600, 1545, 1491, 1467, 1315, 1131, 1100, 1006, 822, 750, 702, 639 cm^{-1}.

HRMS (EI) $[C_{26}H_{21}NS]$ $[M]^+$ calculated: 379.1395, found: 379.1403.

9-(Biphenyl-4-yl)-9,10-dihydroanthracene (5zl)



Compound **5zl** prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a light-yellow solid (50.2 mg, yield: 76%).

m.p. = 151.0 – 151.8 ℃.

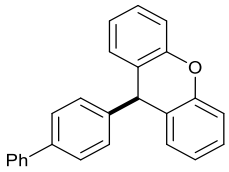
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.45 – 7.41 (m, 2H), 7.40 – 7.34 (m, 4H), 7.32 (dd, *J* = 5.2, 3.7 Hz, 2H), 7.31 – 7.26 (m, 1H), 7.25 – 7.20 (m, 4H), 7.13 (d, *J* = 8.2 Hz, 2H), 5.30 (s, 1H), 4.05 (d, *J* = 18.2 Hz, 1H), 3.92 (d, *J* = 18.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 141.0, 39.5, 139.3, 136.6, 128.8, 128.6, 128.5, 128.0, 127.3, 127.2, 127.1, 126.6, 26.6, 51.3, 35.8.

IR (KBr): 3073, 3025, 2889, 1604, 1512, 1484, 1448, 1405, 1318, 1122, 1073, 1040, 1009, 962, 841, 780, 761, 744, 718, 697, 624 cm^{-1}.

HRMS (EI) $[C_{26}H_{20}]$ $[M]^+$ calculated: 332.1565, found: 332.1576.

9-(Biphenyl-4-yl)-9*H*-xanthene (5zq)



Compound **5zq** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (51.1 mg, yield: 77%).

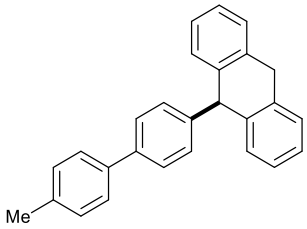
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.53 – 7.47 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.28 (m, 1H), 7.29 – 7.26 (m, 2H), 7.25 – 7.19 (m, 2H), 7.16 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.15 – 7.09 (m, 2H), 7.01 (td, *J* = 7.4, 1.4 Hz, 2H), 5.31 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 145.7, 140.9, 139.7, 129.9, 128.9, 128.1, 127.7, 127.3, 127.1, 124.5, 123.4, 116.8, 44.2.

MS(EI): *m/z* 334 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[147]

9-(4'-Methylbiphenyl-4-yl)-9,10-dihydroanthracene (5zm)



Compound **5zm** was prepared according to the general procedure **D** start from 4'-fluoro-4-methylbiphenyl (37.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (48.8 mg, yield: 71%).

m.p. = 137.3 – 138.1 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 4H), 7.37 – 7.28 (m, 4H), 7.24 – 7.15 (m, 6H), 7.11 (d, *J* = 8.3 Hz, 2H), 5.28 (s, 1H), 4.04 (d, *J* = 18.2 Hz, 1H), 3.91 (d, *J* = 18.2 Hz, 1H), 2.34 (s, 3H).

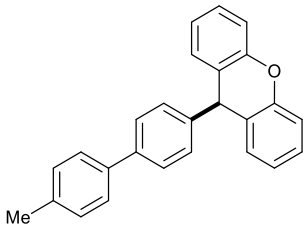
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 139.6, 139.2, 138.1, 137.0, 136.6, 129.6, 128.6, 128.5, 128.0, 127.1, 126.9, 126.6, 126.6, 51.3, 35.8, 21.2.

IR (KBr): 3022, 2963, 1606, 1497, 1452, 1373, 1265, 1148, 1004, 798, 748, 685, 599 cm^{-1}.

HRMS (EI) $[C_{27}H_{22}]$ $[M]^+$ calculated: 346.1722, found: 346.1725.

[147] S. Yang, W. Tang, Z. Yang, J. Xu, Iridium-Catalyzed Highly Efficient and Site-Selective Deoxygenation of Alcohols, *ACS Catal.* **2018**, *8*, 9320–9326.

9-(4'-Methyl-biphenyl-4-yl)-9*H*-xanthene (5zr)



Compound **5zr** was prepared according to the general procedure **D** start from 4'-fluoro-4-methylbiphenyl (37.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (59.0 mg, yield: 85%).

m.p. = 170.6 – 171.8 ℃.

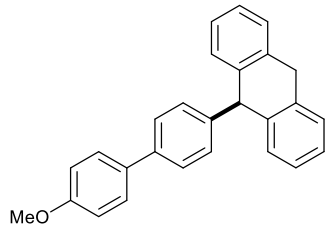
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.19 (m, 2H), 7.19 (dd, *J* = 7.3, 1.6 Hz, 4H), 7.13 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.09 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.97 (td, *J* = 7.4, 1.4 Hz, 2H), 5.27 (s, 1H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 145.3, 139.6, 138.0, 137.1, 129.9, 129.6, 128.8, 128.0, 127.4, 127.0, 124.5, 123.4, 116.7, 44.2, 21.2.

IR (KBr): 3060, 3029, 2916, 2854, 1600, 1573, 1481, 1450, 1397, 1321, 1257, 1119, 1096, 1036, 1006, 801, 751, 619 cm^{-1}.

HRMS (EI) [$C_{26}H_{20}O$] $[M]^+$ calculated: 348.1514, found: 348.1509.

9-(4'-Methoxybiphenyl-4-yl)-9,10-dihydroanthracene (5zn)



Compound **5zn** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 6/1) as a white solid (54.2 mg, yield: 75%).

m.p. = 177.1 – 178.7 ℃.

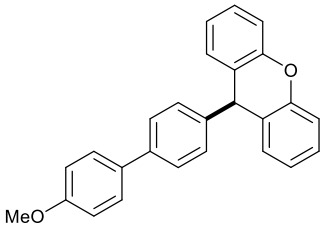
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.31 – 7.25 (m, 4H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 4.10 (d, *J* = 18.2 Hz, 1H), 3.97 (d, *J* = 18.3 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 142.1, 139.6, 138.9, 136.6, 133.5, 128.6, 128.5, 128.1, 128.0, 126.9, 126.6, 126.6, 114.3, 55.4, 51.3, 35.8.

IR (KBr): 3075, 3021, 2994, 2886, 1605, 1525, 1498, 1288, 1205, 1116, 1038, 1014, 800, 749, 686, 612 cm^{-1}.

HRMS (EI) $[C_{27}H_{22}O]$ $[M]^+$ calculated: 362.1671, found: 362.1685.

9-(4'-Methoxy-biphenyl-4-yl)-9*H*-xanthene (5zs)



Compound **5zs** was prepared according to the general procedure **D** start from 4-fluoro-4'-methoxybiphenyl (40.5 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (58.4 mg, yield: 80%).

m.p. = 161.7 – 163.2 ℃.

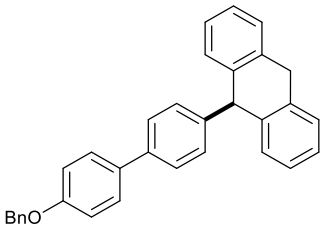
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.0 Hz, 4H), 7.20 (dd, *J* = 14.1, 6.9 Hz, 4H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 1H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 151.2, 145.0, 139.2, 133.4, 129.8, 128.8, 128.1, 128.0, 127.2, 124.5, 123.4, 116.7, 114.3, 55.4, 44.2.

IR (KBr): 3038, 2963, 2908, 2839, 1606, 1477, 1400, 1256, 1182, 1119, 1036, 936, 904, 835, 753, 684, 617 cm^{-1}.

HRMS (EI) $[C_{26}H_{20}O_2]$ $[M]^+$ calculated: 364.1463, found: 364.1462.

9-(4'-(Benzyloxy)-[1,1'-biphenyl]-4-yl)-9,10-dihydroanthracene (5zo)



Compound **5zo** was prepared according to the general procedure **D** start from 4-(benzyloxy)-4'-fluorobiphenyl (55.6 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 6/1) as a white solid (39.4 mg, yield: 45%).

m.p. = 168.7 – 169.8 ℃.

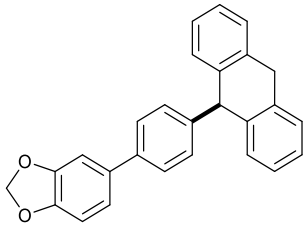
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 13H), 7.25 – 7.18 (m, 4H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 5.29 (s, 1H), 5.07 (s, 2H), 4.05 (d, *J* = 18.2 Hz, 1H), 3.91 (d, *J* = 18.3 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 158.4, 142.2, 139.6, 138.8, 137.1, 136.6, 133.8, 128.7, 128.6, 128.5, 128.1, 128.0, 127.6, 126.9, 126.6, 126.57, 115.2, 70.2, 51.3, 35.8.

IR (KBr): 3063, 3031, 2918, 2894, 1607, 1579, 1498, 1451, 1381, 1253, 1199, 1177, 1041, 1000, 799, 738, 694 cm^{-1}.

HRMS (EI) $[C_{33}H_{26}O]$ $[M]^+$ calculated: 438.1984, found: 438.1989.

5-(4-(9,10-Dihydroanthracen-9-yl)phenyl)benzo[*d*][1,3]dioxole (5zt)



Compound **5zt** was prepared according to the general procedure **D** start from 5-(4-fluorophenyl)benzo[*d*][1,3]dioxole (43.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (53.4 mg, yield: 71%).

m.p. = 127.8 – 129.2 ℃.

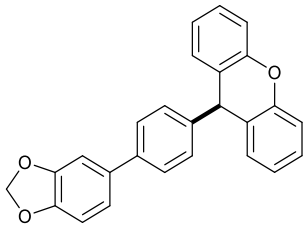
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 6H), 7.30 – 7.26 (m, 4H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.05 – 6.99 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.99 (s, 2H), 5.33 (s, 1H), 4.10 (d, *J* = 18.2 Hz, 1H), 3.97 (d, *J* = 18.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.1, 147.0, 142.5, 139.5, 138.9, 136.5, 135.3, 128.6, 128.5, 128.0, 127.0, 126.6, 126.5, 120.5, 108.6, 107.6, 101.2, 51.2, 35.8.

IR (KBr): 3079, 3011, 2909, 2822, 1611, 1460, 1345, 1253, 1153, 1121, 1036, 962, 938, 892, 837, 799, 756, 625 cm^{-1}.

HRMS (EI) $[C_{27}H_{20}O_2]$ $[M]^+$ calculated: 376.1463, found: 376.1459.

9-(4-(Benzo[*d*][1,3]dioxol-5-yl)phenyl)-9*H*-xanthene (5zp)



Compound **5zp** was prepared according to the general procedure **D** start from 5-(4-fluorophenyl)benzo[*d*][1,3]dioxole (43.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (55.6 mg, yield: 74%).

m.p. = 190.6 – 191.3 ℃.

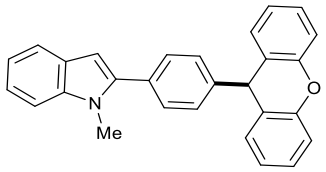
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.22 (m, 4H), 7.17 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.12 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.04 – 6.99 (m, 4H), 6.86 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 5.30 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 148.2, 147.1, 145.3, 139.4, 135.3, 129.8, 128.8, 128.1, 127.3, 124.5, 123.4, 120.6, 116.7, 108.7, 107.6, 101.2, 44.2.

IR (KBr): 3071, 3046, 1603, 1480, 1451, 1326, 1233, 1219, 1107, 1038, 935, 805, 748, 693 cm^{-1}.

HRMS (EI) $[C_{26}H_{18}O_3]$ $[M]^+$ calculated: 378.1256, found: 378.1267.

2-(4-(9*H*-Xanthen-9-yl)phenyl)-1-methyl-1*H*-indole (5zu)



Compound **5zu** was prepared according to the general procedure **D** start from 2-(4-fluorophenyl)-1-methyl-1*H*-indole (45.0 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc = 40/1) as a white solid (57.0 mg, yield: 74%).

m.p. = 130.4 – 131.8 ℃.

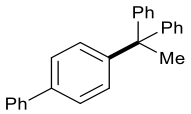
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.41 – 7.35 (m, 1H), 7.36 – 7.30 (m, 2H), 7.33 – 7.25 (m, 3H), 7.23 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.22 – 7.15 (m, 3H), 7.07 (td, *J* = 7.3, 1.4 Hz, 2H), 6.56 (d, *J* = 0.8 Hz, 1H), 5.36 (s, 1H), 3.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 146.3, 141.3, 138.5, 131.3, 129.82, 129.79, 128.4, 128.2, 128.0, 124.3, 123.5, 121.8, 120.5, 120.0, 116.8, 109.7, 101.7, 44.4, 31.3.

IR (KBr): 3060, 3034, 2946, 1600, 1573, 1480, 1448, 1413, 1316, 1256, 1163, 1095, 1007, 905, 860, 753, 736 cm^{-1}.

HRMS (EI) $[C_{28}H_{21}NO]$ $[M]^+$ calculated: 387.1623, found: 387.1617.

4-(1,1-Diphenylethyl)-biphenyl (5zv)



Compound **5zv** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (53.0 mg, yield: 79%).

m.p. = 109.9 – 110.7 ℃.

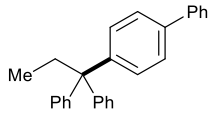
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 6.6 Hz, 2H), 7.56 – 7.45 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.38 – 7.16 (m, 7H), 7.22 – 7.09 (m, 6H), 2.22 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.3, 140.8, 138.8, 129.3, 128.9, 128.0, 127.3, 127.1, 126.6, 126.2, 52.5, 30.6.

IR (KBr): 3056, 3027, 2977, 1596, 1490, 1443, 1402, 1213, 1157, 1028, 1004, 860, 766, 733, 692, 624, 573 cm^{-1}.

HRMS (EI) $[C_{26}H_{22}]$ $[M]^+$ calculated: 334.1722, found: 334.1725.

4-(1,1-Diphenylpropyl)-biphenyl (5zw)



Compound **5zw** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as an orange oil (44.7 mg, yield: 64%).

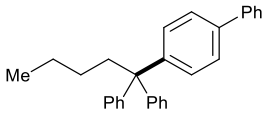
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.55 – 7.53 (m, 2H), 7.46 – 7.43 (m, 2H), 7.40 – 7.38 (m, 2H), 7.37 – 7.34 (m, 5H), 7.32 (t, *J* = 7.6 Hz, 4H), 7.24 – 7.20 (m, 2H), 2.71 (q, *J* = 7.3 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 147.4, 146.6, 140.9, 138.5, 129.8, 129.5, 128.8, 127.9, 127.2, 127.1, 126.5, 125.9, 56.9, 32.9, 10.6.

IR (KBr): 3086, 3056, 3027, 2975, 2935, 2879, 1599, 1487, 1445, 1008, 831, 761, 733, 700, 634 cm^{-1}.

HRMS (EI) $[C_{27}H_{24}]$ $[M]^+$ calculated: 348.1878, found: 348.1883.

4-(1,1-Diphenylpentyl)-biphenyl (5zx)



Compound **5zx** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as an orange oil (38.0 mg, yield: 51%).

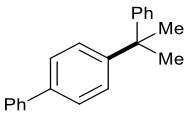
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.37 – 7.31 (m, 7H), 7.31 – 7.27 (m, 4H), 7.23 – 7.18 (m, 2H), 2.66 – 2.57 (m, 2H), 1.38 (h, *J* = 7.4 Hz, 2H), 1.15 – 1.08 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 147.7, 146.9, 140.9, 138.5, 129.8, 129.4, 128.8, 127.9, 127.2, 127.1, 126.5, 125.9, 56.5, 40.4, 28.0, 23.6, 14.2.

IR (KBr): 3085, 3057, 3030, 2955, 2871, 1599, 1487, 1469, 1444, 1007, 763, 731, 701, 635 cm^{-1}.

HRMS (EI) $[C_{29}H_{28}]$ $[M]^+$ calculated: 376.2191, found: 376.2202.

4-(2-Phenylpropan-2-yl)biphenyl (5zy)



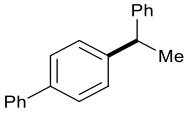
Compound **5zy** prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a clear oil (12.5 mg, yield: 23%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.37 – 7.28 (m, 7H), 7.24 – 7.17 (m, 1H), 1.74 (s, 6H).

MS(EI): *m/z* 272 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[148]

4-(1-Phenylethyl)-biphenyl (5zz)



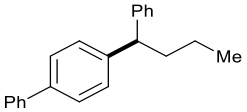
Compound **5zz** prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (13.0 mg, yield: 25%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.18 (m, 8H), 4.21 (q, *J* = 7.2 Hz, 1H), 1.69 (d, *J* = 7.2 Hz, 3H).

MS(EI): *m/z* 258 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[149]

4-(1-Phenylbutyl)biphenyl (5zza)



Compound **5zza** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a light-yellow oil (12.6 mg, yield: 22%).

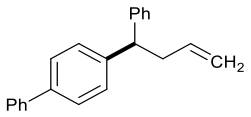
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.36 – 7.28 (m, 7H), 7.23 – 7.16 (m, 1H), 3.96 (t, *J* = 7.7 Hz, 1H), 2.06 (q, *J* = 7.7 Hz, 2H), 1.38 – 1.27 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

[148] K. B. Urkalan, M. S. Sigman, Palladium-Catalyzed Oxidative Intermolecular Difunctionalization of Terminal Alkenes with Organostannanes and Molecular Oxygen, *Angew. Chem. Int. Ed.* **2009**, *48*, 3146–3149.
[149] Y. He, Y. Cai, and S. Zhu, Mild and Regioselective Benzylic C–H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins, *J. Am. Chem. Soc.* **2017**, *139*, 1061–1064.

MS(EI): *m/z* 286 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[150]

4-(1-Phenylbut-3-en-1-yl)biphenyl (5zzb)



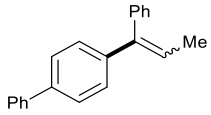
Compound **5zzb** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a light-yellow oil (11.4 mg, yield: 20%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.0 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.37 – 7.26 (m, 7H), 7.26 – 7.14 (m, 1H), 5.76 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.98 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.06 (t, *J* = 7.9 Hz, 1H), 2.86 (t, *J* = 7.9 Hz, 2H).

MS(EI): *m/z* 284 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[151]

1-(4'-Biphenyl)-1-phenyl propene (5zzc)



Compound **5zzc** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (18.3 mg, yield: 34%). ^{1}H NMR spectral copied below consist of two isomers ((*E*)-**5zzc**/(*Z*)-**5zzc** = 1.3/1), the ^{1}H NMR characterization data of the major isomer (*E*)-**5zzc** is:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.17 (m, 14H), 6.25 (q, *J* = 6.9 Hz, 1H), 1.78 (d, *J* = 7.1 Hz, 3H).

MS(EI): *m/z* 270 $[M]^+$.

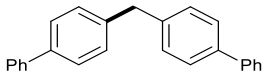
The chemical shifts were consistent with those reported in the literature.[152]

Di(biphenyl-4-yl)methane (5zzd)

[150] E. Grovenstein, J. A. Beres, Y. Cheng, J. A. Pegolotti, Carbanions. XI. Reactions of 4-chloro-1,1,1-triphenylbutane, 5-chloro-1,1,1-triphenylpentane, and 1,1,1-triphenylethane with alkali metals. 1,4 and 1,5 Migration of phenyl, *J. Org. Chem.*, **1972**, *37*, 1281–1292.

[151] Y. He, C. Liu, L. Yu, S. Zhu, Enantio- and Regioselective NiH-Catalyzed Reductive Hydroarylation of Vinylarenes with Aryl Iodides, *Angew. Chem. Int. Ed.* **2020**, *59*, 21530–21534.

[152] S. H. Shin, D. Cizmeciyan, A. E. Keating, S. I. Khan, M. A. Garcia-Garibay, Control of Carbene Reactivity by Crystals. A Highly Selective 1,2-H Shift in the Solid-to-Solid Reaction of 1-(4‘-Biphenylyl)-2-phenyldiazopropane to (Z)-1-(4‘-Biphenylyl)-2-phenylpropene, *J. Am. Chem. Soc.* **1997**, *119*, 1859–1868.



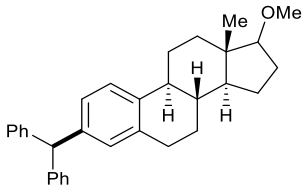
Compound **5zzd** was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane) as a colorless solid (9.7 mg, yield: 15%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.49 (m, 8H), 7.48 – 7.38 (m, 4H), 7.37 – 7.26 (m, 6H), 4.07 (s, 2H).

MS(EI): *m/z* 320 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[137]

(8*R*,9*S*,13*S*,14*S*)-3-Benzhydryl-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (5zze)



Compound **5zze** was prepared according to the general procedure **D** start from fluoro-estron derivative (57.6 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a colorless oil (52.5 mg, yield: 60%).

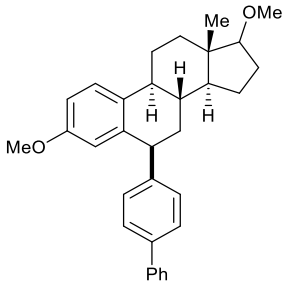
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 4H), 7.26 – 7.17 (m, 3H), 7.19 – 7.10 (m, 4H), 6.92 – 6.84 (m, 1H), 6.85 (s, 1H), 5.49 (s, 1H), 3.39 (s, 3H), 3.33 (t, *J* = 8.4 Hz, 1H), 2.87 – 2.72 (m, 2H), 2.32 – 2.27 (m, 1H), 2.26 – 2.21 (m, 1H), 2.13 – 2.02 (m, 2H), 1.92 – 1.82 (m, 1H), 1.76 – 1.64 (m, 1H), 1.58 – 1.49 (m, 1H), 1.49 – 1.43 (m, 1H), 1.46 – 1.36 (m, 1H), 1.41 – 1.28 (m, 2H), 1.24 – 1.18 (m, 1H), 0.90 (t, *J* = 7.1 Hz, 1H), 0.81 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 144.3, 144.2, 141.1, 138.4, 136.7, 130.0, 129.6, 128.4, 126.8, 126.3, 125.3, 90.9, 58.0, 56.6, 50.6, 44.4, 43.3, 38.4, 29.7, 27.9, 27.4, 26.3, 23.2, 11.7.

IR (KBr): 3060, 3024, 2927, 2866, 1599, 1494, 1449, 1248, 1133, 1108, 1077, 1031, 748, 700 cm^{-1}.

HRMS (ESI) $[C_{32}H_{36}ONa]$ $[M+Na]^+$ calculated: 459.2658, found: 459.2620.

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-([1,1'-Biphenyl]-4-yl)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (5zzf)



Compound **5zzf** was was prepared according to the general procedure **D** start from 4-fluorobiphenyl (34.4 mg, 0.2 mmol), and purified by silica gel column chromatography (toluene) as a colorless oil (24.0 mg, yield: 27%).

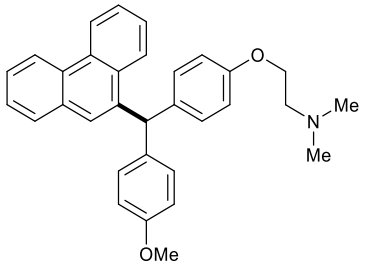
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.51 – 7.47 (m, 2H), 7.45 – 7.40 (m, 2H), 7.34 – 7.30 (m, 2H), 7.11 – 7.08 (m, 2H), 6.80 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.50 (dd, *J* = 2.7, 0.7 Hz, 1H), δ 4.27 (dd, *J* = 6.6, 2.6 Hz, 1H), 3.70 (s, 3H), 3.36 (s, 3H), 3.30 (t, *J* = 8.3 Hz, 1H), 2.39 – 2.34 (m, 1H), 2.28 – 2.21 (m, 1H), 2.10 – 2.05 (m, 1H), 2.04 – 1.96 (m, 1H), 1.93 – 1.88 (m, 1H), 1.88 – 1.81 (m, 1H), 1.69 – 1.58 (m, 2H), 1.57 – 1.51 (m, 1H), 1.47 – 1.38 (m, 2H), 1.25 – 1.17 (m, 1H), 1.12 – 1.04 (m, 1H), 0.72 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 157.7, 147.3, 141.1, 139.6, 138.6, 133.7, 129.3, 128.8, 127.2, 127.1, 126.9, 126.2, 115.4, 112.5, 90.9, 58.0, 55.3, 50.1, 44.3, 44.2, 43.6, 38.2, 36.0, 33.2, 27.8, 26.6, 23.0, 11.8.

IR (KBr): 3050, 3031, 2929, 2847, 1609, 1572, 1499, 1486, 1450, 1282, 1233, 1133, 1040, 847, 738, 697, cm^{-1}.

HRMS (ESI) $[C_{32}H_{36}O_2Na]$ $[M+Na]^+$ calculated: 475.2608, found: 475.2613.

2-(4-((4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenoxy)-*N*,*N*-dimethylethan-1-amine (5zzg)



Compound **5zzg** was prepared according to the general procedure **D** start from 9-fluorophenanthrene (39.3 mg, 0.2 mmol), and purified by silica gel column chromatography (EtOAc with 3% Et_3N) as a colorless oil (63.9 mg, yield: 68%).

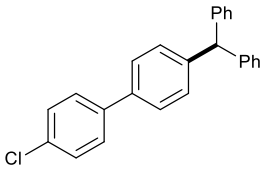
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.2 Hz, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.54 – 7.51 (m, 1H), 7.50 – 7.47 (m, 1H), 7.15 (s, 1H), 7.06 (t, *J* = 8.7 Hz, 4H), 6.91 – 6.76 (m, 4H), 6.15 (s, 1H), 4.04 (t, *J* = 5.7 Hz, 2H), 3.78 (s, 3H), 2.72 (d, *J* = 5.6 Hz, 2H), 2.33 (s, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 158.2, 157.5, 139.0, 136.1, 136.0, 131.6 131.3, 130.9, 130.7, 130.6, 129.9, 128.8, 128.5, 126.7, 126.6, 126.5, 126.2, 125.4, 123.1, 122.5, 114.5, 113.9, 66.0, 58.4, 55.3, 51.9, 46.0.

IR (KBr): 3063, 3029, 2941, 1608, 1507, 1463, 1254, 1176, 1119, 1037, 839, 771, 748 cm^{-1}.

HRMS (ESI) $[C_{32}H_{31}NNaO_2]$ $[M+Na]^+$ calculated: 484.2247, found: 484.2254.

4-Benzhydryl-4'-chlorobiphenyl (5zzh)



Compound **5zzh** was prepared according to the general procedure **D** start from 4-chloro-4'-fluorobiphenyl (41.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (16.4 mg, yield: 23%).

m.p. = 108.5 – 111.0 °C.

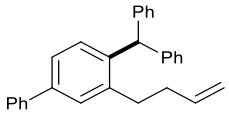
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 1H), 7.54 – 7.50 (m, 2H), 7.48 – 7.39 (m, 2H), 7.35 – 7.27 (m, 5H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.20 – 7.07 (m, 7H), 5.59 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 143.2, 141.0, 139.3, 130.0, 129.6, 128.9, 128.5, 127.3, 127.2, 126.5, 115.7, 56.7.

IR (KBr): 3055, 3029, 1598, 1494, 1448, 1222, 1159, 1078, 1030, 1008, 832, 801, 760, 747, 735, 606 cm^{-1}.

HRMS (EI) $[C_{25}H_{19}Cl]$ $[M]^+$ calculated:354.1175, found: 354.1189.

4-Benzhydryl-3-(but-3-en-1-yl)biphenyl (5zzi)



Compound **5zzi** was prepared according to the general procedure **D** start from 3-(but-3-en-1-yl)-4-fluorobiphenyl (45.3 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (51.0 mg, yield: 68%).

m.p. = 93.5 – 94.1 °C.

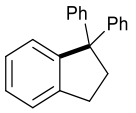
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.38 (m, 3H), 7.36 – 7.19 (m, 8H), 7.10 (d, *J* = 7.4 Hz, 4H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.91 – 5.78 (m, 1H), 5.80 (s, 1H), 4.97 (d, *J* = 11.8 Hz, 2H), 2.73 (dd, *J* = 9.5, 6.5 Hz, 2H), 2.24 (q, *J* = 7.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 141.1, 140.6, 139.3, 138.2, 130.6, 129.7, 128.8, 128.9, 128.5, 127.2, 127.1, 126.5, 124.7, 115.2, 52.7, 35.3, 32.6.

IR (KBr): 3060, 3026, 1640, 1599, 1483, 1449, 1300, 1231, 1077, 1030, 916, 748, 697, 607 cm^{-1}.

HRMS (EI) $[C_{29}H_{26}]$ $[M]^+$ calculated: 374.2035, found: 374.2025.

1,1-Diphenyl-2,3-dihydro-1*H*-indene (5zzj)



Compound **5zzj** was prepared according to the general procedure **D** start from (3-(2-Fluorophenyl)propane-1,1-diyl)dibenzene (58.0 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a colorless oil (48.0 mg, yield: 89%).

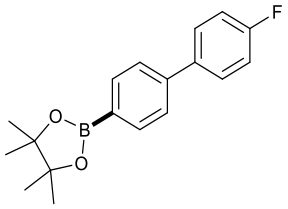
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 5H), 7.19 – 7.12 (m, 8H), 7.10 – 7.00 (m, 1H), 2.98 – 2.70 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 147.4, 143.9, 128.6, 128.0, 127.0, 126.4, 126.2, 126.1, 124.8, 62.0, 43.6, 30.8.

IR (KBr): 3059, 3021, 2948, 2905, 2845, 1596, 1492, 1473, 1443, 1025, 751, 700 cm^{-1}.

HRMS (EI) $[C_{21}H_{18}]$ $[M]^+$ calculated: 270.1409, found: 270.1411.

2-(4'-Fluoro-biphenyl-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10)



Compound **10** was prepared according to the general procedure **D** start from 4-chloro-4'-fluorobiphenyl (41.2 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM = 5/1) as a white solid (34 mg, yield: 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.64 – 7.49 (m, 4H), 7.13 (t, *J* = 8.7 Hz, 2H), 1.37 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.78 (d, *J* = 246.6 Hz), 143.0, 137.3, 135.5, 134.8, 128.9, 126.4, 115.8 (d, *J* = 21.4 Hz), 84.0, 25.0.

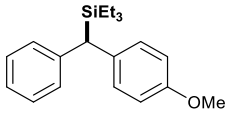
^{19}F NMR (282 MHz, $CDCl_3$) δ -115.19 – -116.27 (m, 1F).

HRMS (EI) $[C_{18}H_{20}BFO_2]$ $[M]^+$ calculated: 298.1540, found: 298.1546.

The chemical shifts were consistent with those reported in the literature.[153]

Triethyl((4-methoxyphenyl)(phenyl)methyl)silane (12)

[153] H. Ochiai, Y. Uetake, T. Niwa, T. Hosoya, Rhodium-Catalyzed Decarbonylative Borylation of Aromatic Thioesters for Facile Diversification of Aromatic Carboxylic Acids, *Angew. Chem. Int. Ed.* **2017**, *56*, 2482–2486.



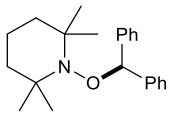
Compound **12** was purified by silica gel column chromatography (*n*-hexane/toluene = 1/1) as a colorless oil (6.2 mg, yield: 10%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28 – 7.18 (m, 4H), 7.22 – 7.14 (m, 2H), 7.15 – 7.06 (m, 1H), 6.91 – 6.71 (m, 2H), 3.77 (s, 3H), 3.59 (s, 1H), 0.85 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H).

MS(EI): *m/z* 312 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[154]

1-(Benzhydryloxy)-2,2,6,6-tetramethylpiperidine (Int-TEMPO)



Compound **Int-TEMPO** was purified by silica gel column chromatography (*n*-hexane/DCM = 10/1) as a white solid (37.9 mg, yield: 58%).

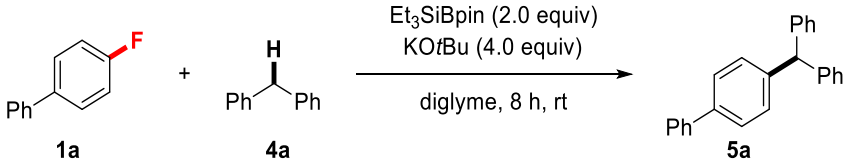
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 4H), 7.32 – 7.19 (m, 4H), 7.21 – 7.09 (m, 2H), 5.64 (s, 1H), 1.47 – 1.35 (m, 4H), 1.28 (d, *J* = 12.8 Hz, 2H), 1.15 (s, 6H), 0.74 (s, 6H).

MS(EI): *m/z* 323 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[155]

3.5 Preliminary Mechanistic Investigations

3.5.1 The NMR spectroscopic studies



Following the **General Procedure D**, charging **1a** (17.2 mg, 0.1 mmol), **4a** (33.6 mg, 0.2 mmol), silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol, 2.0 equiv), KO*t*Bu (45 mg, 0.4 mmol, 4.0 equiv), and then anhydrous diglyme (0.75 mL) sequentially. And then stirred in glovebox at room temperature for 8 h. The reaction mixture was then subjected to ^{11}B NMR and ^{19}F NMR analysis using THF-d^8 as a solvent to show the details of the reaction. After that the reaction mixture was quenched by adding D_2O (2.0 mL) while stirring for 5 min, then the ^{19}F NMR analysis of the water system was conducted to show the details of the reaction. The organic

[154] Z. Liu, J. Huo, T. Fu, H. Tan, F. Ye, M. L. Hossain, J. Wang, Palladium(0)-catalyzed C(sp3)–Si bond formation via formal carbene insertion into a Si–H bond, *Chem. Commun.*, **2018**, *54*, 11419–11422.
[155] C. Bo, Q. Bu, X. Li, G. Ma, D. Wei, C. Guo, B. Dai, N. Liu, Highly Active and Robust Ruthenium Complexes Based on Hemilability of Hybrid Ligands for C–H Oxidation, *J. Org. Chem.*, **2020**, *85*, 4324–4334.

system was extracted with Et_2O, washed by water, dried over Na_2SO_4, and concentrated under vacuum, followed by 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. Then the ^{1}H NMR analysis and ^{19}F NMR analysis of the crude mixture were conducted to show the details of the model reaction.

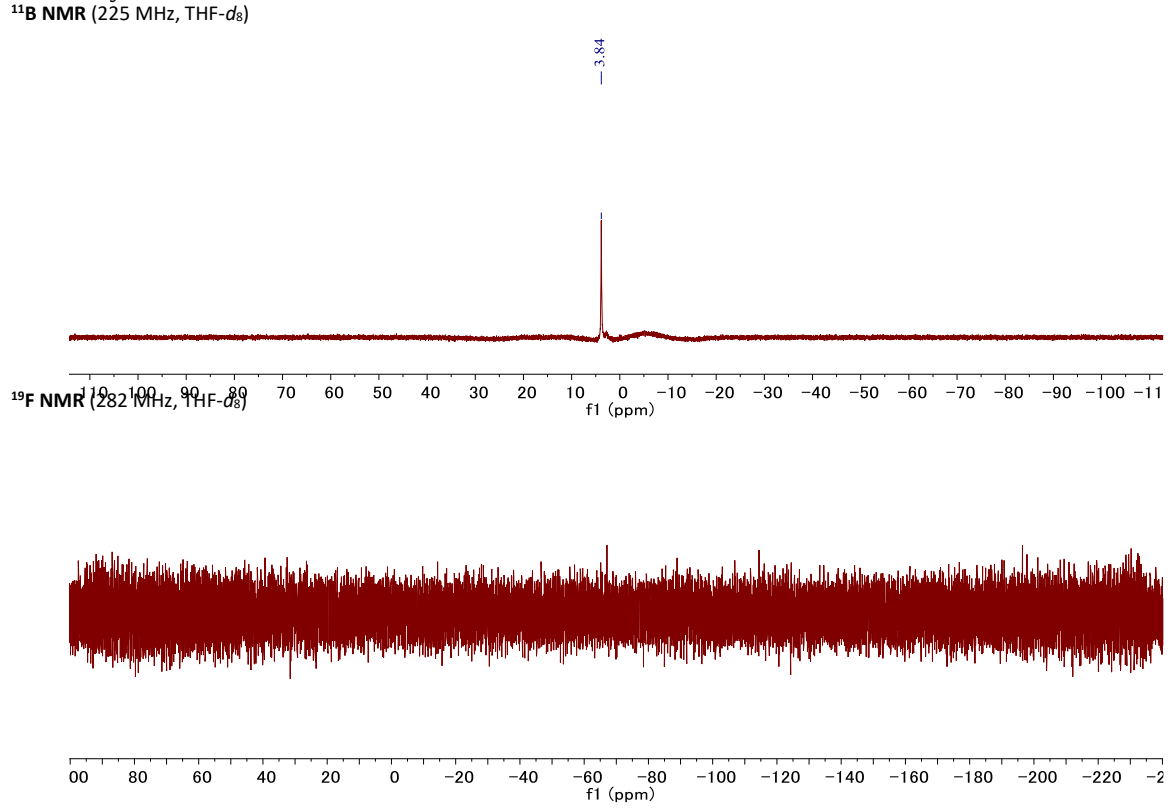


Figure S1.^{11}B NMR and ^{19}F NMR observation of the crude model reaction

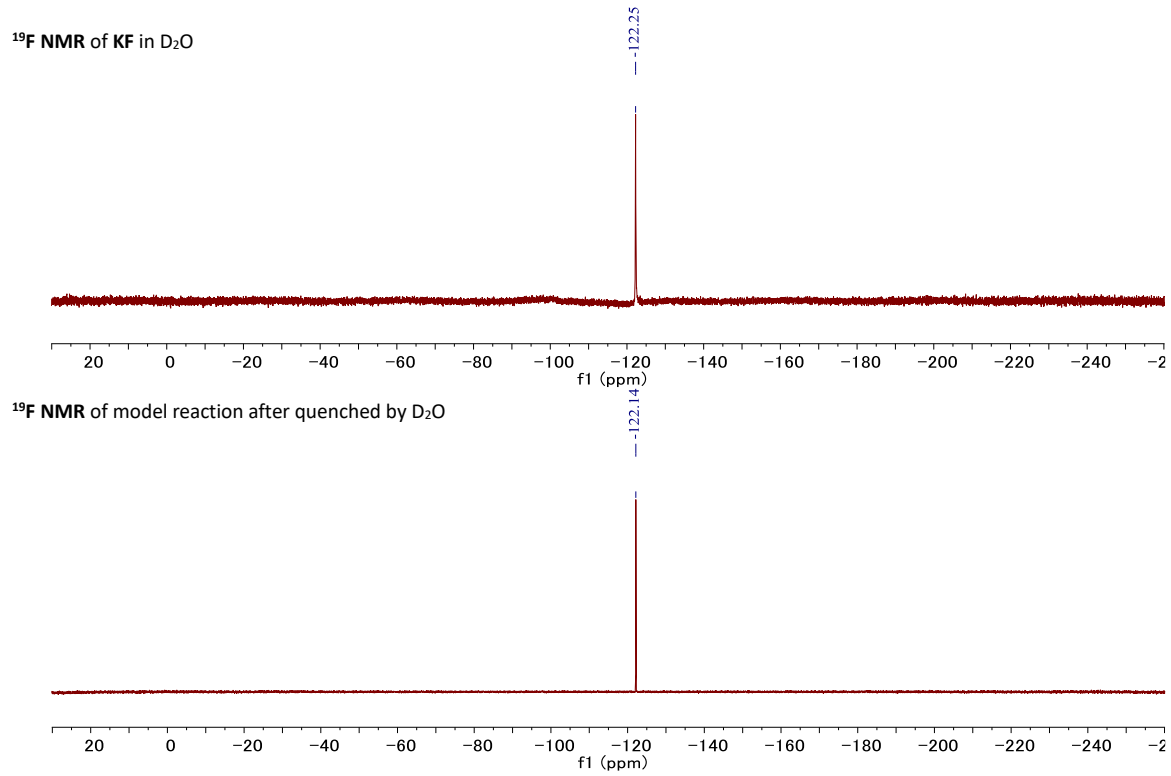


Figure S2. ^{19}F NMR observation of KF in D_2O and KF released in the model reaction

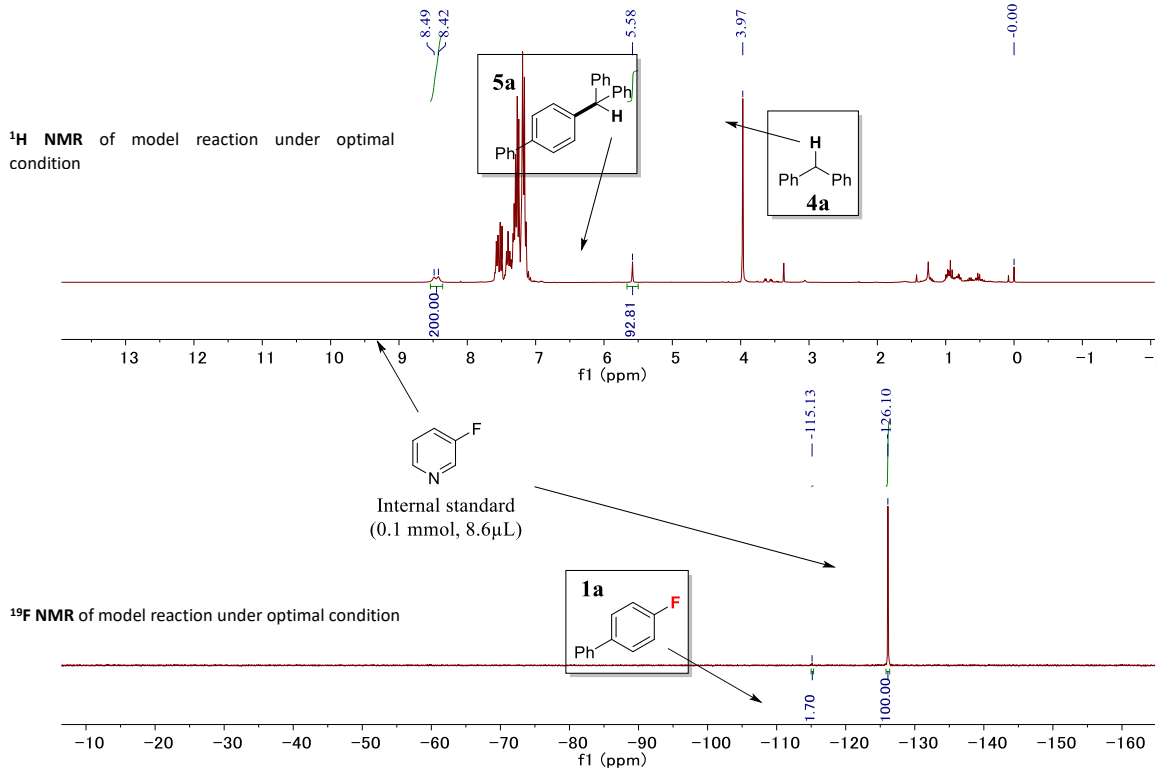


Figure S3. ^{1}H NMR and ^{19}F NMR observation of model reaction details.

3.5.2 Reaction with radical scavenger

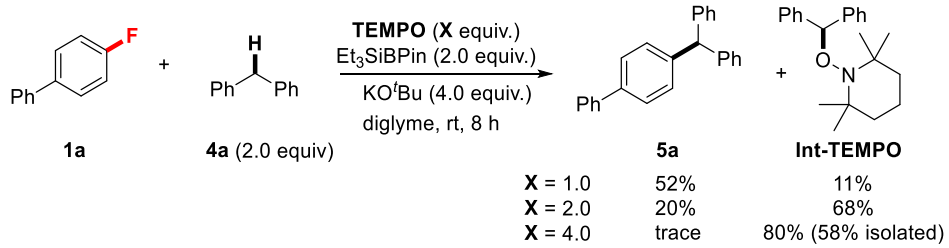


Figure S4. Effect of TEMPO to the silylboronate-mediated coupling reaction.

Following the **General Procedure D**, charging **1a** (17.2 mg, 0.1 mmol), **4a** (33.6 mg, 0.2 mmol), silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol, 2.0 equiv), KO*t*Bu (45 mg, 0.4 mmol, 4.0 equiv), TEMPO, and then anhydrous diglyme (0.75 mL) sequentially. And then move out from glovebox and stirred at room temperature for 8 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard, then ^1H NMR analysis was taken to show the reaction details.

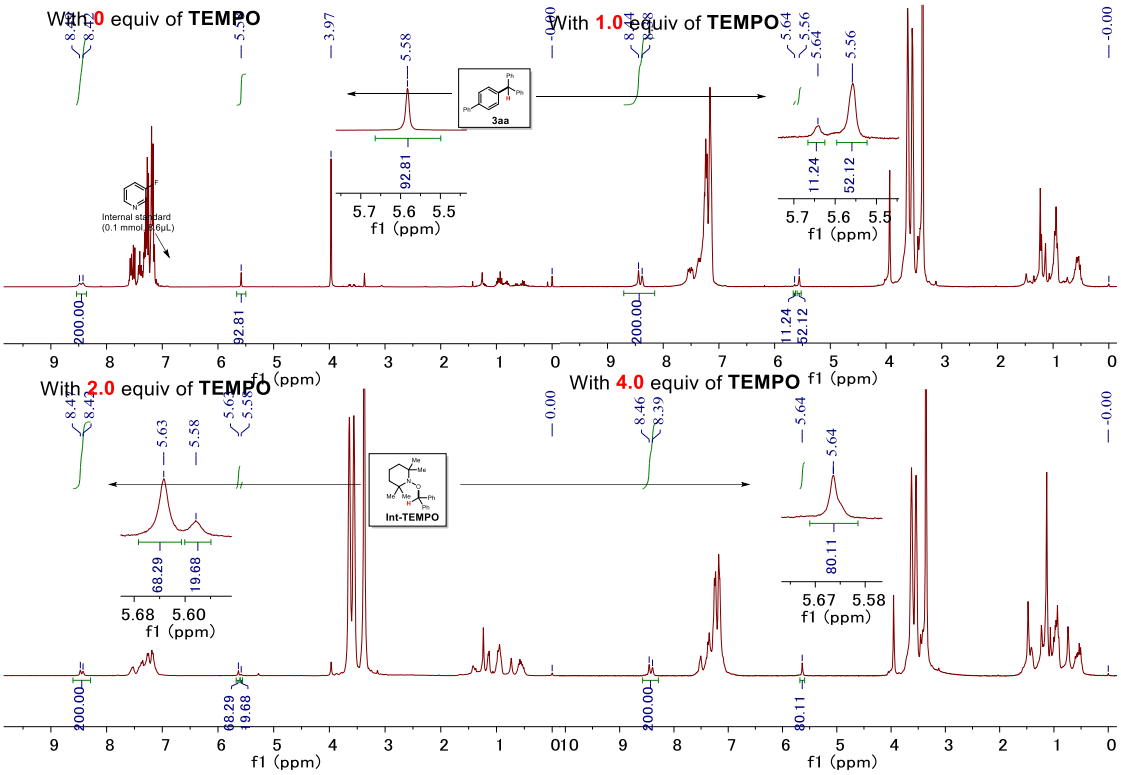
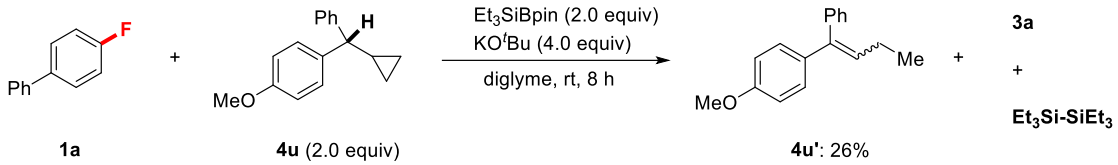


Figure S5. ^1H NMR observation of the Effect of TEMPO to the radical coupling reaction

6.3 Control experiments involve radical-clock reactions

Ring-opening reaction attempt of 1a and 4u



Following the general procedure **D**, charging **1a** (0.1 mmol), **4u** (47.5 mg, 0.2 mmol), silyl boronate (48.4 mg, 0.2 mmol), KO*t*Bu (45.0 mg, 0.4 mmol), and then anhydrous diglyme (1.0 mL) sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stir at room temperature for 8 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard, then ^{19}F NMR analysis of the reaction crude and ^{1}H NMR analysis of isolated products was taken to show the reaction details.

The reaction using **1a** and **4u** failed to afford the corresponding cross-coupling product, however, the ring-opening product **4u'** was isolated instead (26% yield), and we also detected the concomitant by-products, such as **3a** and hexaethyldisilane. The ^{1}H NMR of isolated products of **4u'** are copied below.

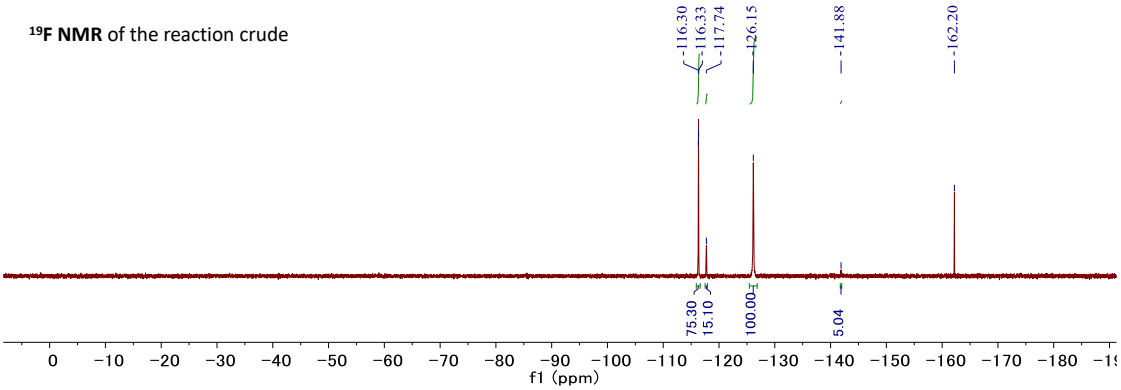


Figure S6. ^{19}F NMR of the reaction crude

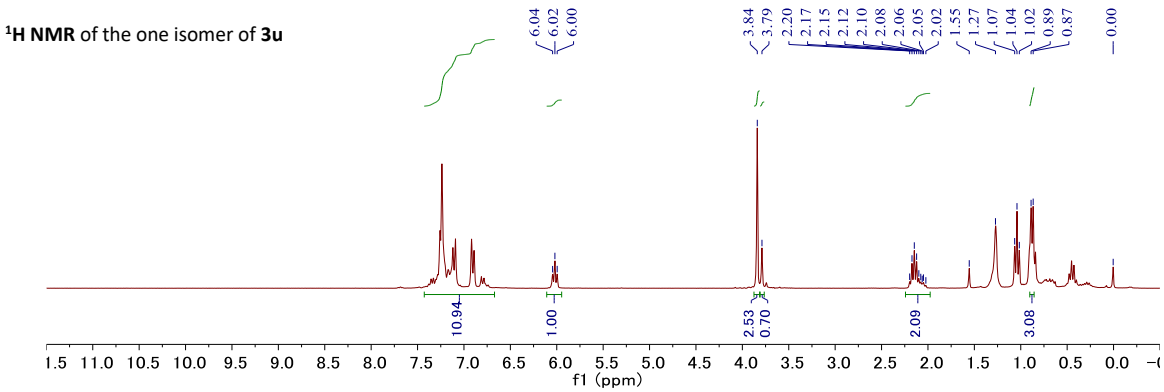


Figure S7. ^{1}H NMR of the one isomer of **4u'**

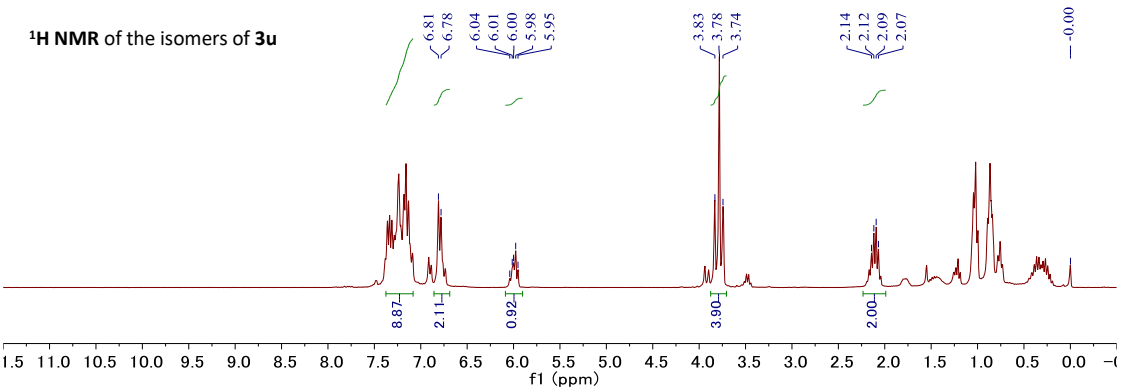
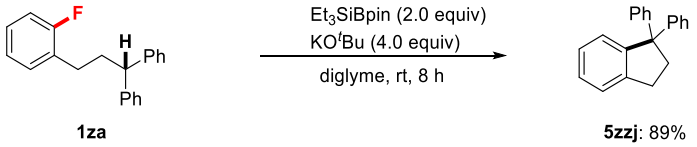


Figure S8. ^{1}H NMR of the isomers of **4u'**

Ring-cyclization attempt of 1za



1za **5zzj**: 89%

Following the general procedure **D**, charging **1za** (0.2 mmol), silyl boronate (96.8 mg, 0.4 mmol), KO*t*Bu (90.0 mg, 0.8 mmol), and then anhydrous diglyme (2.0 mL) sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stir at room temperature for 8 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by ^{19}F NMR and ^{1}H NMR analysis of the reaction crude to show the reaction details. Therefore, the intramolecular cross-coupling reaction was achieved by furnishing cyclization product **5zzj** in 89% yield, and trace of starting material **1za** (^{19}F NMR: –119.07 ppm) remains.

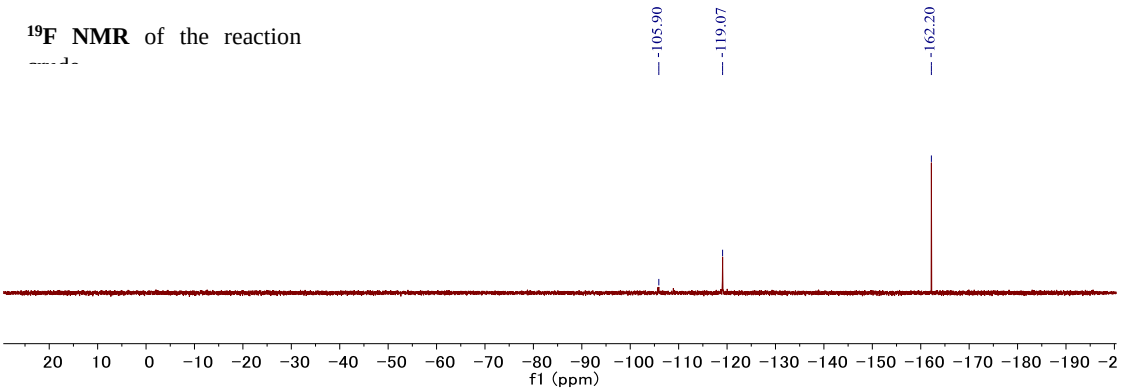


Figure S9. ^{19}F NMR observation of the ring-cyclization reaction crude

^{1}H NMR of the reaction crude

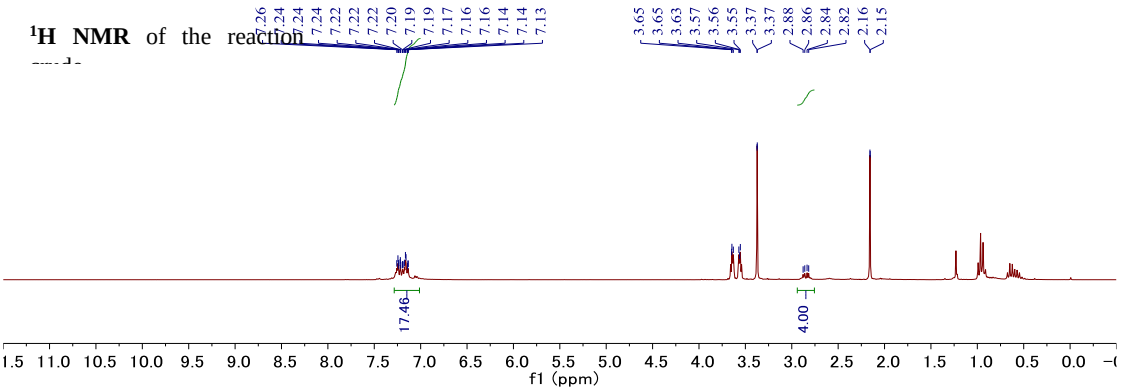
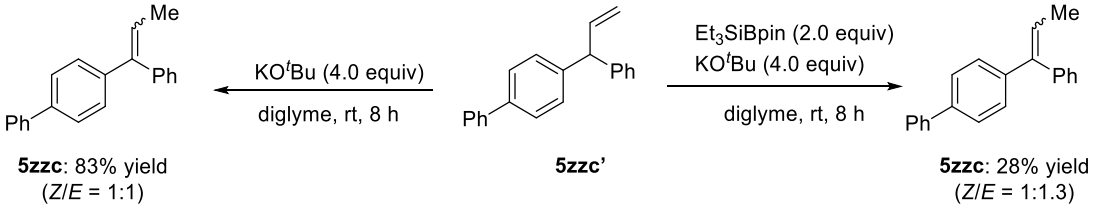


Figure S10. ^{1}H NMR observation of the ring-cyclization reaction crude.

3.5.3 Radical process regarding to the formation of 5zzc



5zzc: 83% yield (*Z*/*E* = 1:1)

5zzc'

5zzc: 28% yield (*Z*/*E* = 1:1.3)

Left reaction: In a N_2-filled glovebox, charging **5zzc'** (54.0 mg, 0.2 mmol), anhydrous diglyme (1.0 mL), and then KO*t*Bu (45.0 mg, 0.4 mmol), sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stir at room temperature for 8 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by ^{1}H NMR analysis of the reaction crude to show the reaction details.

Right reaction: In a N_2-filled glovebox, charging **5zzc'** (54.0 mg, 0.2 mmol), $Et_3SiBpin$ (48.4 mg, 0.2 mmol), anhydrous diglyme (1.0 mL), and then KO*t*Bu (45.0 mg, 0.4 mmol), sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stir at room temperature for 8 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by ^{1}H NMR analysis of the reaction crude to show the reaction details.

According to the above two control experiments, further insight into this reaction process was revealed. When the new synthesized **5zzc'** was only treated with KO^{t}Bu in diglyme for 8 h at room temperature, **5zzc'** was transformed into **5zzc** in 83% ^{1}H NMR yield with *Z*/*E* = 1:1 ratio. However, when treated **5zzc'** under standard conditions, **5zzc** was detected in 28% ^{1}H NMR yield with *Z*/*E* = 1:1.3 ratio. Therefore, the optimal reaction system (combination of $Et_3SiBpin$ and KO^{t}Bu) didn't proceed through the deprotonation process.

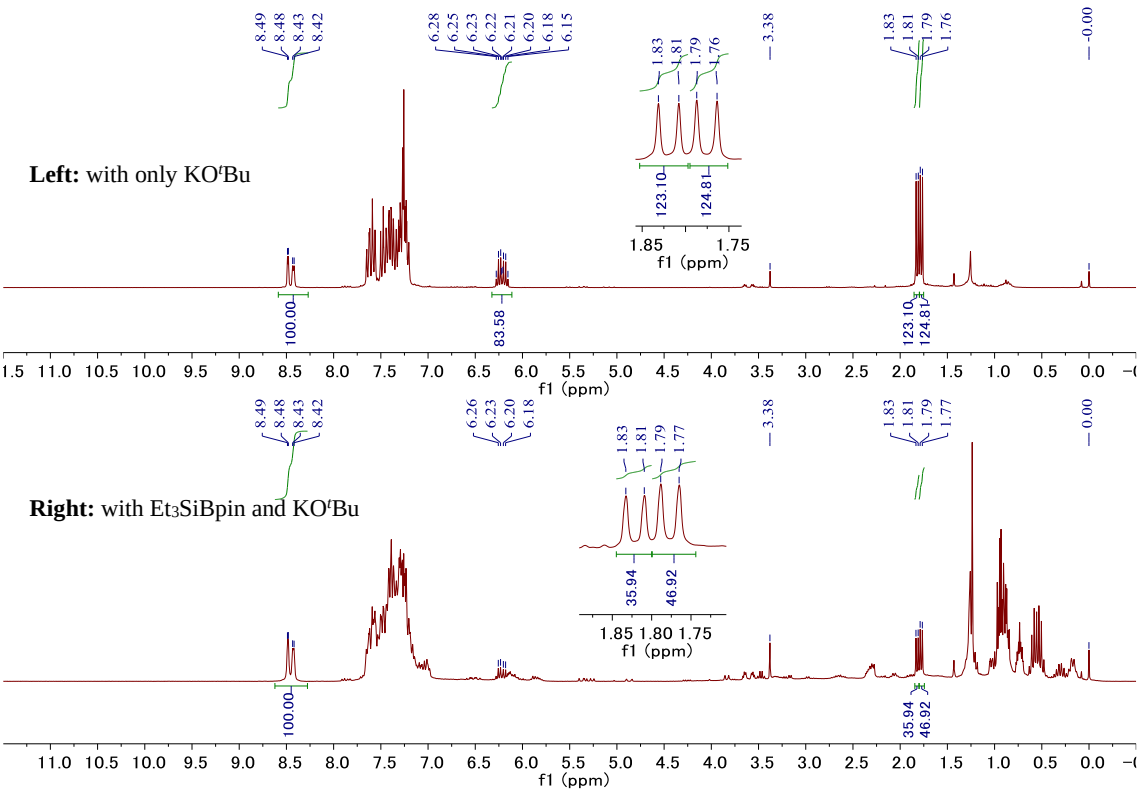
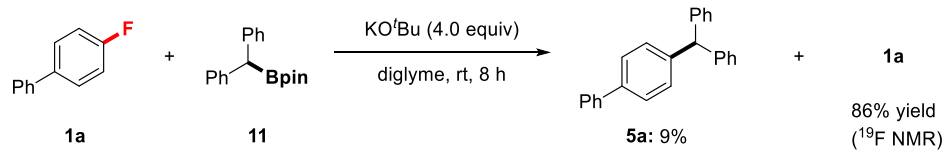


Figure S11. ^{1}H NMR observation of the crudes of the comparison reactions.

3.5.4 Control experiment involve nucleophilic aromatic substitution (S_NAr) process



In a N_2-filled glovebox, charging **1a** (34.4 mg, 0.2 mmol), 2-benzhydryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **11** (118 mg, 0.4 mmol), KO*t*Bu (90.0 mg, 0.8 mmol), and then anhydrous diglyme (2.0 mL) sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stirred at room temperature for 8 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by ^{19}F NMR and ^{1}H NMR analysis of the reaction crude to show the reaction details.

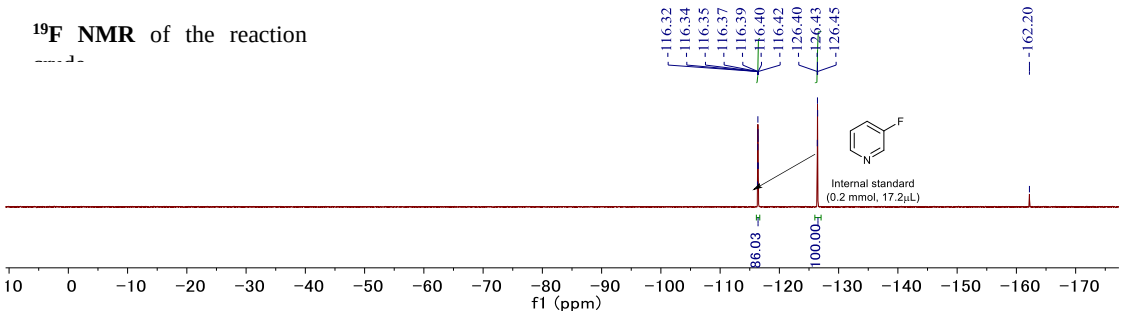


Figure S12. ^{19}F NMR observation of the reaction crude

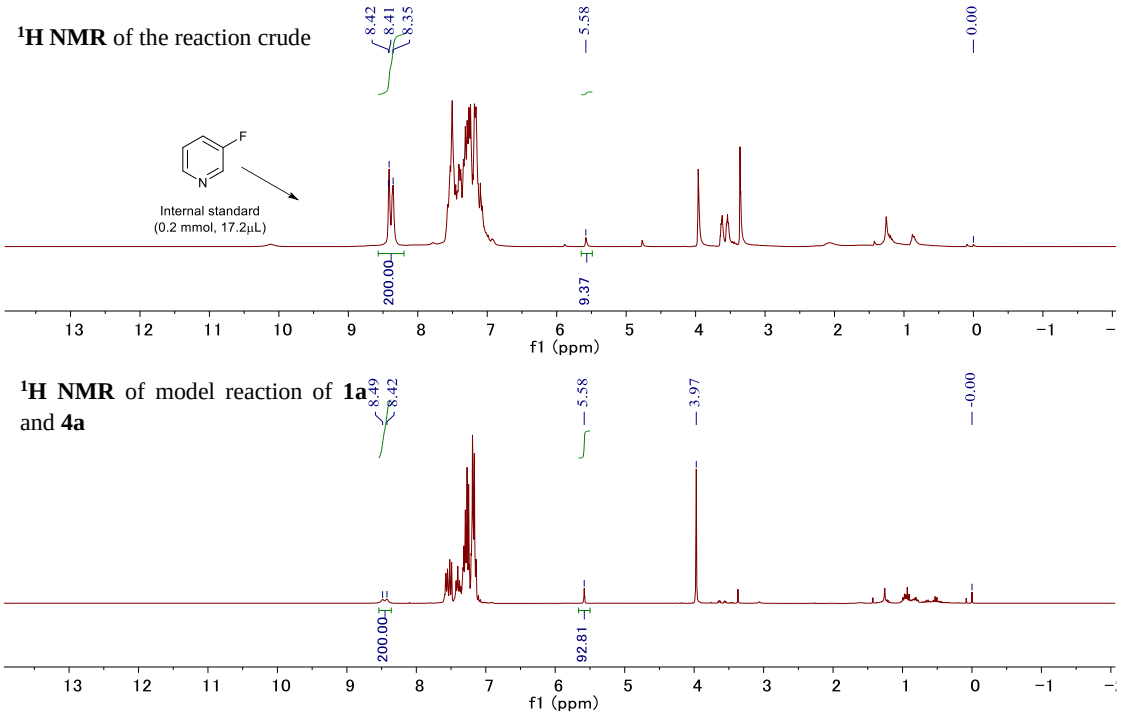


Figure S13. ^{1}H NMR spectrum comparison of the reaction crude

3.5.5 Electron spin resonance (ESR) studies

Electron spin resonance (ESR) spectra, also referred to as electron paramagnetic resonance (EPR) spectra, were performed on a JEOL FA200 ESR spectrometer. ESR spectra were obtained at a microwave power level of 0.0997 ~ 0.998 mW and 100kHz filed modulation at room temperature (~ 288 K). The magnetic field was calibrated with the well-known splitting constants of Mn^{2+} in MgO. The *g*-values were determined by comparison with the spectrum of Mn^{2+} in MgO. Tri-*tert*-butyl nitrosobenzene (TTBNB, Aldrich) was used as spin-trapping reagent. TTBNB was purified by sublimation under reduced pressure.

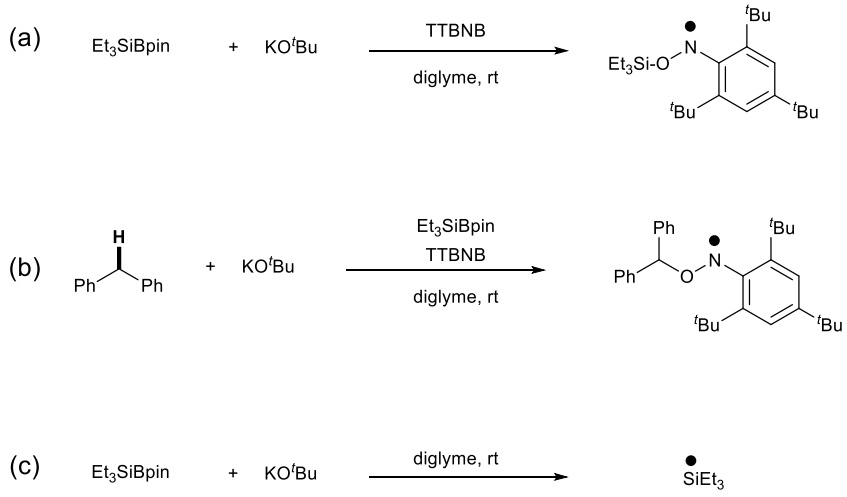


Figure S14. ESR experiments

Sample (a): In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added KO*t*Bu (11.2 mg, 0.1 mmol, 1.0 equiv), silyl boronates $Et_3SiBpin$ (0.1 mmol, 1.0 equiv), dry diglyme (0.5 mL) sequentially. Stir the mixture till it turns to pale yellow, then 20 μL of TTBNB (0.01 M in diglyme) solution was added. Transfer 30 μL of mixture into a capillary tube that furtherly be put in the ESR test tube, the tube then was sealed and removed from the glovebox for conducting ESR measurement quickly.

Sample (b): In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added KO*t*Bu (2.3 mg, 0.02 mmol, 2.0 equiv), silyl boronates $Et_3SiBpin$ (0.01 mmol, 1.0 equiv), diphenylmethane (0.02 mmol, 2.0 equiv), dry diglyme (0.2 mL) sequentially. Stir the mixture till it turns to pale yellow. then 20 μL of TTBNB (0.01 M in diglyme) solution was added, dilute the mixture by adding 1.5 mL diglyme. Transfer 30 μL of the mixture into a capillary tube that furtherly be put in the ESR test tube, the tube then was sealed and removed from the glovebox for conducting ESR measurement.

Sample (c): In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added KO*t*Bu (11.2 mg, 0.1 mmol, 1.0 equiv), silyl boronates $Et_3SiBpin$ (0.1 mmol, 1.0 equiv), dry diglyme (0.5 mL) sequentially. Stir mixture till it turns to pale yellow, transfer 30 μL of the mixture into a capillary tube that furtherly be put in the ESR test tube, the tube then was sealed and removed from the glovebox for conducting ESR measurement quickly.

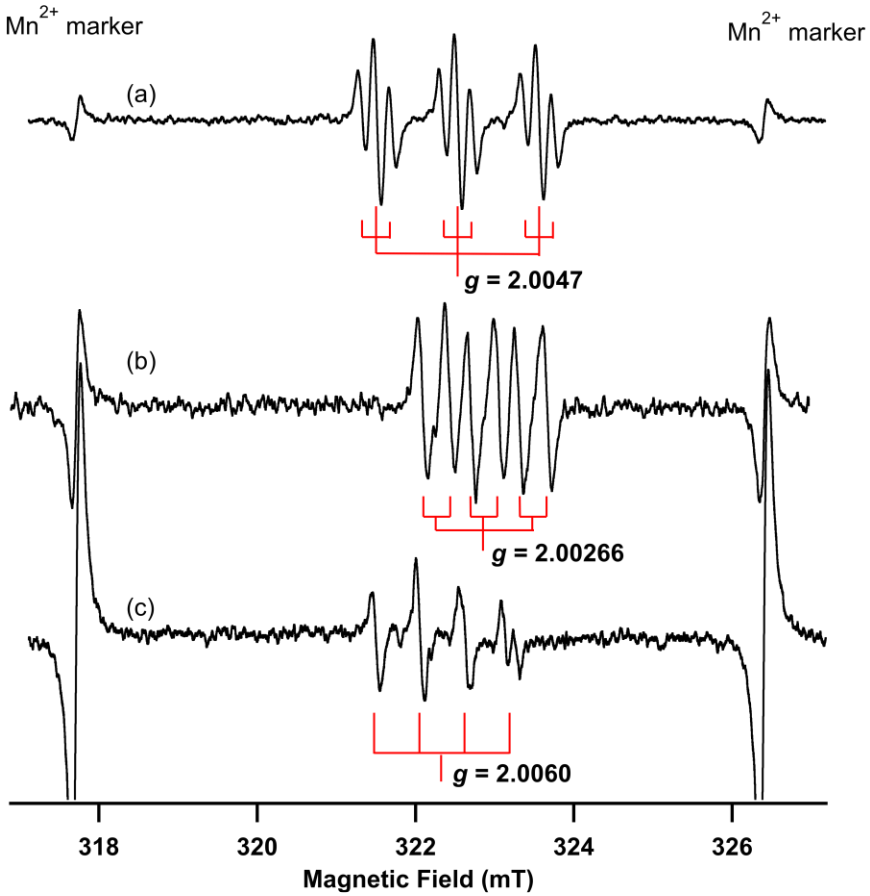


Figure S15. ESR spectra of spin-adducts: (a) the triethyl silyl radicals (silyl radicals) and (b) diphenyl methyl radicals (benzyl radicals) trapped with TTBNB in diglyme solvent. Spectrum (c) can be assigned to triethyl silyl radicals

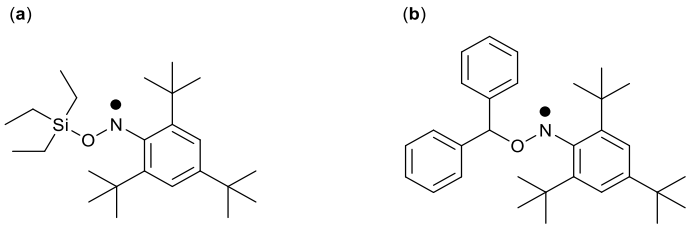


Figure S16. Chemical structure of spin-adducts; (a) triethyl silyl radical (anilino-type) and (b) diphenyl methyl radical trapped with TTBNB (anilino-type)

Figure S15(a) indicates the ESR spectrum (triple-triplet) from the spin-adduct of the silyl radical trapped with TTBNB. The hyperfine splitting (*hfs*) constant A_N due to nitrogen (the spin quantum number I = 1) was 1.03 mT, and the small splitting A_{Hm} due to two hydrogens (I = 1/2) at *meta* position of TTBNB benzene ring was 0.175 mT. The *g*-value of 2.0047 was assigned to the anilino-type radical,[70] as shown in Figure S16(a). The spectrum Figure S15(b) (double-triplet; sextet line) was assigned to the benzyl type radicals trapped with TTBNB. The *hfs* constant A_N and $A_{H\alpha}$ due to an alpha proton were 0.62 and 0.34 mT, respectively. The splitting due to the meta hydrogens was too small to be resolved (less than 0.06 mT). The *g*-value of 2.00266 was assigned to the anilino-type radical, as shown in Figure S16(b).[156]

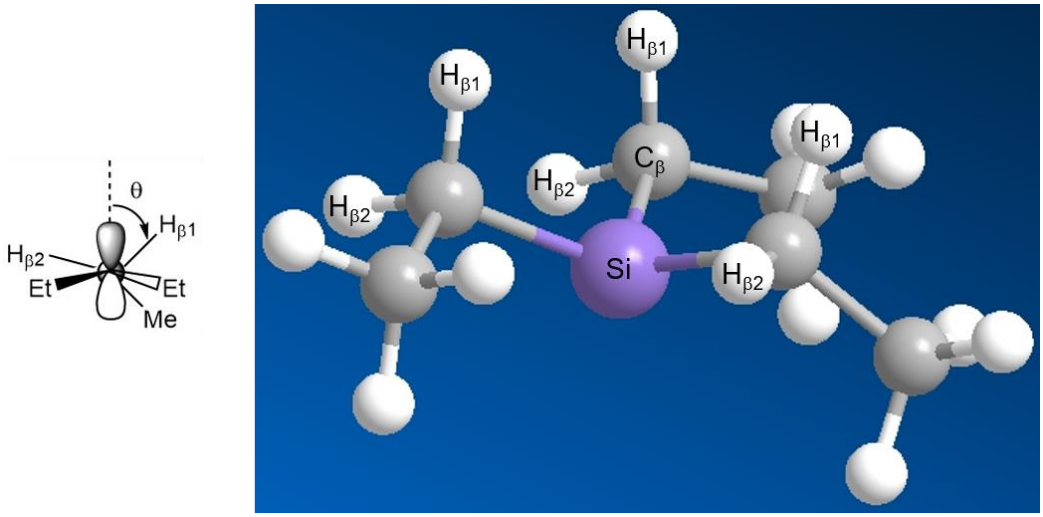


Figure S17. Illustration of the Newman projection of the Siα-C_β bond (left) and the steric structure of triethylsilyl radical after energy minimization (right).

Figure S15(c) indicates the quartet line with the splitting constant of 0.57 mT. The relative intensity ratio of 1 : 3 : 3 : 1 means the radical has three equivalent nuclei. The ^{28}Si (I = 0) and ^{29}Si (I = 1/2) radicals essentially give singlet and doublet peaks, respectively. Since the natural abundance of ^{29}Si was ~ 4%, the signal due to ^{29}Si was buried in noise level in this experiment. We suggested that this signal can be assigned to the $Si(Et)_3$

[156] D. C. Doetschman, R. C. Mehlenbacher, D. Cywar, Stable Free Radicals Produced in Acrylate and Methacrylate Free Radical Polymerization: Comparative EPR Studies of Structure and the Effects of Cross-Linking, *Macromolecules*, **1996**, *29*, 1807–1816.

radicals. The *hfs* constant due to hydrogens H_β on the carbon (β-position) atoms connected to the silicon atom depends on the torsional angle between the axis of the *p*-orbital of the unpaired electron on the silyl radical and the C_β-H_β bond axis in the Newman projection of the Si_α-C_β bond as shown in Figure S17. The dihedral angle is θ formed by the projection of the Si_α-C_β bond on the axis of the *p*-orbital of the unpaired electron. The *hfs* constants were assumed to be given by the following equation. This form is the well-established empirical relation carbon-center radical species.[70]

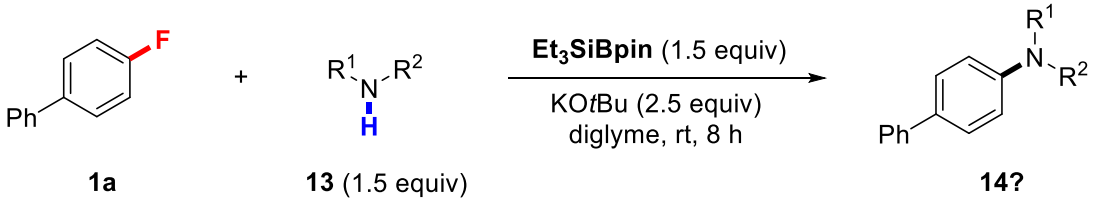
$$A_{H_\beta} = B_0 + B_2 cos^2\theta \sim B_2 cos^2\theta$$

The values of B_0 are typically small to be ignored for simplicity (still unknown). The *hfs* constant of the A_{H_β} was reported to be 0.642 mT. In the report, the ESR spectrum of trimethylsilyl radicals was obtained at 203K by hydrogen abstraction of $SiH(CH_3)_3$ by the initially produced *tert*-butoxy radicals. The presence of nine equivalent protons gave the 10-lines spectrum, which means all protons of the methyl groups indicate the same *hfs* value of 0.642 mT where the free rotation of the methyl groups is permitted (faster than measurement time scale). In such a situation, the term of $cos^2\theta$ is averaged to be 0.5, $\langle cos^2\theta \rangle = 0.5$. Thus, the value of B_2 is approximately 1.28 mT. From our experiment, since the value of the *hfs* constant was 0.57 mT, the dihedral angle θ is calculated to be 48° ($H_{\beta1}$). For one other proton ($H_{\beta2}$), the dihedral angle is predicted to be -72° (120° apart from $H_{\beta1}$), giving the *hfs* of 0.12 mT. In this case, the quadra quartet lines would be observed if highly resolved. Experimentally, however, the spectrum was a simple quartet line (a small undefined peak was observed, though). That means the values of the dihedral angles and constant B_2 are inappropriate, and/or different environmental situations surrounded the radicals affected on the constants, including *g*-value, which is a higher value (2.006) than the reported value of trimethylsilyl radicals (2.003).[157] Diglyme solution (polar solvent) was used in our case. Here, we will consider the effect of dihedral angle on the ESR spectrum, although we are not sure about the influence of the solvent on the inherent values so far. We carried out the calculation of the energy minimization of the steric structure of triethylsilyl radical using Chem3D, the obtained structure was shown in Figure S17. From the resulting structure, the dihedral angle of $H_{\beta1}$ was small (C_β-$H_{\beta1}$ bond axis is nearly parallel to the *p*-orbital). On the other hand, the dihedral angle of $H_{\beta2}$ is around 90°, resulting in the *hfs* of zero. Therefore, three $H_{\beta1}$ do not contribute to the splitting. We concluded that the quartet line spectrum could be attributed to three equivalent protons $H_{\beta1}$ in our case.

Chapter 4. Transition-metal-free silylboronate-mediated cross-couplings of organic fluorides with amines

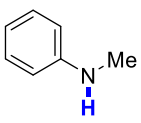
4.1 Optimization of Reaction Conditions

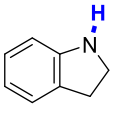
Table S1. Screening proper secondary amine for the defluoroamination of aryl fluoride[a]

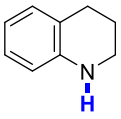


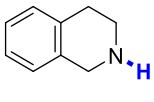
1a **13** (1.5 equiv) **14?**

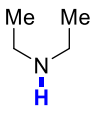
[157] S. W. Bennett, C. Eaborn, A. Hudson, H. A. Hussain, R. A. Jackson, Electron spin resonance spectra of trimethylsilyl, trimethylgermyl and related free radicals in solution, *J. Organometal. Chem.*, **1969**, *16*, P36–P38.

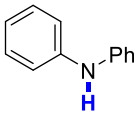

13a

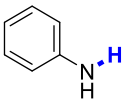

13n


13o


13t


13u

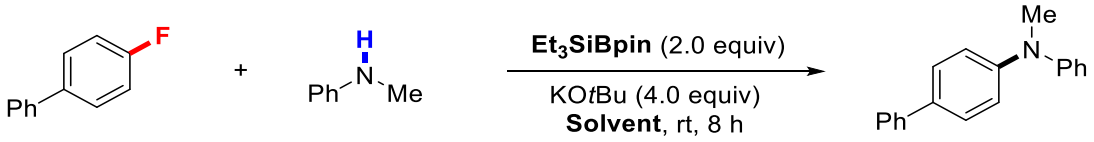

13x


13y

Entry	Amine	4? (%)[b]
1	**3a**	**41**
2	**3n**	16
3	**3o**	14
4	**3t**	9
5	**3u**	trace
6	**3x**	N.R.
7	**3y**	N.R.
8[c]	**3a**	44

[a] Reactions were carried out with **1a** (17.2 mg, 0.1 mmol), **13** (0.15 mmol), $Et_3SiBpin$ (36.3 mg, 0.15 mmol), and KO*t*Bu (28.0 mg, 0.25 mmol) in diglyme (0.5 mL) at room temperature for 8 h; [b] Yields were determined by ^1H NMR and ^{19}F NMR analysis of the crude reaction mixture using 3-fluoropyridine as an internal standard; [c] $Et_3SiBpin$ (48.4 mg, 0.2 mmol), and KO*t*Bu (44.8 mg, 0.4 mmol) were used.

Table S2. Screening solvent for the defluoroamination of aryl fluoride[a]



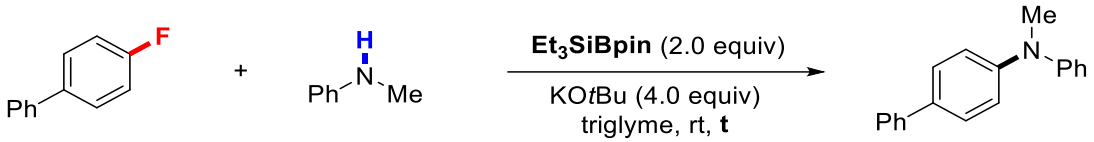
1a **13a** (3.0 equiv) **14a**

Entry	**Solvent**	Conversion (%)[b]	Yield of **14a** (%)[b]
1	diglyme	62	58
2	**triglyme**	**85**	**81**
3	tetraglyme	81	74
4	dioxane	49	39
5	DME	34	31
6	CPME	--	N.R.
7	THF	29	5
8	**18-crown-6** (4.0 equiv) in THF	78	75
9	cyclohexane	--	N.R.
10	toluene	--	N.R.

[a] Unless otherwise noted, reactions were conducted with **1a** (17.2 mg, 0.1 mmol), **13a** (32 μL, 0.3 mmol), $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol) and solvent (0.5 mL) at room temperature for 8 h; [b] Yields were determined by ^1H NMR and ^{19}F NMR analysis of the crude reaction mixture using 3-fluoropyridine as an internal standard.

Triethylene glycol dimethyl ether: triglyme; tetraethylene glycol dimethyl ether: tetraglyme.

Table S3. Reaction time optimization for the defluoroamination of aryl fluoride[a]

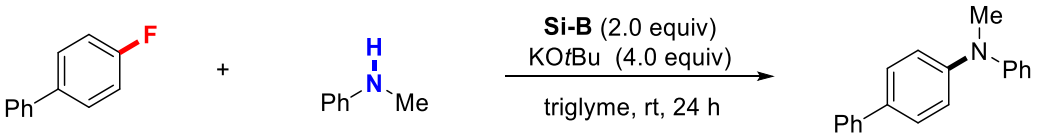


1a **13a** (3.0 equiv) **14a**

Entry	**t** (h)	Conversion (%)[b]	Yield of **14a** (%)[b]
1	8 h	85	81
2	2 h	49	47
3	12 h	88	85
4[c]	**24 h**	**93**	**91**(88)

[a] Unless otherwise noted, reactions were conducted with **1a** (17.2 mg, 0.1 mmol), **13a** (32 µL, 0.3 mmol), $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol) and triglyme (0.5 mL) at room temperature for indicated hours; [b] Determined by ^{19}F NMR and ^{1}H NMR spectroscopy using 3-fluoropyridine as an internal standard; [c] The isolated yield was shown in the parenthesis.

Table S4. Evaluation of silylboronates for the defluoroamination of aryl fluoride[a]

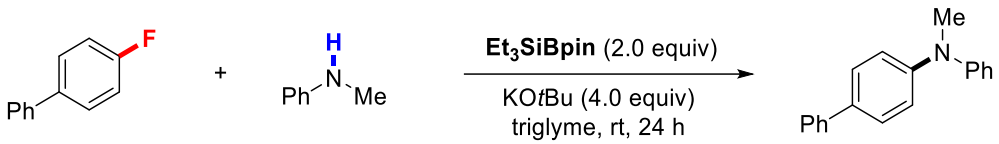


1a **13a** (3.0 equiv) **14aa**

Entry	**Si-B**	**Conversion (%)**	**4aa (%)**[b]
1	$Et_3SiBpin$	93	91
2	$^{n}Pr_3SiBpin$	100	95
3	$^{t}BuMe_2SiBpin$	100	70
4	$PhMe_2SiBpin$	50	44
5	$TMS_3SiBpin$	67	13

[a] Unless otherwise noted, reactions were conducted with **1a** (17.2 mg, 0.1 mmol), 1**3a** (32 µL, 0.3 mmol), silylboronates **(Si-B**, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol) and triglyme (0.5 mL) at room temperature for 24 h; [b] Determined by ^{19}F NMR and ^{1}H NMR spectroscopy using 3-fluoropyridine as an internal standard.

Table S5. Variations from the optimal reaction conditions[a]



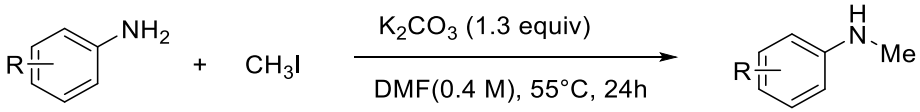
1a **13a** (3.0 equiv) **"*Standard Condition*"** **14a**

Entry	Variations from "***Standard Condition***"	**14a** (%)[b]
1[c]	none	91(88)
2	Without $Et_3SiBpin$	0
3	Without KO*t*Bu	0
4	KOMe instead of KO*t*Bu	42
5	NaO*t*Bu, LiO*t*Bu or KHMDS instead of KO*t*Bu	<3
6	2.0 equiv of KO*t*Bu	7
7	5.0 equiv of KO*t*Bu	88
8	1.5 equiv of $Et_3SiBpin$ instead of 2.0 equiv	80
9	1.5 equiv of **3a** instead of 3.0 equiv	53
10	2.0 equiv of **3a** instead of 3.0 equiv	64
11[c]	0.2 mmol **1a** was used	93(89)

[a] Unless otherwise noted, reactions were conducted with **1a** (17.2 mg, 0.1 mmol) and triglyme (0.5 mL), indicated amount of **13a**, $Et_3SiBpin$, KO*t*Bu were used and react at room temperature for 24 h; [b] Determined by ^{19}F NMR and ^{1}H NMR spectroscopy using 3-fluoropyridine as an internal standard; [c] The isolated yield was shown in the parenthesis.

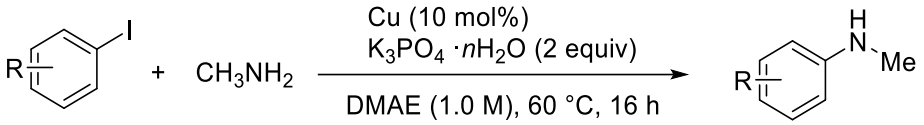
4.2 General procedure for the synthesis of *N*-alkyl anilines 13

N-methyl anilines 1**3a**, **13l**, **13n**, **13o**, **13p**, **13q**, **13r**, **13s**, **13t** and **13u** were purchased from TCI or Sigma Aldrich. *N*-methyl anilines 1**3b**, 1**3c**, 1**3d**, 1**3e**, 1**3f**, 1**3g**, 1**3h**, 1**3i**, **13j**, **13k** and **13m** were prepared according to known methods. A typical experimental procedure for the preparation of *N*-methyl anilines was described below.



13

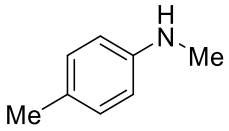
General procedure B: Synthetic intermediates were prepared according to the procedures previously described.[14] In a flame-dried flask was charged with anilines (10.0 mmol), iodomethane (0.75 mL, 12.0 mmol), potassium carbonate (1.80 g, 13.0 mmol), and DMF (25 mL). The flask was then sealed and heated to 55 °C for 24 h. After reaction cooling, water was added into the mixture. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine and dried over Na_2SO_4. After filtered and evaporated under reduced pressure to give the reaction crude. Which was purified by column chromatography on silica gel using *n*-hexane/EtOAc as the eluent to give *N*-methyl anilines **13**. Compounds **13c**, **13e**, **13f**, **13g**, **13h**, **13j** were synthesized by using **General procedure B**.



13

General procedure C: Synthetic intermediates were prepared according to the procedures previously described.[15] In a flame-dried flask was charged with aryl iodide (10.0 mmol), methylamine (15.0 mmol, 33 wt% in absolute ethanol), Cu powder (64.0 mg, 10 mol%), K_3PO_4·nH_2O (5.34 g, 20.0 mmol) in 2-(dimethylamino)ethanol (DMAE, 10 mL) was heated at 60 °C for 16 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phase was washed with brine and dried over Na_2SO_4. After filtered and evaporated under reduced pressure to give the reaction crude. Which was purified by column chromatography on silica gel using *n*-hexane/EtOAc as the eluent to give *N*-methyl anilines **13**. Compounds **13b**, **13d**, **13i**, and **13m** were synthesized by using **General procedure C**.

***N*,4-Dimethylaniline (13b)**



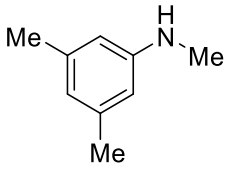
Compound **13b** was obtained from 4-iodotoluene (**S25a**) by using **General procedure C** as a light-yellow oil (0.92 g, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.0 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.56 (bs, 1H), 2.82 (s, 3H), 2.25 (s, 3H).

MS(EI): *m/z* 121 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[158]

***N*,3,5-Trimethylaniline (13c)**



Compound **13c** was obtained from 3,5-dimethylaniline by using **General procedure B** as a light-yellow oil (0.43 g, 32% yield).

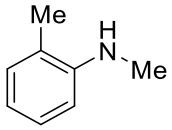
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H), 6.29 (s, 2H), 3.57 (brs, 1H), 2.84 (s, 3H), 2.29 (s, 6H).

MS(EI): *m/z* 135 $[M]^+$.

[158] L. Wang, H. Neumann, M. Beller, Palladium-catalyzed methylation of nitroarenes with methanol. *Angew. Chem. Int. Ed.* **2019**, *58*, 5417–5421.

The chemical shifts were consistent with those reported in the literature.[158]

***N*,2-Dimethylaniline (13d)**



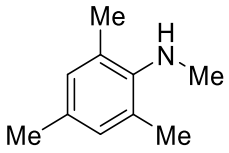
Compound **13d** was obtained from 2-iodotoluene by using **General procedure C** as a light-yellow oil (0.22 g, 18% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.67 (t, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.56 (brs, 1H), 2.90 (s, 3H), 2.14 (s, 3H).

MS(EI): *m/z* 121 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[158]

***N*,2,4,6-Tetramethylaniline (13e)**



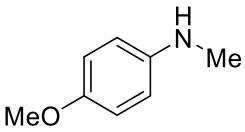
Compound **13e** was obtained from 2,4,6-trimethylaniline by using **General procedure B** as a light-yellow oil (0.36 g, 24% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.96 (brs, 1H), 2.74 (s, 3H), 2.26 (s, 6H), 2.23 (s, 3H).

MS(EI): *m/z* 149 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[159]

4-Methoxy-*N*-methylaniline (13f)



Compound **13f** was obtained from *p*-anisidine by using **General procedure B** as a light-yellow oil (0.38 g, 28% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H), 3.43 (brs, 1H),

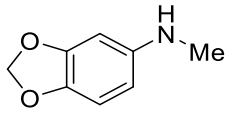
[159] E. Falk, V. C. M. Gasser, B. Morandi, Synthesis of *N*-alkyl anilines from arenes via iron-promoted aromatic C–H amination. *Org. Lett.* **2021**, *23*, 1422–1426.

2.81 (s, 3H).

MS(EI): *m/z* 137 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[158]

***N*-Methylbenzo[*d*][1,3]dioxol-5-amine (13g)**



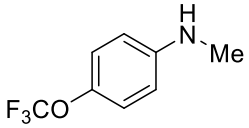
Compound **13g** was obtained from 3,4-methylenedioxyaniline by using **General procedure B** as a light-yellow oil (0.36 g, 24% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.3 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.04 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.85 (s, 2H), 2.78 (s, 3H).

MS(EI): *m/z* 151 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[158]

***N*-Methyl-4-(trifluoromethoxy)aniline (13h)**



Compound **3h** was obtained from 4-(trifluoromethoxy)aniline by using **General procedure B** as a light-yellow oil (0.69 g, 47% yield).

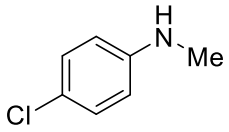
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 1H), 2.83 (s, 3H).

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.54 (s, 3F).

MS(EI): *m/z* 191 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[160]

4-Chloro-*N*-methylaniline (13i)



Compound **13i** was obtained from 1-chloro-4-iodobenzene by using **General procedure C** as a light-yellow

[160] F. Li, J. Xie, H. Shan, C. Sun, L. Chen, General and efficient method for direct *N*-monomethylation of aromatic primary amines with methanol. *RSC Adv.* **2012**, *2*, 8645–8652.

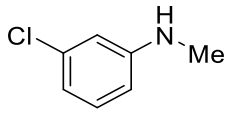
oil (1.10 g, 79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.71 (brs, 1H), 2.81 (s, 3H).

MS(EI): *m/z* 141 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[159]

3-Chloro-*N*-methylaniline (13j)



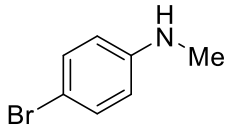
Compound **13j** was obtained from 3-chloroaniline by using **General procedure B** as a light-yellow oil (0.52 g, 37% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (t, *J* = 8.0 Hz, 1H), 6.68 – 6.65 (m, 1H), 6.58 – 6.57 (m, 1H), 6.50 – 6.44 (m, 1H), 3.79 (brs, 1H), 2.82 (s, 3H).

MS(EI): *m/z* 141 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[160]

4-Bromo-*N*-methylaniline (13k)



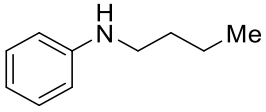
Compound **13k** was obtained from 4-bromoaniline by using **General procedure B** as a light-yellow oil (1.21 g, 65% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 1H), 2.78 (s, 3H).

MS(EI): *m/z* 186 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[160]

***N*-Butylaniline (13m)**



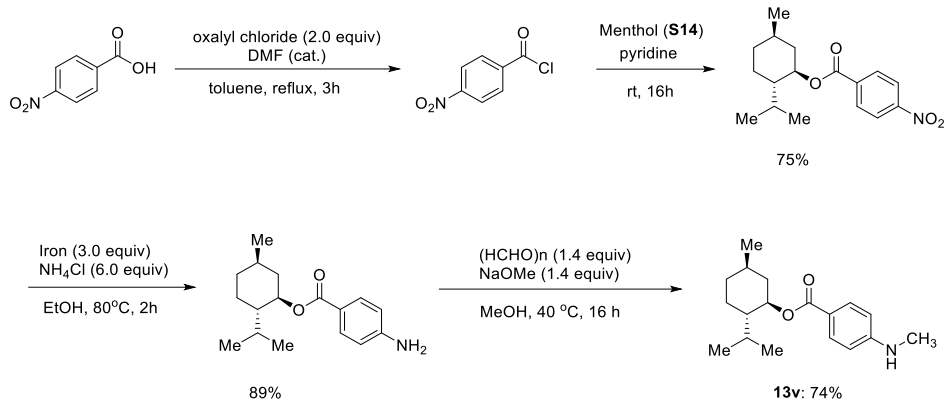
Compound **13m** was obtained from iodobenzene and *n*-$BuNH_2$ by using **General procedure C** as a light-yellow oil (0.74 g, 50% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.73 – 6.65 (m, 1H), 6.61 (d, *J* = 7.6 Hz, 2H), 3.59 (brs, 1H), 3.11 (t, *J* = 7.1 Hz, 2H), 1.68 – 1.51 (m, 2H), 1.50 – 1.35 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

MS(EI): *m/z* 149 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[157]

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-(methylamino)benzoate (13v)



To a solution of *p*-nitrobenzoic acid (1.67 g, 10.0 mmol) in anhydrous toluene (20 mL) were added oxalyl chloride (1.72 mL, 20.0 mmol) and 3 drops of DMF at 0 °C. The reaction mixture was stirred for 8 h at 0 °C under N_2. The solvent was removed under reduced pressure to afford the *p*-nitrobenzoyl chloride as a light-yellow solid. To the former flask was charged with (-)-menthol (1.56 g, 10.0 mmol) and followed by anhydrous pyridine (20 mL), the resulted solution was stirred for 16 h at room temperature. After the reaction finished, removal of pyridine under reduced pressure, the residue was dissolved in DCM (30 mL) and washed with 1 N HCl, saturated $NaHCO_3$ aqueous solution and brine, the separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, the residue was purified by column chromatography (*n*-hexane/EtOAc: 10/1) to afford the ester as a light-yellow solid (2.29 g, 75% yield).

In a 100 mL round bottom flask, previous obtained ester (2.20 g, 7.2 mmol), Iron powder (1.20 g, 21.6 mmol) and NH_4Cl (2.30 g, 43.2 mmol) was added subsequently into H_2O/EtOH (50 mL, *v*/*v*=1:5). The mixture was stirred at 80° C for 2 h. Completion of the reaction was monitored by TLC. Filtered through a pad of celite to remove the solid, and then extracted with DCM, dried, and concentrated under reduced pressure. Purification by chromatography on a short silica gel column (*n*-hexane/EtOAc: 5/1) to afford corresponding aniline **S30** as a light-yellow oil (1.80 g, 89% yield).

Synthetic procedure was followed previously reported method.[161] To a solution of previous obtained aniline (0.55 g, 2.0 mmol), paraformaldehyde (84.0 mg, 2.8 mmol) in MeOH (10 mL, 0.2 M) was added sodium methoxide solution (0.56 mL, 2.8 mmol, 5 M in methanol) and stirred at 50 °C for 5 hours. Then sodium borohydride (0.23 g, 6.0 mmol) was added under nitrogen and the reaction was stirred at room temperature. The reaction mixture was monitored by TLC until aniline was fully consumed, the solvent was removed under reduced pressure, then washed with saturated NH_4Cl and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography (*n*-hexane/EtOAc: 10/1) to afford corresponding *N*-methylaniline 1**3v** as a light-yellow solid (0.42 g, 74% yield).

[161] S. Choi, J. Park, E. Yu, J. Sim, C. Park, Electrosynthesis of dihydropyrano[4,3-*b*]indoles based on a double oxidative [3+3] cycloaddition. *Angew. Chem. Int. Ed.* **2020**, *132*, 11984–11989.

m.p. = 106.5 – 109.0 °C.

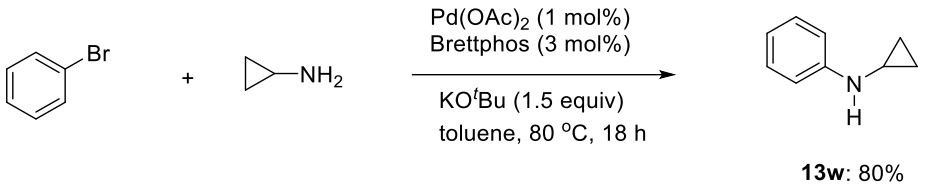
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.96 – 7.82 (m, 2H), 6.71 – 6.41 (m, 2H), 4.87 (td, *J* = 10.9, 4.4 Hz, 1H), 4.19 (br, 1H), 2.88 (s, 3H), 2.14 – 2.07 (m, 1H), 2.00 – 1.93 (m, 1H), 1.74 – 1.68 (m, 2H), 1.58 – 1.48 (m, 2H), 1.15 – 1.09 (m, 1H), 1.06 (td, *J* = 12.2, 10.9 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, 7H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.5, 152.9, 131.6, 119.1, 111.2, 74.0, 47.5, 41.3, 34.5, 31.6, 30.3, 26.6, 23.8, 22.2, 20.9, 16.7.

IR (KBr): 3387, 2961, 2919, 2893, 2860, 1681, 1601, 1535, 1500, 1455, 1346, 1287, 1174, 1119, 1102, 981, 964, 832, 769, 700 cm^{-1}.

HRMS (ESI) $[C_{19}H_{17}NNa]$ $[M+Na]^+$ calculated: 312.1939, found: 312.1943.

***N*-Cyclopropylaniline (13w)**



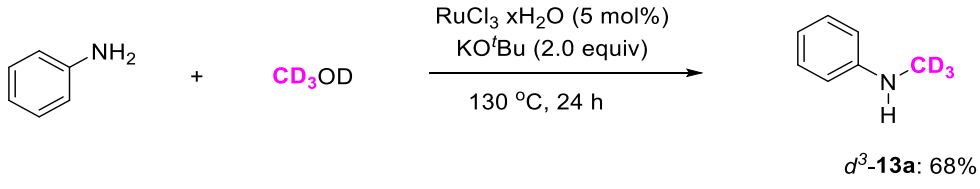
Synthetic procedure was followed previously reported method with modification.[162] In a glovebox, a flame-dried flask was charged with $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) and BrettPhos (160 mg, 0.3 mmol), bromobenzene (1.57 g, 10.0 mmol), cyclopropylamine (0.68 g, 12.0 mmol), KO^{t}Bu (1.68 g, 15.0 mmol), and degassed toluene (50 mL), then sealed and removed from the glovebox, the mixture stirred at 80 °C in an oil bath for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered over a short pad of silica gel, and concentrated in vacuo. The crude was purified by column chromatography (*n*-hexane/EtOAc: 20/1) to afford desired product **13w** as a light-yellow oil (1.07g, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.05 (m, 2H), 6.95 – 6.59 (m, 3H), 4.18 (s, 1H), 2.54 – 2.36 (m, 1H), 0.83 – 0.64 (m, 2H), 0.64 – 0.39 (m, 2H).

MS(EI): *m/z* 133 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[163]

***N*-(Methyl-*d*^{3})aniline (*d*^{3}-3a)**



[162] N. C. Pflug, M. Schmitt, K. Mcneill, Development of *N*-cyclopropylanilines to probe the oxidative properties of triplet-state photosensitizers. *Environ. Sci. Technol.* **2019**, *53*, 4813–4822.
[163] T. V. Nykaza, J. Yang, A. T. Radosevich, PEt_3-mediated deoxygenative C–N coupling of nitroarenes and boronic acids. *Tetrahedron* **2019**, *75*, 3248–3252.

Synthetic procedure was followed previously reported method with modification.[164] In a nitrogen glovebox, to a 20 mL ACE® pressure tube was charged with $RuCl_3$•nH_2O (20.6 mg, 0.1 mmol), KO*t*Bu (0.45 g, 4.0 mmol), aniline (200 μL, 2.0 mmol), and MeOH-d^3 (5 mL). The pressure tube was then sealed and allowed to stir at 130 ºC in an oil bath for 24 h. After completion of the reaction, the pressure tube was cooled to room temperature, and then filtered through a short silica pad and washed with EtOAc to remove the solid catalyst and base. After concentrating the solvent, the crude mixture was purified by column chromatography (*n*-hexane/EtOAc: 20/1) to afford desired product ***d*^{3}-13a** as a light-yellow oil (150 mg, 68% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 2H), 3.68 (br, 1H), 2.82 (s, 0.2H).

MS(EI): *m/z* 110 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[165]

4.3 General procedure

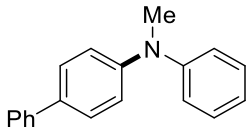
4.3.1 General procedure for the optimization of defluoroamination reaction

General procedure D: In a nitrogen-filled glovebox, to a flame-dried screw-capped test tube was added 4-fluorobiphenyl **1a** (17.2 mg, 0.10 mmol), *N*-methylaniline **13a**, base, solvent (0.5 mL), and silyl boronate, sequentially. The tube then was sealed and moved out from the glovebox. The solution was stirred at room temperature for indicated hours. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4. After filtered and concentrated under vacuum, the obtained reaction crude was followed by adding 3-fluoropyridine (8.6 μl, 0.1 mmol) as an internal standard. Corresponding yields were copied from the ^{1}H NMR and ^{19}F NMR analysis.

4.3.2 General procedure for the defluoroamination reaction

General procedure E: In a nitrogen-filled glovebox, to a flame-dried screw-capped test tube was added organic fluorides **1** (0.2 mmol), KO*t*Bu (89.6 mg, 0.8 mmol), dry triglyme (1.0 mL), and secondary amines **13** (0.6 mmol), sequentially. After stirring for 5 min, silyl boronate (96.8 mg, 0.4 mmol) was added to the mixture, and the tube then was sealed and moved out from the glovebox. The solution was stirred at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O and water, washed with brine, dried over Na_2SO_4. After filtered and concentrated under vacuum, the obtained reaction crude was followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After NMR analysis was conducted, the mixture was then concentrated again to give the crude, which was purified by column chromatography on silica gel to give the corresponding amines **14**.

***N*-Methyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14a)**



[164] N. Sarki, V. Goyal, N. K. Tyagi, Puttaswamy, A. Narani, A. Ray, K. Natte, Simple $RuCl_3$-catalyzed *N*-methylation of amines and transfer hydrogenation of nitroarenes using methanol. *ChemCatChem* **2021**, *13*, 1722–1729.
[165] L. Ke, G. Zhu, H. Qian, G. Xiang, Q. Chen, Z. Chen, Catalytic selective oxidative coupling of secondary *N*-alkylanilines: an approach to azoxyarene. *Org. Lett.* **2019**, *21*, 4008–4013.

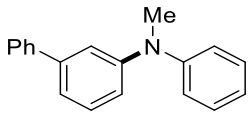
Compound **14a** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (46.1 mg, 89% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.56 – 7.49 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.28 (m, 3H), 7.19 – 6.99 (m, 5H), 3.38 (s, 3H).

MS(EI): *m/z* 259 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[166]

***N*-Methyl-*N*-phenyl-[1,1'-biphenyl]-3-amine (14b)**



Compound **14b** was prepared according to the **General procedure E** from **1b** (34.4 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (44.2 mg, 85% yield)

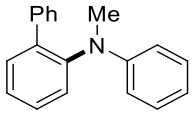
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.29 (m, 5H), 7.27 – 7.21 (m, 1H), 7.18 – 7.12 (m, 2H), 7.09 – 7.01 (m, 2H), 3.42 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 149.0, 142.5, 141.5, 129.7, 129.4, 128.8, 127.4, 127.3, 121.6, 120.9, 120.2, 119.2, 119.1, 40.5.

IR (KBr): 3058, 3032, 2941, 2879, 2812, 1591, 1495, 1450, 1418, 1345, 1232, 1131, 990, 895, 755, 698 cm^{-1}.

HRMS (EI) $[C_{19}H_{17}N]$ $[M]^+$ calculated: 259.1361, found: 259.1373.

***N*-Methyl-*N*-phenyl-[1,1'-biphenyl]-2-amine (14c)**



Compound **14c** was prepared according to the **General procedure E** from **1c** (34.4 mg, 0.2 mmol) and 1**3a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (41.5 mg, 80% yield).

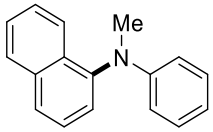
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 1H), 7.44 – 7.29 (m, 8H), 7.23 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.81 – 6.70 (m, 3H), 2.85 (s, 3H).

MS(EI): *m/z* 259 $[M]^+$.

[166] Q. Shao, Z. Jaing, W. Su, Solvent-free mechanochemical Buchwald-Hartwig amination of aryl chlorides without inert gas protection. *Tetrahedron Lett.* **2018**, *59*, 2277–2280.

The chemical shifts were consistent with those reported in the literature.[167]

***N*-Methyl-*N*-phenylnaphthalen-1-amine (14d)**



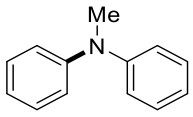
Compound **14d** was prepared according to the **General procedure E** from **1d** (26.0 μL, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (38.1 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (t, *J* = 6.8 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.36 (m, 4H), 7.20 (dd, *J* = 8.8, 7.3 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.67 (dd, *J* = 8.8, 1.1 Hz, 2H), 3.43 (s, 3H).

MS(EI): *m/z* 233 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[166]

***N*-Methyl-*N*-phenylaniline (4ea)**



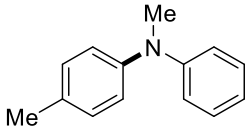
Compound **14e** was prepared according to the **General procedure E** from **1i** (38.0 μL, 0.4 mmol) and **13a** (128.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 20/1) as a light-yellow oil (57.9 mg, 79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 7.10 – 7.02 (m, 4H), 6.98 (t, *J* = 7.3 Hz, 2H), 3.34 (s, 3H).

MS(EI): *m/z* 183 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[166]

***N*,4-Dimethyl-*N*-phenylaniline (14f)**



Compound **14f** was prepared according to the **General procedure E** from **1s** (44.0 μL, 0.4 mmol) and **13a** (128.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a light-yellow oil (58 mg, 74% yield).

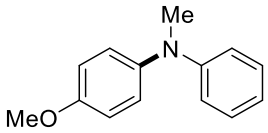
[167] S. Cho, Q. Wang, 1,2-Difunctionalization of aryl triflates: a direct and modular access to diversely functionalized anilines. *Org. Lett.* **2020**, *22*, 1670–1674.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.96 – 6.79 (m, 3H), 3.28 (s, 3H), 2.32 (s, 3H).

MS(EI): *m/z* 197 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[166]

4-Methoxy-*N*-methyl-*N*-phenylaniline (14g)



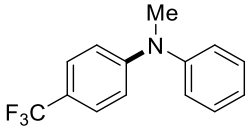
Compound **14g** was prepared according to the **General procedure E** from **1j** (45.0 μL, 0.4 mmol) and 1**3a** (128.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a light-yellow oil (56 mg, 66% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 2H), 7.12 – 7.05 (m, 2H), 6.94 – 6.85 (m, 2H), 6.79 (d, *J* = 6.9 Hz, 3H), 3.80 (s, 3H), 3.25 (s, 3H).

MS(EI): *m/z* 213 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[166]

***N*-Methyl-*N*-phenyl-4-(trifluoromethyl)aniline (14h)**



Compound **14h** was prepared according to the **General procedure E** from **1zb** (51.0 μL, 0.4 mmol) and **13a** (128.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (82.0 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.34 (m, 4H), 7.21 (dd, *J* = 8.0, 2.6 Hz, 3H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.36 (s, 3H).

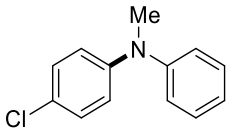
^{19}F NMR (282 MHz, $CDCl_3$) δ -61.63 (s, 3F).

MS(EI): *m/z* 251 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[168]

4-Chloro-*N*-methyl-*N*-phenylaniline (14i)

[168] Z. Chen, X. Chen, C. M. So, Palladium-catalyzed C(sp^2)–N bond cross-coupling with triaryl phosphates. *J. Org. Chem.* **2019**, *84*, 6366–6376.



Compound **14i** was prepared according to the **General procedure E** from **1zc** (52.0 mg, 0.4 mmol) and **13a** (128.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a light-yellow oil (44.1 mg, 51% yield).

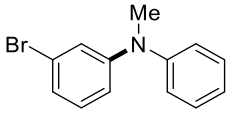
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.24 – 7.17 (m, 2H), 7.10 – 6.98 (m, 3H), 6.95 – 6.87 (m, 2H), 3.30 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 147.8, 129.5, 129.2, 125.7, 122.3, 121.6, 120.7, 40.5.

MS(EI): *m/z* 217 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[169]

3-Bromo-*N*-methyl-*N*-phenylaniline (14j)



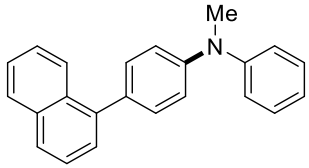
Compound **14j** was prepared according to the **General procedure E** from **1zd** (70.0 mg, 0.4 mmol) and 1**3a** (128.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 15/1) as a light-yellow oil (41.1 mg, 39% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 2H), 7.18 – 7.07 (m, 3H), 7.12 – 7.04 (m, 2H), 7.02 – 6.96 (m, 1H), 6.88 – 6.80 (m, 1H), 3.31 (s, 3H).

MS(EI): *m/z* 262 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[170]

***N*-Methyl-4-(naphthalen-1-yl)-*N*-phenylaniline (14k)**



Compound **14k** was prepared according to the **General procedure E** from **1e** (44.4 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid

[169] M. H. Ali, S. L. Buchwald, An improved method for the palladium-catalyzed amination of aryl iodides. *J. Org. Chem.* **2001**, *66*, 2560–2565.
[170] S, S. Bhojgude, T. Kaicharla, A. T. Biju, Employing arynes in transition-metal-free monoarylation of aromatic tertiary amines. *Org. Lett.* **2013**, *15*, 5452–5455.

(47.5 mg, 77% yield).

m.p. = 124.5 – 125.3 ℃.

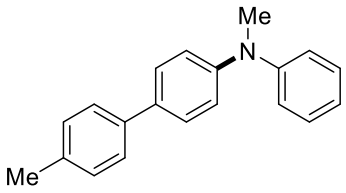
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.48 (m, 4H), 7.48 – 7.44 (m, 2H), 7.39 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.23 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.18 – 7.14 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 148.3, 140.2, 134.0, 133.0, 131.9, 130.9, 129.5, 128.4, 127.3, 127.0, 126.3, 126.0, 125.8, 125.6, 122.2, 121.7, 119.1, 40.4.

IR (KBr): 3059, 3032, 2929, 2902, 2818, 1590, 1497, 1392, 1345, 1252, 1185, 1131, 849, 801, 780, 759, 694 cm^{-1}.

HRMS (EI) $[C_{23}H_{19}N]$ $[M]^+$ calculated: 309.1517, found: 309.1532.

***N*,*4'*-Dimethyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14l)**



Compound **14l** was prepared according to the **General procedure E** from **1f** (37.2 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (50.0 mg, 86% yield).

m.p. = 113.8 – 114.6 ℃.

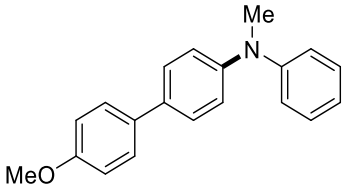
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 10.4, 8.4 Hz, 4H), 7.33 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.12 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 3.38 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.2, 138.1, 136.4, 133.8, 129.6, 129.4, 127.7, 126.6, 121.8, 121.2, 120.1, 40.4, 21.2.

IR (KBr): 3059, 3026, 2917, 2884, 2819, 1590, 1496, 1342, 1255, 1128, 868, 808, 758, 699 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}N]$ $[M]^+$ calculated: 273.1517, found: 273.1505.

***4'*-Methoxy-*N*-methyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14m)**



Compound **14m** was prepared according to the **General procedure E** from **1g** (40.4 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (48.3 mg, 83% yield).

m.p. = 144.1 – 144.9 ℃.

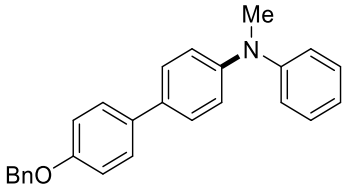
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.32 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.12 – 7.06 (m, 4H), 7.03 – 6.96 (m, 3H), 3.87 (s, 3H), 3.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 149.0, 147.9, 133.7, 133.6, 129.4, 127.7, 127.5, 121.6, 120.9, 120.5, 114.3, 55.5, 40.4.

IR (KBr): 3033, 3003, 2953, 2835, 1594, 1496, 1349, 1281, 1250, 1181, 1036, 824, 766, 704 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}NO]$ $[M]^+$ calculated: 289.1467, found: 289.1480.

***4'*-(Benzyloxy)-*N*-methyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14n)**



Compound **14n** was prepared according to the **General procedure E** from **1w** (56.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (44.5 mg, 61% yield).

m.p. = 163.1 – 163.5 ℃.

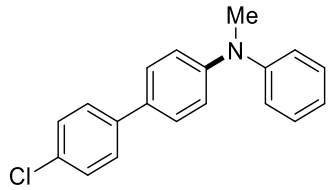
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.51 – 7.47 (m, 4H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.11 (dd, *J* = 9.0, 1.4 Hz, 3H), 7.09 – 7.05 (m, 3H), 7.04 – 6.99 (m, 1H), 5.13 (s, 2H), 3.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 149.0, 147.9, 137.2, 133.9, 133.6, 129.4, 128.7, 128.1, 127.7, 127.6, 127.5, 121.6, 120.9, 120.4, 115.2, 70.2, 40.4.

IR (KBr): 3061, 3037, 2910, 2864, 2835, 1594, 1503, 1378, 1348, 1279, 1248, 1179, 1085, 1004, 860, 824, 739, 700 cm^{-1}.

HRMS (EI) $[C_{26}H_{23}NO]$ $[M]^+$ calculated: 365.1780, found: 365.1772.

***4'*-Chloro-*N*-methyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14o)**



Compound **14o** was prepared according to the **General procedure E** from **1ze** (41.2 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (46.0 mg, 77% yield).

m.p. = 145.3 – 146.0 ℃.

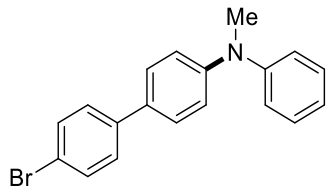
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.49 – 7.44 (m, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.35 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.15 (dd, *J* = 8.7, 1.1 Hz, 2H), 7.09 – 7.02 (m, 3H), 3.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 139.4, 132.6, 131.8, 129.5, 129.0, 127.8, 127.7, 122.6, 122.2, 119.2, 40.4.

IR (KBr): 3094, 3060, 3028, 2926, 2899, 2828, 1593, 1487, 1396, 1417, 1340, 1255, 1090, 821, 760, 695 cm^{-1}.

HRMS (EI) $[C_{19}H_{16}ClN]$ $[M]^+$ calculated: 293.0971, found: 293.0972.

4'-Bromo-*N*-methyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14p)



Compound **14p** was prepared according to the **General procedure E** from **1zf** (51.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (40.2 mg, 59% yield).

m.p. = 98.6 – 99.3 ℃.

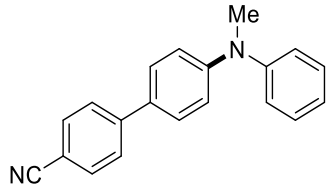
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.53 (m, 2H), 7.56 – 7.47 (m, 2H), 7.48 – 7.36 (m, 2H), 7.36 – 7.28 (m, 2H), 7.17 – 6.96 (m, 5H), 3.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 148.5, 141.0, 133.5, 129.4, 128.8, 127.9, 126.71, 126.69, 122.1, 121.6, 119.8, 40.4.

IR (KBr): 3055, 3033, 2939, 2884, 2817, 1590, 1523, 1488, 1344, 1256, 1131, 870, 817, 753, 692 cm^{-1}.

HRMS (ESI) $[C_{19}H_{17}BrN]$ $[M+H]^+$ calculated: 338.0544, found: 338.0552.

4'-(Methyl(phenyl)amino)-[1,1'-biphenyl]-4-carbonitrile (14q)



Compound **14q** was prepared according to the **General procedure E** from **1zg** (39.4 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (29.0 mg, 51% yield).

m.p. = 139.2 – 140.0 ℃.

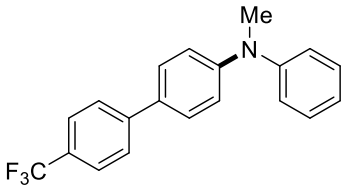
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.51 – 7.47 (m, 2H), 7.37 (dd, *J* = 8.4, 7.3 Hz, 2H), 7.19 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.02 – 6.96 (m, 2H), 3.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 148.3, 145.4, 132.7, 129.7, 129.6, 127.9, 126.8, 123.8, 123.7, 119.4, 117.5, 109.7, 40.3.

IR (KBr): 3055, 2997, 2901, 2218, 1591, 1525, 1491, 1345, 1291, 1178, 1117, 818, 773, 700 cm^{-1}.

HRMS (EI) $[C_{20}H_{16}N_2]$ $[M]^+$ calculated: 284.1313, found: 284.1317.

***N*-Methyl-*N*-phenyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14r)**



Compound **14r** was prepared according to the **General procedure E** from **1v** (48.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (55.1 mg, 84% yield).

m.p. = 121.6 – 122.4 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 4H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.09 (t, *J* = 6.9 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 3.38 (s, 3H).

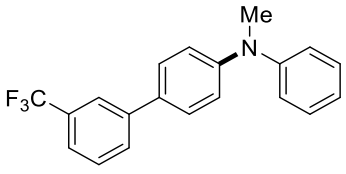
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 148.6, 144.5, 130.9, 129.6, 128.5 (q, *J* = 32.7 Hz), 128.0, 126.7, 125.8, 124.6 (q, *J* = 270.4 Hz), 123.2, 123.1, 118.4, 40.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.73 (s, 3F).

IR (KBr): 3035, 2953, 2889, 2826, 1602, 1532, 1498, 1333, 1250, 1171, 1115, 1073, 1011, 829, 814, 759, 701 cm^{-1}.

HRMS (EI) $[C_{20}H_{16}F_3N]$ $[M]^+$ calculated: 327.1235, found: 327.1230.

***N*-Methyl-*N*-phenyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14s)**



Compound **4sa** was prepared according to the **General procedure E** from **1zh** (48.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (53.6 mg, 82% yield).

m.p. = 80.0 – 80.5 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.59 – 7.50 (m, 4H), 7.37 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.18 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.08 – 7.05 (m, 2H), 3.40 (s, 3H).

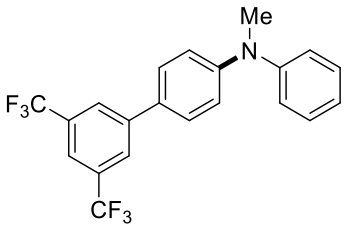
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.6, 141.8, 131.22, 131.19 (d, *J* = 32.1 Hz), 129.8, 129.6, 129.3, 127.9, 124.4 (q, *J* = 272.9 Hz), 123.3, 123.2, 123.0, 122.7, 118.7, 40.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.06 (s, 3F).

IR (KBr): 3068, 3027, 2940, 2884, 2815, 1591, 1521, 1496, 1440, 1336, 1122, 1072, 1036, 802, 771, 701 cm^{-1}.

HRMS (EI) $[C_{20}H_{16}F_3N]$ $[M]^+$ calculated: 327.1235, found: 327.1242.

***N*-Methyl-*N*-phenyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14t)**



Compound **14t** was prepared according to the **General procedure E** from **1zi** (62.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (42.7 mg, 54% yield).

m.p. = 41.6 – 42.3 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.78 (s, 1H), 7.53 – 7.47 (m, 2H), 7.38 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.20 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.40 (s, 3H).

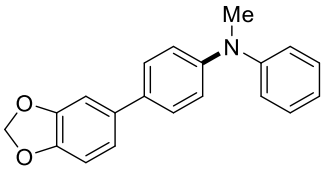
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 148.3, 143.1, 132.1 (q, *J* = 33.0 Hz), 129.7, 128.8, 128.0, 126.4, 123.9, 123.7 (q, *J* = 272.7 Hz), 119.9, 117.7, 40.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.32 (s, 6F).

IR (KBr): 3064, 3037, 2956, 2933, 2897, 1594, 1520, 1496, 1467, 1383, 1273, 1168, 1126, 1052, 836, 701 cm^{-1}.

HRMS (EI) $[C_{21}H_{15}F_6N]$ $[M]^+$ calculated: 395.1109, found: 395.1096.

4-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-*N*-phenylaniline (14u)



Compound **14u** was prepared according to the **General procedure E** from **1h** (43.3 mg, 0.2 mmol) and **13a** (64.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (49.4 mg, 81% yield).

m.p. = 98.3 – 99.1 ℃.

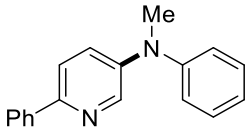
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.7 Hz, 2H), 7.34 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.13 (dd, *J* = 8.7, 1.1 Hz, 2H), 7.10 – 7.05 (m, 4H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H), 3.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 148.2, 148.1, 146.6, 135.4, 133.5, 129.4, 127.6, 121.9, 121.2, 120.03, 120.00, 108.6, 107.3, 101.1, 40.4.

IR (KBr): 3033, 2954, 2917, 2823, 1595, 1503, 1437, 1349, 1304, 1251, 1233, 1180, 1106, 1044, 928, 804, 755, 699 cm^{-1}.

HRMS (EI) $[C_{20}H_{17}NO_2]$ $[M]^+$ calculated: 303.1259, found: 303.1267.

***N*-Methyl-*N*,*6*-diphenylpyridin-3-amine (14v)**



Compound **14v** was prepared according to the **General procedure E** from **1o** (35.0 mg, 0.2 mmol) and **13a** (64.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 1/1) as a white solid (48.4 mg, 93% yield).

m.p. = 85.7 – 86.3 ℃.

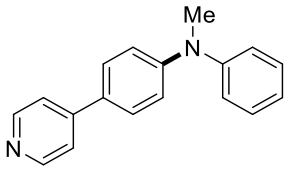
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.99 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.62 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.33 (m, 3H), 7.31 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.17 (dd, *J* = 8.7, 1.1 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 3.39 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 147.8, 143.9, 140.0, 139.3, 129.6, 128.7, 128.0, 126.1, 125.4, 123.3, 122.5, 120.3, 40.1.

IR (KBr): 3065, 3025, 2960, 2884, 2814, 1577, 1556, 1477, 1348, 1228, 1133, 1070, 1007, 907, 830, 734, 699 cm^{-1}.

HRMS (EI) $[C_{18}H_{16}N_2]$ $[M]^+$ calculated: 260.1313, found: 260.1325.

***N*-Methyl-*N*-phenyl-4-(pyridin-4-yl)aniline (14w)**



Compound **14w** was prepared according to the **General procedure E** from **1zq** (35.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 4/1) as a light-yellow solid (47.6 mg, 91% yield), m.p. = 109.8 – 110.6 ˚C.

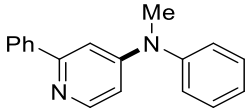
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 6.2 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.37 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.19 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 149.9, 148.2, 147.9, 129.6, 128.3, 127.6, 123.9, 123.8, 120.7, 117.3, 40.3.

IR (KBr): 3032, 3003, 2952, 2885, 2821, 1588, 1486, 1345, 1227, 1200, 1124, 990, 811, 766, 703 cm^{-1}.

HRMS (EI) $[C_{18}H_{16}N_2]$ $[M]^+$ calculated: 260.1313, found: 260.1320.

***N*-Methyl-*N*,2-diphenylpyridin-4-amine (14x)**



Compound **14x** was prepared according to the **General procedure E** from **1zj** (35.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 4/1) as a colorless oil (48.0 mg, 94% yield).

m.p. = 70.2 – 70.7 ℃.

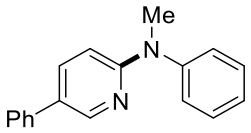
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.8 Hz, 1H), 7.86 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.46 – 7.38 (m, 4H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.29 – 7.21 (m, 3H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.53 (dd, *J* = 5.9, 2.5 Hz, 1H), 3.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 154.6, 149.8, 146.4, 140.4, 130.0, 128.6, 127.0, 126.7, 126.4, 107.2, 105.5, 39.7.

IR (KBr): 3033, 2920, 2854, 1577, 1539, 1493, 1413, 1360, 1248, 1139, 1081, 913, 825, 769, 731, 693 cm^{-1}.

HRMS (EI) $[C_{18}H_{16}N_2]$ $[M]^+$ calculated: 260.1313, found: 260.1324.

***N*-Methyl-*N*,5-diphenylpyridin-2-amine (14y)**



Compound **14y** was prepared according to the **General procedure E** from **1zp** (35.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a colorless oil (49.1 mg, 94% yield).

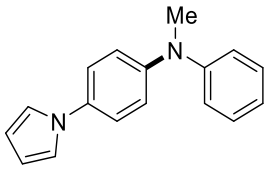
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.5 Hz, 1H), 7.59 – 7.46 (m, 3H), 7.39 (d, *J* = 7.0 Hz, 4H), 7.28 (d, *J* = 7.4 Hz, 3H), 7.25 – 7.17 (m, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 3.52 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 146.8, 146.0, 138.5, 135.4, 129.8, 129.0, 126.8, 126.4, 126.2, 125.6, 109.1, 38.6.

IR (KBr): 3060, 3021, 2899, 1607, 1550, 1496, 1381, 1296, 1127, 1079, 1025, 767, 746, 699 cm^{-1}.

HRMS (EI) $[C_{18}H_{16}N_2]$ $[M]^+$ calculated: 260.1313, found: 260.1320.

***N*-Methyl-*N*-phenyl-4-(1*H*-pyrrol-1-yl)aniline (14z)**



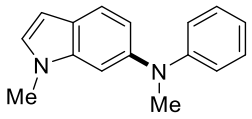
Compound **14z** was prepared according to the **General procedure E** from **1n** (32.2 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (48.6 mg, 97% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.3, 6.9 Hz, 4H), 7.12 – 7.03 (m, 6H), 7.00 (td, *J* = 7.3, 1.0 Hz, 1H), 6.39 – 6.31 (m, 2H), 3.35 (s, 3H).

MS(EI): *m/z* 248 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[171]

***N*,*1*-Dimethyl-*N*-phenyl-1*H*-indol-6-amine (14za)**



Compound **14za** was prepared according to the **General procedure E** from **1p** (30.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 4/1) as a light brown

[171] P. Weber, T. Scherpf, I. Rodstein, D. Lichte, L. T. Scharf, L. J. Gooßen, V. H. Gessner, A highly active ylide-functionalized phosphine for palladium-catalyzed aminations of aryl chlorides. *Angew. Chem. Int. Ed.* **2019**, *58*, 3203–3207.

solid (40.0 mg, 85% yield)

m.p. = 62.4 – 63.1 ℃.

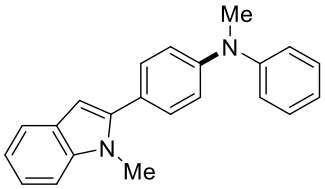
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 2H), 7.11 (s, 1H), 6.99 (d, *J* = 3.1 Hz, 1H), 6.94 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 3.1 Hz, 1H), 3.69 (s, 3H), 3.34 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 150.3, 143.9, 137.5, 129.03, 128.96, 125.6, 121.7, 118.2, 115.9, 105.9, 101.0, 41.0, 32.9.

IR (KBr): 3057, 3020, 2996, 2938, 2874, 1597, 1498, 1473, 1331, 1309, 1254, 1100, 751, 713, 694 cm^{-1}.

HRMS (EI) $[C_{16}H_{16}N_2]$ $[M]^+$ calculated: 236.1313, found: 236.1305.

***N*-Methyl-4-(1-methyl-1*H*-indol-2-yl)-*N*-phenylaniline (14zb)**



Compound **14zb** was prepared according to the **General procedure E** from **1q** (45.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (61.0 mg, 96% yield).

m.p. = 119.9 – 120.7 ℃.

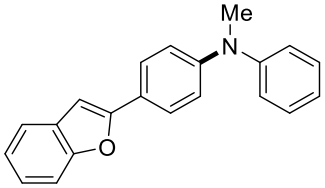
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.41 (dd, *J* = 8.6, 7.4 Hz, 3H), 7.33 – 7.26 (m, 1H), 7.24 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.23 – 7.16 (m, 1H), 7.14 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.58 (d, *J* = 0.9 Hz, 1H), 3.81 (s, 3H), 3.44 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 148.6, 141.9, 138.3, 130.2, 129.6, 128.2, 124.2, 123.1, 122.9, 121.4, 120.3, 119.8, 117.9, 109.6, 100.9, 40.3, 31.3.

IR (KBr): 3056, 3036, 2938, 2904, 2882, 1611, 1591, 1561, 1497, 1430, 1343, 1253, 1113, 1067, 821, 782, 735, 694 cm^{-1}.

HRMS (EI) $[C_{22}H_{20}N_2]$ $[M]^+$ calculated: 312.1626, found: 312.1632.

4-(Benzofuran-2-yl)-*N*-methyl-*N*-phenylaniline (14zc)



Compound **14zc** was prepared according to the **General procedure E** from **1u** (42.4 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (53.9 mg, 90% yield).

m.p. = 128.5 – 129.1 ℃.

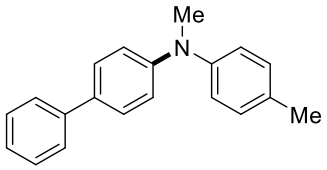
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.53 – 7.50 (m, 1H), 7.49 – 7.45 (m, 1H), 7.33 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.24 – 7.17 (m, 2H), 7.14 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 1.0 Hz, 1H), 3.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 154.8, 149.3, 148.4, 129.7, 129.6, 126.1, 123.6, 123.4, 122.9, 121.9, 120.5, 117.7, 111.0, 99.3, 40.3.

IR (KBr): 3114, 3062, 3034, 2924, 2899, 2830, 1608, 1593, 1492, 1451, 1346, 1256, 1135, 1032, 917, 802, 745, 700 cm^{-1}.

HRMS (EI) $[C_{21}H_{17}NO]$ $[M]^+$ calculated: 299.1310, found: 299.1307.

***N*-Methyl-*N*-(*p*-tolyl)-[1,1'-biphenyl]-4-amine (4zd)**



Compound **14zd** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13b** (75.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (47.3 mg, 87% yield).

m.p. = 132.8 – 133.4 ℃.

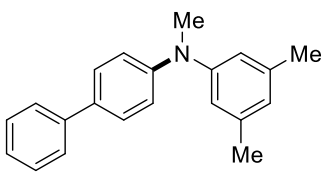
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.12 – 7.08 (m, 2H), 7.02 – 6.97 (m, 2H), 3.36 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 146.4, 141.1, 132.9, 132.1, 130.2, 128.8, 127.7, 126.6, 126.5, 123.5, 117.6, 40.5, 22.0.

IR (KBr): 3060, 3029, 2916, 2819, 1600, 1510, 1487, 1340, 1255, 1120, 1073, 819, 761, 691 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}N]$ $[M]^+$ calculated: 273.1517, found: 273.1519.

***N*-(3,5-Dimethylphenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14ze)**



Compound **14ze** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13c** (85.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (47.0 mg, 82% yield).

m.p. = 92.4 – 93.0 ℃.

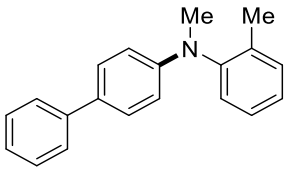
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 6.8 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.77 (s, 2H), 6.71 (s, 1H), 3.35 (d, *J* = 1.4 Hz, 3H), 2.38 – 2.16 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 148.7, 141.1, 139.1, 132.9, 128.8, 127.8, 126.7, 126.6, 124.4, 120.0, 119.1, 40.5, 21.6.

IR (KBr): 3061, 3026, 2919, 2816, 1593, 1521, 1486, 1348, 1318, 1201, 1091, 841, 759, 722, 690 cm^{-1}.

HRMS (EI) $[C_{21}H_{21}N]$ $[M]^+$ calculated: 287.1674, found: 287.1683.

***N*-Methyl-*N*-(*o*-tolyl)-[1,1'-biphenyl]-4-amine (14zf)**



Compound **14zf** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13d** (72.6 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (16.7 mg, 31% yield).

m.p. = 99.5 – 101.6 ℃.

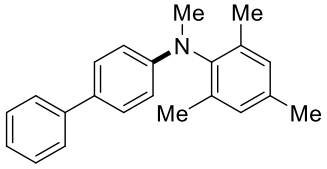
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.46 – 7.33 (m, 4H), 7.32 – 7.11 (m, 5H), 6.75 – 6.46 (m, 2H), 3.25 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 146.7, 141.3, 136.9, 131.5, 129.6, 128.8, 128.5, 127.8, 127.7, 126.7, 126.4, 126.1, 113.1, 39.3, 18.0.

IR (KBr): 3058, 3028, 2921, 2812, 1612, 1578, 1520, 1487, 1345, 1253, 1197, 1118, 1074, 824, 762, 728, 697 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}N]$ $[M]^+$ calculated: 273.1517, found: 273.1527.

***N*-Mesityl-*N*-methyl-[1,1'-biphenyl]-4-amine (14zg)**



Compound **14zg** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13e** (94.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (19.4 mg, 32% yield).

m.p. = 119.3 – 119.9 ℃.

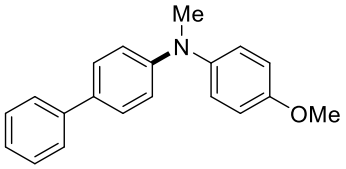
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.47 – 7.32 (m, 4H), 7.26 – 7.18 (m, 1H), 7.02 – 6.93 (m, 2H), 6.48 (s, 2H), 3.22 (s, 3H), 2.34 (s, 3H), 2.09 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 141.5, 141.4, 137.5, 136.7, 129.7, 128.7, 128.66, 127.9, 126.3, 125.9, 37.4, 21.1, 18.0.

IR (KBr): 3072, 3022, 2917, 2809, 1613, 1520, 1486, 1345, 1318, 1250, 1191, 1119, 1073, 816, 761, 695 cm^{-1}.

HRMS (EI) $[C_{22}H_{23}N]$ $[M]^+$ calculated:301.1830, found: 301.1823.

***N*-(4-Methoxyphenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14zh)**



Compound **14zh** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13f** (80.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (35.1 mg, 61% yield).

m.p. = 132.8 – 133.4 ℃.

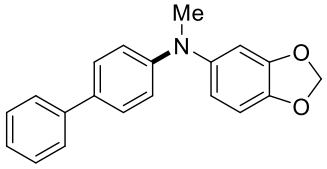
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 2H), 7.50 – 7.36 (m, 4H), 7.33 – 7.23 (m, 1H), 7.20 – 7.10 (m, 2H), 6.98 – 6.90 (m, 2H), 6.89 – 6.81 (m, 2H), 3.84 (s, 3H), 3.32 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 156.7, 149.2, 142.0, 141.2, 131.0, 128.8, 127.7, 126.8, 126.5, 126.3, 115.6, 115.0, 55.6, 40.7.

IR (KBr): 3035, 3002, 2948, 2932, 2899, 2830, 1607, 1509, 1487, 1454, 1341, 1246, 1109, 1031, 831, 767, 695 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}NO]$ $[M]^+$ calculated: 289.1467, found: 289.1461.

***N*-([1,1'-Biphenyl]-4-yl)-*N*-methylbenzo[*d*][1,3]dioxol-5-amine (14zi)**



Compound **14zi** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13g** (72.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 4/1) as a white solid (40.6 mg, 82% yield).

m.p. = 131.7 – 132.1 ℃.

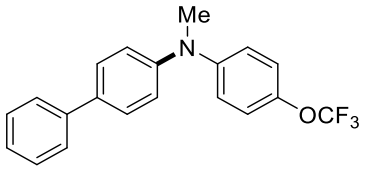
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.43 – 7.38 (m, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 2.1 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.98 (s, 2H), 3.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.5, 144.5, 143.5, 141.2, 131.5, 128.8, 127.7, 126.6, 126.4, 118.1, 116.3, 108.8, 106.8, 101.4, 40.8.

IR (KBr): 3070, 3019, 2926, 2898, 2814, 1604, 1519, 1480, 1446, 1364, 1326, 1220, 1112, 1038, 922, 764, 719, 692 cm^{-1}.

HRMS (EI) $[C_{20}H_{17}NO_2]$ $[M]^+$ calculated: 303.1259, found: 303.1273.

***N*-methyl-*N*-(4-(trifluoromethoxy)phenyl)-[1,1'-biphenyl]-4-amine (14zj)**



Compound **14zj** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13h** (90.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (33.7 mg, 49% yield).

m.p. = 123.7– 124.1 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.49 (m, 4H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.28 (m, 1H), 7.17 – 7.07 (m, 4H), 7.07 – 7.00 (m, 2H), 3.36 (s, 3H).

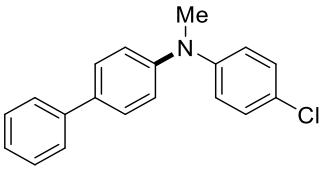
^{13}C NMR (176 MHz, $CDCl_3$) δ 148.0, 147.7, 143.2, 140.8, 134.9, 128.9, 128.1, 127.0, 126.8, 122.2, 121.3, 120.9, 120.76 (q, *J* = 256.3 Hz), 40.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.67 (s, 3F).

IR (KBr): 3078, 3029, 2940, 2887, 1601, 1507, 1489, 1345, 1267, 1254, 1223, 1198, 1146, 839, 764, 693 cm^{-1}.

HRMS (EI) $[C_{20}H_{16}F_3NO]$ $[M]^+$ calculated: 343.1184, found: 343.1198.

***N*-(4-Chlorophenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14zk)**



Compound **14zk** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13i** (72.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 15/1) as a white solid (35.4 mg, 60% yield).

m.p. = 134.2 – 135.0 ℃.

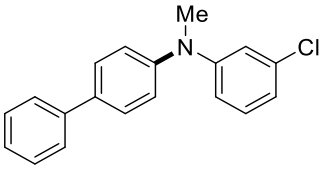
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 6.9 Hz, 2H), 7.42 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.1 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 147.6, 140.8, 134.6, 129.3, 128.9, 128.1, 126.9, 126.8, 126.4, 121.8, 120.9, 40.5.

IR (KBr): 3033, 2886, 1606, 1586, 1518, 1488, 1335, 1252, 1100, 1070, 822, 761, 699 cm^{-1}.

HRMS (EI) $[C_{19}H_{16}ClN]$ $[M]^+$ calculated: 293.0971, found: 293.0970.

***N*-(3-Chlorophenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14zl)**



Compound **14zl** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13j** (72.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (31.6 mg, 54% yield).

m.p. = 97.6 – 98.3 ℃.

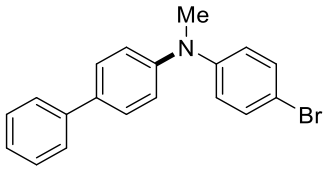
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.58 – 7.53 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.19 – 7.14 (m, 3H), 6.98 (t, *J* = 2.1 Hz, 1H), 6.89 – 6.85 (m, 2H), 3.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 147.6, 140.7, 135.9, 135.0, 130.2, 128.9, 128.3, 127.1, 126.9, 122.9, 120.3, 118.5, 116.8, 40.4.

IR (KBr): 3052, 3027, 2925, 2905, 2887, 1587, 1554, 1483, 1333, 1247, 1104, 1079, 901, 839, 762, 689 cm^{-1}.

HRMS (EI) $[C_{19}H_{16}ClN]$ $[M]^+$ calculated: 293.0971, found: 293.0957.

***N*-(4-Bromophenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14zm)**



Compound **14zm** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13k** (112.0 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 20/1) as a white solid (22.1 mg, 33% yield), m.p. = 131.0 – 132.1 ℃.

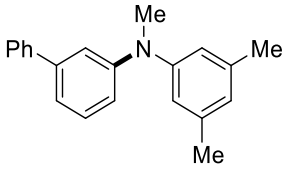
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.49 (m, 4H), 7.49 – 7.28 (m, 5H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 3.34 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 147.9, 140.8, 134.9, 132.2, 128.9, 128.1, 127.0, 126.8, 121.7, 121.4, 113.5, 40.4.

IR (KBr): 3059, 3031, 2935, 2886, 2820, 1604, 1583, 1522, 1488, 1341, 1256, 1205, 1123, 1006, 824, 764, 693 cm^{-1}.

HRMS (ESI) $[C_{19}H_{17}BrN]$ $[M+H]^+$ calculated: 338.0544, found: 338.0529.

***N*-(3,5-Dimethylphenyl)-*N*-methyl-[1,1'-biphenyl]-3-amine (14zn)**



Compound **14zn** was prepared according to the **General procedure E** from **1b** (34.4 mg, 0.2 mmol) and **13c** (85.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a light-yellow oil (43.5 mg, 76% yield).

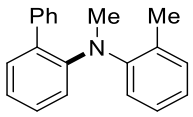
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 2H), 7.45 – 7.40 (m, 2H), 7.37 – 7.31 (m, 2H), 7.22 (t, *J* = 2.1 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.00 – 6.96 (m, 1H), 6.75 (s, 2H), 6.68 (s, 1H), 3.35 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.7, 149.1, 142.4, 141.6, 139.0, 129.5, 128.8, 127.4, 127.3, 123.9, 119.7, 119.3, 118.7, 118.5, 40.6, 21.6.

IR (KBr): 3031, 2916, 2812, 1588, 1568, 1482, 1417, 1346, 1203, 1130, 991, 848, 756, 698 cm^{-1}.

HRMS (ESI) $[C_{21}H_{22}N]$ $[M+H]^+$ calculated: 288.1752, found: 288.1747.

***N*-Methyl-*N*-(*o*-tolyl)-[1,1'-biphenyl]-2-amine (14zo)**



Compound **14zo** was prepared according to the **General procedure E** from **1c** (34.4 mg, 0.2 mmol) and **13d** (72.6 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 15/1) as a white solid (12.1 mg, 22% yield).

m.p. = 93.7 – 94.2 ℃.

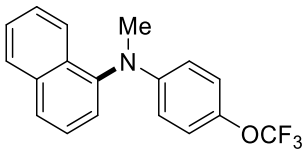
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.26 – 7.20 (m, 4H), 7.20 – 7.16 (m, 1H), 7.06 (qd, *J* = 7.3, 1.2 Hz, 2H), 6.96 (dd, *J* = 8.0, 1.0 Hz, 2H), 6.90 – 6.85 (m, 2H), 2.93 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 149.0, 141.5, 135.1, 132.5, 132.1, 131.4, 128.8, 128.2, 128.0, 126.6, 126.5, 123.2, 123.0, 122.4, 121.2, 41.2, 19.4.

IR (KBr): 3059, 3014, 2966, 2929, 2871, 1593, 1477, 1434, 1278, 1127, 1053, 775, 760, 699 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}N]$ $[M]^+$ calculated: 273.1517, found: 273.1521.

***N*-Methyl-*N*-(4-(trifluoromethoxy)phenyl)naphthalen-1-amine (14zp)**



Compound **14zp** was prepared according to the **General procedure E** from **1d** (26.0 μL, 0.2 mmol) and **3h** (90.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (34.2 mg, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.56 – 7.50 (m, 2H), 7.47 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.37 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.02 (dd, *J* = 9.3, 0.9 Hz, 2H), 6.59 – 6.53 (m, 2H), 3.40 (s, 3H).

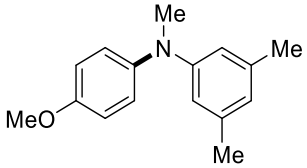
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 145.0, 140.5, 135.3, 131.2, 128.7, 127.2, 126.7, 126.6, 126.5, 125.5, 123.7, 122.1, 120.9 (q, *J* = 255.4 Hz), 113.8, 40.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.91 (s, 3F).

IR (KBr): 3051, 3027, 2951, 1611, 1595, 1505, 1474, 1394, 1336, 1268, 1204, 1160, 1115, 1016, 832, 775 cm^{-1}.

HRMS (EI) $[C_{18}H_{14}F_3NO]$ $[M]^+$ calculated: 317.1027, found: 317.1035.

***N*-(4-methoxyphenyl)-*N*,3,5-trimethylaniline (14zq)**



Compound **14zq** was prepared according to the **General procedure E** from **1j** (45.0 μL, 0.4 mmol) and **13c** (170.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a light-yellow solid (65.7 mg, 68% yield).

m.p. = 50.0 – 51.2 ℃.

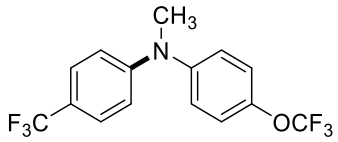
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.13 – 6.99 (m, 2H), 6.91 – 6.86 (m, 2H), 6.47 (s, 1H), 6.44 (s, 2H), 3.83 (s, 3H), 3.24 (s, 3H), 2.24 (s, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 156.2, 150.0, 142.6, 138.7, 126.1, 120.6, 114.8, 114.0, 55.6, 40.7, 21.7.

IR (KBr): 3006, 2950, 2912, 2831, 1595, 1508, 1476, 1353, 1298, 1243, 1205, 1185, 1106, 1098, 1035, 839, 820, 693 cm^{-1}.

HRMS (ESI) $[C_{16}H_{20}NO]$ $[M+H]^+$ calculated: 242.1545, found: 242.1544.

N-Methyl-4-(trifluoromethoxy)-N-(4-(trifluoromethyl)phenyl)aniline (14zr)



Compound **14zr** was prepared according to the **General procedure E** from **1zb** (51.0 μL, 0.4 mmol) and **13h** (180.0 μL, 1.2 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a light-yellow oil (60.4 mg, 45% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.54 – 7.39 (m, 2H), 7.27 – 7.12 (m, 4H), 6.93 – 6.83 (m, 2H), 3.35 (s, 3H).

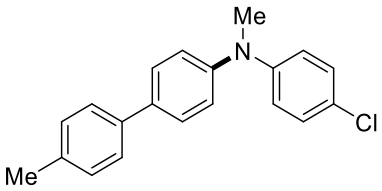
^{13}C NMR (176 MHz, $CDCl_3$) δ 151.3, 146.6, 145.7, 126.5 (q, J = 3.9 Hz), 125.8, 124.8 (q, J = 270.7 Hz), 122.6, 121.1 (q, J = 32.8 Hz), 119.9 (q, J = 256.9 Hz), 116.0, 40.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.46 (s, 3F), -61.80 (s, 3F).

IR (KBr): 3052, 2954, 2893, 2825, 1620, 1505, 1333, 1270, 1208, 1120, 1078, 1062, 828 cm^{-1}.

HRMS (ESI) $[C_{15}H_{12}F_6NO]$ $[M+H]^+$ calculated: 336.0825, found: 336.0829.

***N*-(4-Chlorophenyl)-*N*,4'-dimethyl-[1,1'-biphenyl]-4-amine (14zs)**



Compound **14zs** was prepared according to the **General procedure E** from **1f** (37.2 mg, 0.2 mmol) and **13i** (72.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (42.6 mg, 69% yield).

m.p. = 136.3 – 136.9 ℃.

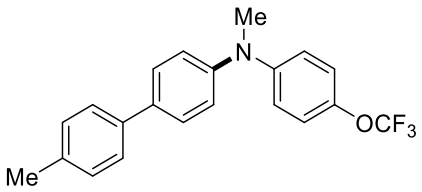
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.21 (m, 4H), 7.12 – 7.05 (m, 2H), 7.03 – 6.92 (m, 2H), 3.33 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 147.6, 137.9, 136.7, 134.8, 129.6, 129.3, 127.9, 126.6, 126.1, 121.3, 121.2, 40.5, 21.2.

IR (KBr): 3031, 2917, 2822, 1605, 1590, 1485, 1341, 1253, 1181, 1131, 1104, 1004, 803, 753, 686 cm^{-1}.

HRMS (EI) $[C_{20}H_{18}ClN]$ $[M]^+$ calculated: 307.1128, found: 307.1139.

***N*,4'-Dimethyl-*N*-(4-(trifluoromethoxy)phenyl)-[1,1'-biphenyl]-4-amine (14zt)**



Compound **14zt** was prepared according to the **General procedure E** from **1f** (37.2 mg, 0.2 mmol) and **3h** (90.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (38.8 mg, 54% yield), m.p. = 127.4 – 128.1 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.17 – 7.09 (m, 4H), 7.06 – 6.97 (m, 2H), 3.36 (s, 3H), 2.41 (s, 3H).

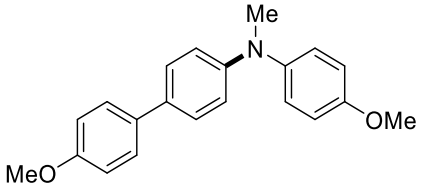
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 143.0, 137.9, 136.7, 135.1, 129.6, 128.0, 126.7, 122.2, 121.8, 121.7, 120.8 (q, *J* = 256.0 Hz), 120.4, 40.6, 21.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.72 (s, 3F).

IR (KBr): 3024, 2925, 2883, 2819, 1603, 1497, 1343, 1288, 1196, 1155, 1107, 844, 810, 509 cm^{-1}.

HRMS (EI) $[C_{21}H_{18}F_3NO]$ $[M]^+$ calculated: 357.1340, found: 357.1355.

4'-Methoxy-*N*-(4-methoxyphenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14zu)



Compound **14zu** was prepared according to the **General procedure E** from **1g** (40.4 mg, 0.2 mmol) and **13f** (82.0 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 3/1) as a white solid (42.0 mg, 66% yield).

m.p. = 170.0 – 170.5 ℃.

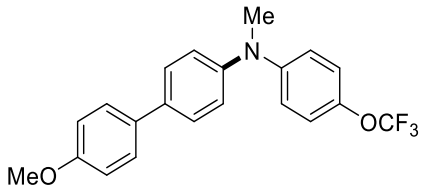
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.43 – 7.39 (m, 2H), 7.16 – 7.11 (m, 2H), 6.97 – 6.94 (m, 2H), 6.93 – 6.90 (m, 2H), 6.86 – 6.83 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.30 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 156.5, 148.8, 142.2, 133.9, 130.9, 127.5, 127.3, 126.5, 115.9, 114.9, 114.2, 55.6, 55.5, 40.7.

IR (KBr): 3035, 3012, 2951, 2912, 2836, 1606, 1505, 1441, 1344, 1246, 1182, 1110, 1030, 831, 787 cm^{-1}.

HRMS (EI) $[C_{21}H_{21}NO_2]$ $[M]^+$ calculated: 319.1572, found: 319.1586.

4'-Methoxy-*N*-methyl-*N*-(4-(trifluoromethoxy)phenyl)-[1,1'-biphenyl]-4-amine (14zv)



Compound **4mh** was prepared according to the **General procedure E** from **1g** (40.4 mg, 0.2 mmol) and **13h** (90.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (35.0 mg, 47% yield).

m.p. = 127.4 – 128.1 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (td, *J* = 6.6, 2.1 Hz, 4H), 7.15 – 7.09 (m, 4H), 7.02 – 6.95 (m, 4H), 3.86 (s, 3H), 3.35 (s, 3H).

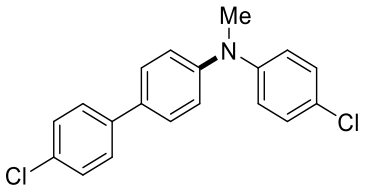
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 147.8, 147.5, 142.9, 135.0, 133.4, 127.9, 127.7, 122.2, 122.0, 120.8 (q, *J* = 256.1 Hz), 120.1, 114.3, 55.5, 40.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.70 (s, 3F).

IR (KBr): 3063, 3037, 2952, 2908, 2834, 1607, 1579, 1509, 1353, 1181, 1041, 1015, 820 cm^{-1}.

HRMS (EI) $[C_{21}H_{18}F_3NO_2]$ $[M]^+$ calculated: 373.1290, found: 373.1298.

4'-Chloro-*N*-(4-chlorophenyl)-*N*-methyl-[1,1'-biphenyl]-4-amine (14zw)



Compound **14zw** was prepared according to the **General procedure E** from **1ze** (41.2 mg, 0.2 mmol) and **13i** (72.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (60.6 mg, 92% yield).

m.p. = 170.8 – 171.3 ℃.

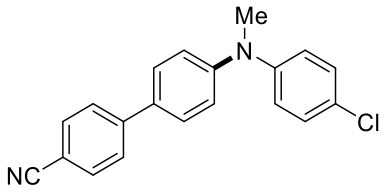
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 4H), 7.41 – 7.36 (m, 2H), 7.28 – 7.23 (m, 2H), 7.09 – 7.03 (m, 2H), 7.04 – 6.99 (m, 2H), 3.34 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.4, 139.3, 132.9, 132.8, 129.4, 129.0, 127.9, 127.8, 126.9, 122.4, 120.3, 40.5.

IR (KBr): 3082, 3037, 2937, 2891, 1606, 1586, 1520, 1485, 1342, 1254, 1124, 1093, 1007, 824, 730 cm^{-1}.

HRMS (EI) $[C_{19}H_{15}Cl_2N]$ $[M]^+$ calculated: 327.0582, found: 327.0582.

4'-((4-Chlorophenyl)(methyl)amino)-[1,1'-biphenyl]-4-carbonitrile (14zx)



Compound **14zx** was prepared according to the **General procedure E** from **1zg** (39.4 mg, 0.2 mmol) and **3i** (72.6 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (55.4 mg, 87% yield).

m.p. = 139.5 – 140.3 ℃.

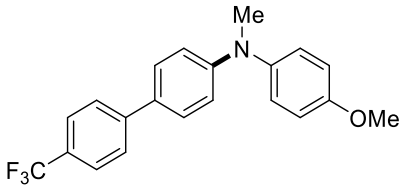
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.54 – 7.48 (m, 2H), 7.32 – 7.28 (m, 2H), 7.10 – 7.06 (m, 2H), 7.04 – 7.00 (m, 2H), 3.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 146.9, 145.2, 132.7, 130.6, 129.6, 128.2, 128.0, 126.9, 124.1, 119.3, 118.6, 109.9, 40.3.

IR (KBr): 3035, 2935, 2915, 2814, 1586, 1522, 1485, 1397, 1336, 1258, 1184, 1123, 1111, 1002, 837, 803, 748, 718, 677 cm^{-1}.

HRMS (EI) $[C_{20}H_{15}ClN_2]$ $[M]^+$ calculated: 318.0924, found: 318.0915.

***N*-(4-Methoxyphenyl)-*N*-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14zy)**



Compound **14zy** was prepared according to the **General procedure E** from **1v** (48.0 mg, 0.2 mmol) and **13f** (82.0 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (63.5 mg, 89% yield).

m.p. = 139.9 – 140.5 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 4H), 7.51 – 7.46 (m, 2H), 7.21 – 7.14 (m, 2H), 6.98 – 6.94 (m, 2H), 6.89 – 6.81 (m, 2H), 3.86 (s, 3H), 3.33 (s, 3H).

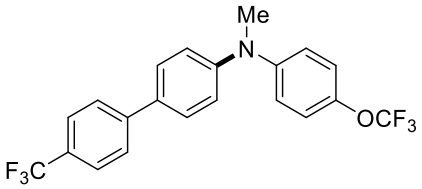
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1, 149.9, 144.6, 141.5, 128.8, 128.1 (d, *J* = 32.5 Hz), 128.0, 127.8, 127.4, 126.4, 125.7, 124.6 (d, *J* = 271.8 Hz), 115.1, 55.6, 40.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.70 (s, 3F).

IR (KBr): 3099, 3026, 2955, 2898, 1602, 1513, 1332, 1282, 1253, 1210, 1124, 1074, 1032, 835, 816, 729, 598 cm^{-1}.

HRMS (EI) $[C_{21}H_{18}F_3NO]$ $[M]^+$ calculated: 357.1340, found: 357.1346.

***N*-Methyl-*N*-(4-(trifluoromethoxy)phenyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14zz)**



Compound **14zz** was prepared according to the **General procedure E** from **1v** (48.0 mg, 0.2 mmol) and **13h** (90.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (74.5 mg, 91% yield).

m.p. = 111.3 – 112.0 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 4H), 7.57 – 7.53 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.15 – 7.07 (m, 4H), 3.38 (s, 3H).

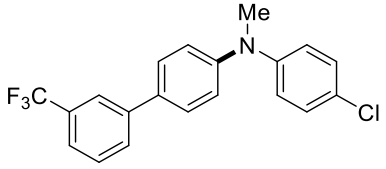
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 147.4, 144.3, 144.1, 132.3, 128.8 (q, *J* = 32.7 Hz), 128.2, 126.8, 125.9, 124.54 (q, *J* = 271.7 Hz), 122.6, 122.4, 119.9, 119.7 (q, *J* = 256.1 Hz), 40.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -58.50 (s, 3F), -62.61 (s, 3F).

IR (KBr): 3053, 3033, 2951, 2890, 1602, 1531, 1508, 1350, 1328, 1273, 1163, 1130, 1012, 854, 820 cm^{-1}.

HRMS (EI) $[C_{21}H_{15}F_6NO]$ $[M]^+$ calculated: 411.1058, found: 411.1047.

***N*-(4-Chlorophenyl)-*N*-methyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14zza)**



Compound **14zza** was prepared according to the **General procedure E** from **1zh** (48.0 mg, 0.2 mmol) and **13i** (72.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (62.4 mg, 86% yield).

m.p. = 106.8 – 107.4 ℃.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.75 (d, *J* = 7.3 Hz, 1H), 7.60 – 7.49 (m, 4H), 7.31 – 7.26 (m, 2H), 7.11 – 7.01 (m, 4H), 3.36 (s, 3H).

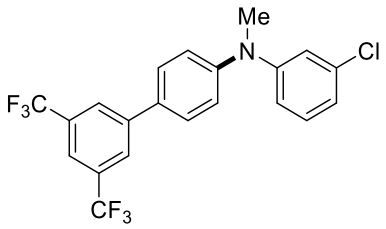
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 147.3, 141.6, 132.3, 131.2 (q, *J* = 32.0 Hz), 129.9, 129.5, 129.3, 128.1, 127.3, 123.4, 123.3 (q, *J* = 271.8 Hz), 122.9, 119.9, 40.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.07 (s, 3F).

IR (KBr): 3036, 2893, 1604, 1586, 1521, 1492, 1444, 1335, 1253, 1166, 1125, 1073, 1034, 833, 801, 694 cm^{-1}.

HRMS (EI) $[C_{20}H_{15}ClF_3N]$ $[M]^+$ calculated: 361.0845, found: 361.0840.

***N*-(3-Chlorophenyl)-*N*-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-4-amine (14zzb)**



Compound **14zzb** was prepared according to the **General procedure E** from **1zi** (62.0 mg, 0.2 mmol) and **13j** (72.6 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (72.8 mg, 84% yield).

m.p. = 68.1 – 68.9 ℃.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.01 – 7.98 (m, 2H), 7.84 – 7.80 (m, 1H), 7.58 – 7.53 (m, 2H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.16 – 7.12 (m, 2H), 7.09 (t, *J* = 2.1 Hz, 1H), 7.02 – 6.96 (m, 2H), 3.38 (s, 3H).

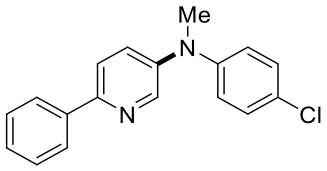
^{13}C NMR (176 MHz, $CDCl_3$) δ 149.7, 149.1, 142.9, 135.1, 132.2 (q, *J* = 33.0 Hz), 131.1, 130.4, 128.3, 126.6, 123.6 (q, *J* = 272.7 Hz), 122.2, 121.1, 120.7, 119.3, 100.0, 40.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.32 (s, 6F).

IR (KBr): 3071, 3043, 2960, 2882, 2818, 1590, 1521, 1485, 1381, 1278, 1260, 1168, 1134, 1051, 897, 838, 770, 683 cm^{-1}.

HRMS (EI) $[C_{20}H_{14}ClF_6N]$ $[M]^+$ calculated: 429.0719, found: 429.0722.

***N*-(4-Chlorophenyl)-*N*-methyl-6-phenylpyridin-3-amine (14zzc)**



Compound **14zzc** was prepared according to the **General procedure E** from **1o** (35.0 mg, 0.2 mmol) and **13i** (72.6 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (57.4 mg, 97% yield).

m.p. = 88.5 – 89.2 ℃.

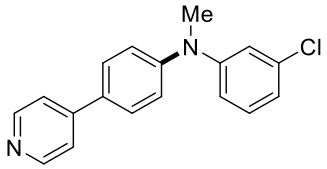
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.96 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.63 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.32 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.07 – 7.01 (m, 2H), 3.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 146.6, 143.6, 141.1, 139.1, 129.6, 128.8, 128.3, 127.8, 126.6, 126.3, 122.8, 120.5, 40.2.

IR (KBr): 3054, 3029, 2952, 2894, 1580, 1556, 1481, 1445, 1340, 1088, 1010, 835, 777, 736, 694 cm^{-1}.

HRMS (EI) $[C_{18}H_{15}ClN_2]$ $[M]^+$ calculated: 294.0924, found: 294.0927.

3-Chloro-*N*-methyl-*N*-(4-(pyridin-4-yl)phenyl)aniline (14zzd)



Compound **14zzd** was prepared according to the **General procedure E** from **1zq** (35.0 mg, 0.2 mmol) and **13j** (72.6 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 4/1) as a light-yellow oil (56.6 mg, 96% yield).

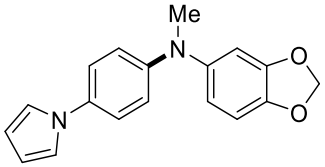
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.9 Hz, 2H), 7.61 – 7.55 (m, 2H), 7.52 – 7.43 (m, 2H), 7.24 – 7.17 (m, 1H), 7.14 – 7.03 (m, 3H), 7.01 – 6.91 (m, 2H), 3.36 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 150.3, 149.6, 149.2, 147.7, 135.1, 130.7, 130.4, 128.0, 122.2, 121.2, 121.0, 120.4, 119.4, 40.3.

IR (KBr): 3033, 3022, 2906, 2886, 1579, 1523, 1484, 1404, 1343, 1248, 1229, 1137, 1118, 1084, 988, 905, 809, 776, 713 cm^{-1}.

HRMS (ESI) $[C_{18}H_{16}ClN_2]$ $[M+H]^+$ calculated: 295.1002, found: 295.1006.

***N*-(4-(1*H*-Pyrrol-1-yl)phenyl)-*N*-methylbenzo[*d*][1,3]dioxol-5-amine (14zze)**



Compound **14zze** was prepared according to the **General procedure E** from **1n** (32.2 mg, 0.2 mmol) and **13g** (72.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 4/1) as a white solid (37.9 mg, 65% yield).

m.p. = 119.7 – 120.5 ℃.

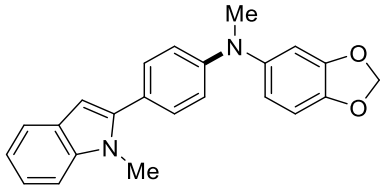
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 7.01 (t, *J* = 2.2 Hz, 2H), 6.89 – 6.84 (m, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.63 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.32 (t, *J* = 2.2 Hz, 2H), 5.98 (s, 2H), 3.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 147.9, 144.3, 143.6, 133.1, 122.0, 119.8, 117.5, 117.2, 109.7, 108.8, 106.3, 101.4, 41.0.

IR (KBr): 3040, 2951, 2897, 1609, 1522, 1486, 1322, 1260, 1217, 1126, 1038, 923, 829, 720, 630 cm^{-1}.

HRMS (EI) $[C_{18}H_{16}N_2O_2]$ $[M]^+$ calculated: 292.1212, found: 292.1222.

***N*-Methyl-*N*-(4-(1-methyl-1*H*-indol-2-yl)phenyl)benzo[*d*][1,3]dioxol-5-amine (14zzf)**



Compound **14zzf** was prepared according to the **General procedure E** from **1q** (45.0 mg, 0.2 mmol) and **13g** (72.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (70.0 mg, 98% yield).

m.p. = 127.1 – 128.2 ℃.

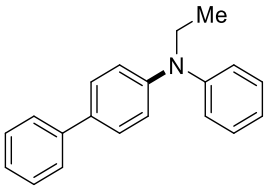
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 3H), 7.24 – 7.19 (m, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.49 (s, 1H), 5.97 (s, 2H), 3.73 (s, 3H), 3.30 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.3, 148.5, 144.9, 143.0, 142.1, 138.2, 130.1, 128.2, 122.5, 121.2, 120.2, 119.8, 118.8, 115.0, 109.5, 108.9, 107.3, 101.5, 100.6, 40.7, 31.2.

IR (KBr): 3056, 2955, 2887, 1607, 1478, 1435, 1361, 1338, 1303, 1246, 1214, 1188, 1110, 1037, 937, 821, 778, 755 cm^{-1}.

HRMS (ESI) $[C_{23}H_{21}N_2O_2]$ $[M+H]^+$ calculated: 357.1603, found: 357.1611.

***N*-Ethyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14zzg)**



Compound **14zzg** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **3l** (76.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (15.0 mg, 27% yield).

m.p. = 64.3 – 64.8 ℃.

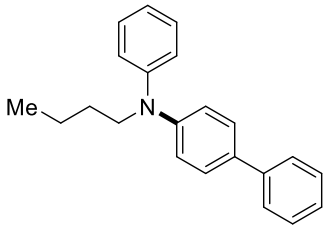
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H), 7.52 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.37 – 7.28 (m, 3H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.08 – 7.00 (m, 3H), 3.85 (q, *J* = 7.0 Hz, 2H), 1.28 (td, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 147.2, 141.0, 133.2, 129.5, 128.8, 127.9, 126.6, 122.3, 122.1, 119.9, 46.6, 12.9.

IR (KBr): 3050, 3032, 2966, 2925, 2870, 1589, 1522, 1486, 1372, 1353, 1244, 1125, 1097, 832, 762, 745, 689 cm^{-1}.

HRMS (EI) $[C_{20}H_{19}N]$ $[M]^+$ calculated: 273.1517, found: 273.1529.

***N*-Butyl-*N*-phenyl-[1,1'-biphenyl]-4-amine (14zzh)**



Compound **14zzh** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13m** (96.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 20/1) as a white solid (16.1 mg, 27% yield).

m.p. = 80.8 – 81.3 ℃.

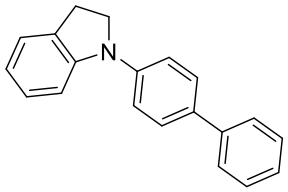
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.30 (q, *J* = 7.4 Hz, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 7.7 Hz, 3H), 3.74 (t, *J* = 7.4 Hz, 2H), 1.70 (p, *J* = 7.8 Hz, 2H), 1.40 (h, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 147.7, 141.0, 133.1, 129.5, 128.8, 127.9, 126.7, 122.3, 122.0, 119.9, 52.3, 29.8, 20.5, 14.1.

IR (KBr): 3057, 3033, 2960, 2862, 1587, 1457, 1361, 1318, 1284, 1132, 1070, 816, 764, 698, 597 cm^{-1}.

HRMS (EI) $[C_{22}H_{23}N]$ $[M]^+$ calculated: 301.1830, found: 301.1844.

1-([1,1'-Biphenyl]-4-yl)indoline (14zzi)



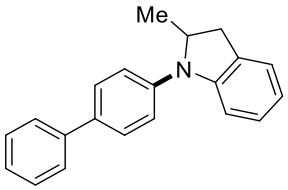
Compound **14zzi** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13n** (67.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (25.7 mg, 47% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.56 (m, 4H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.27 – 7.18 (m, 2H), 7.16 – 7.08 (m, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 4.01 (t, *J* = 8.5 Hz, 2H), 3.17 (t, *J* = 8.4 Hz, 2H).

MS(EI): *m/z* 271 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[172]

1-([1,1'-Biphenyl]-4-yl)-2-methylindoline (14zzj)



Compound **14zzj** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13o** (78.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (26.0 mg, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 2.6 Hz, 4H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 3H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.80 – 6.66 (m, 1H), 4.52 – 4.28 (m, 1H), 3.32 (dd, *J* = 15.4, 8.8 Hz, 1H), 2.73 (dd, *J* = 15.4, 7.0 Hz, 1H), 1.33 (d, *J* = 6.2 Hz, 3H).

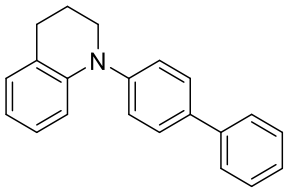
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 142.8, 140.9, 135.2, 129.9, 128.9, 128.0, 127.3, 126.9, 126.8, 125.1, 121.2, 119.0, 108.7, 59.8, 37.2, 20.3.

IR (KBr): 3254, 3033, 2970, 2897, 1598, 1522, 1487, 1461, 1380, 1280, 1026, 975, 840, 763, 697 cm^{-1}.

HRMS (EI) $[C_{21}H_{19}N]$ $[M]^+$ calculated: 285.1517, found: 285.1511.

[172] B. H. Lipshutz, D, M. Nihan, E. Vinogradova, B. R. Taft, Ž. V. Bošković, Copper + Nickel-in-Charcoal (Cu−Ni/C): a bimetallic, heterogeneous catalyst for cross-couplings. *Org. Lett.* **2008**, *10*, 4279–4282.

1-([1,1'-Biphenyl]-4-yl)-1,2,3,4-tetrahydroquinoline (14zzk)



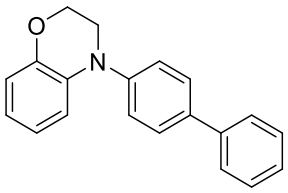
Compound **14zzk** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13p** (75.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (33.9 mg, 59% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (t, *J* = 8.5 Hz, 4H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.29 (m, 3H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.76 (t, *J* = 7.7 Hz, 1H), 3.75 – 3.64 (t, *J* = 6.5 Hz, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.08 (p, *J* = 6.3 Hz, 2H).

MS(EI): *m/z* 285 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[173]

4-([1,1'-Biphenyl]-4-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (14zzl)



Compound **14zzl** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13q** (70.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (20.0 mg, 35% yield).

m.p. = 126.2 – 127.0 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.8, 6.0 Hz, 4H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.32 (m, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.97 – 6.91 (m, 1H), 6.85 – 6.76 (m, 2H), 4.36 – 4.31 (m, 2H), 3.79 – 3.76 (m, 2H).

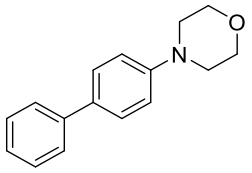
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 145.2, 140.7, 136.2, 132.0, 128.9, 128.1, 127.1, 126.9, 123.3, 121.0, 120.7, 117.4, 117.3, 64.5, 48.6.

IR (KBr): 3077, 3056, 3027, 2983, 2898, 1596, 1520, 1502, 1370, 1336, 1259, 1056, 750, 695 cm^{-1}.

HRMS (EI) $[C_{20}H_{17}NO]$ $[M]^+$ calculated: 287.1310, found: 287.1321.

4-([1,1'-Biphenyl]-4-yl)morpholine (14zzm)

[173] M. T. Barros, S. S. Dey, C. D. Maycock, Metal-free synthesis of secondary arylamines: an aliphatic-to-aromatic transformation. *Eur. J. Org. Chem.* **2013**, *2013*, 742–747.



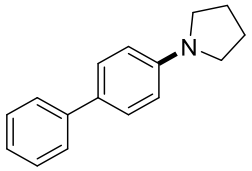
Compound **14zzm** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13r** (52.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 5/1) as a white solid (10.3 mg, 21% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.24 (m, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.94 – 3.84 (m, 4H), 3.26 – 3.16 (m, 4H).

MS(EI): *m/z* 239 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[172]

1-([1,1'-Biphenyl]-4-yl)pyrrolidine (14zzn)



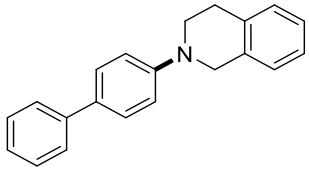
Compound **14zzn** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13s** (50.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (5.0 mg, 11% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.52 – 7.47 (m, 2H), 7.42 – 7.34 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 2H), 3.41 – 3.25 (m, 4H), 2.09 – 1.94 (m, 4H).

MS(EI): *m/z* 223 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[174]

2-([1,1'-Biphenyl]-4-yl)-1,2,3,4-tetrahydroisoquinoline (14zzo)



Compound **14zzo** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13t** (76.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 3/1) as a white solid

[174] K. Matsumoto, S. Takeda, T. Hirokane, M. Yoshida, A highly selective palladium-catalyzed aerobic oxidative aniline–aniline cross-coupling reaction. *Org. Lett.* **2019**, *21*, 7279–7283.

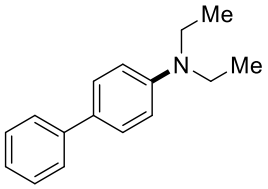
(14.9 mg, 26% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, *J* = 7.8 Hz, 4H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.22 (s, 4H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.49 (s, 2H), 3.64 (t, *J* = 5.9 Hz, 2H), 3.03 (t, *J* = 5.8 Hz, 2H).

MS(EI): *m/z* 285 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[175]

***N*,*N*-Diethyl-[1,1'-biphenyl]-4-amine (14zzp)**



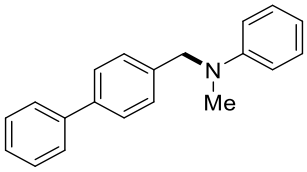
Compound **14zzp** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13u** (62.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane) as a white solid (8.3 mg, 18% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 4H), 1.19 (t, *J* = 7.0 Hz, 6H).

MS(EI): *m/z* 225 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[176]

***N*-(Biphenyl-4-ylmethyl)-*N*-methylaniline (14zzq)**



Compound **14zzq** was prepared according to the **General procedure E** from **1zzd** (37.2 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (44.3 mg, 81% yield).

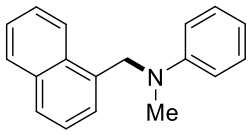
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, *J* = 9.0 Hz, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.16 (m, 5H), 6.84 – 6.66 (m, 3H), 4.55 (s, 2H), 3.03 (s, 3H).

MS(EI): *m/z* 273 $[M]^+$.

[175] H. Tian, W. Xu, Y. Liu, Q. Wang, Radical alkylation of C(sp3)–H bonds with diacyl peroxides under catalyst-free conditions. *Chem. Commun.* **2019**, *55*, 14813–14816.
[176] Y. Zhang, X. Yang, Q. Yao, D. Ma, CuI/DMPAO-catalyzed *N*-arylation of acyclic secondary amines. *Org. Lett.* **2012,** *14*, 3056–3059.

The chemical shifts were consistent with those reported in the literature.[177]

***N*-Methyl-*N*-(naphthalen-1-ylmethyl)aniline (14zzs)**



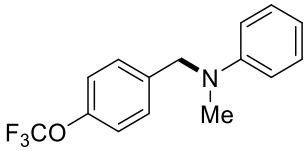
Compound **14zzs** was prepared according to the **General procedure E** from **1zzf** (32.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (43.1 mg, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 1H), 7.94 – 7.85 (m, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.44 – 7.33 (m, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.22 (t, *J* = 7.0 Hz, 2H), 6.83 – 6.66 (m, 3H), 4.97 (s, 2H), 3.08 (s, 3H).

MS(EI): *m/z* 247 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[178]

***N*-Methyl-*N*-(4-(trifluoromethoxy)benzyl)aniline (14zzr)**



Compound **14zzr** was prepared according to the **General procedure E** from **1zze** (38.8 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (43.0 mg, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.00 (m, 6H), 6.73 (d, *J* = 8.8 Hz, 3H), 4.52 (s, 2H), 3.01 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.6, 148.2, 137.9, 129.4, 128.1, 121.3, 120.6 (q, *J* = 256.9 Hz), 117.0, 112.5, 56.2, 38.7.

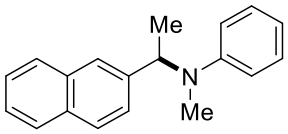
^{19}F NMR (282 MHz, $CDCl_3$) δ -58.39 (s, 3F).

IR (KBr): 3062, 3035, 2898, 2821, 1600, 1505, 1347, 1270, 1215, 1161, 1118, 929, 749, 692 cm^{-1}.

HRMS (EI) $[C_{15}H_{14}F_3NO]$ $[M]^+$ calculated: 281.1027, found: 281.1022.

***N*-Methyl-*N*-(1-(naphthalen-2-yl)ethyl)aniline (14zzt)**

[177] C. Houle, P. R. Savoie, C. Davies, D. Jardel, P. A. Champagne, B. Bibal, J. Paquin, Thiourea-catalyzed C−F bond activation: amination of benzylic fluorides. *Chem. Eur. J.* **2020**, *26*, 10620–10625.
[178] Y. Gui, L. Liao, L. Sun, Z. Zhang, J. Ye, G. Shen, Z. Lu, W. Zhou, D. Yu, Coupling of C(sp3)–H bonds with C(sp2)–O electrophiles: mild, general and selective. *Chem. Commun.* **2017**, *53*, 1192–1195.



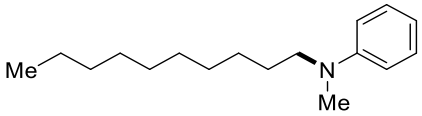
Compound **14zzt** was prepared according to the **General procedure E** from **1zzg** (34.8 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a white solid (22.2 mg, 43% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.68 (m, 4H), 7.52 – 7.40 (m, 3H), 7.33 – 7.19 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 5.28 (q, *J* = 6.8 Hz, 1H), 2.69 (s, 3H), 1.64 (d, *J* = 6.8 Hz, 3H).

MS(EI): *m/z* 261 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[179]

***N*-Decyl-*N*-methylaniline (14zzu)**



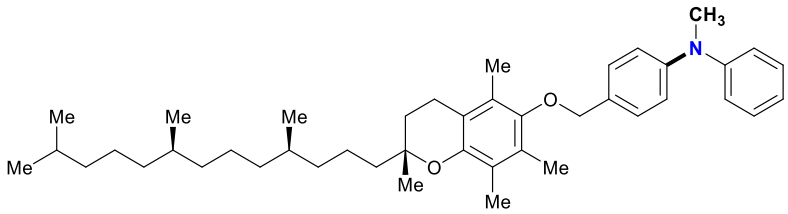
Compound **14zzu** was prepared according to the **General procedure E** from **1zzh** (32.0 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a colorless oil (9.7 mg, 20% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.0 Hz, 2H), 6.67 (m, 3H), 3.29 (t, *J* = 7.6 Hz, 2H), 2.92 (s, 3H), 1.57 (s, 2H), 1.27 (m, 14H), 0.88 (t, *J* = 6.5 Hz, 3H).

MS(EI): *m/z* 247 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[180]

***N*-Methyl-*N*-phenyl-4-((((*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)aniline (14zzv)**



Compound **14zzv** was prepared according to the **General procedure E** from **1zk** (107.8 mg, 0.2 mmol) and **13a** (64.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 3/1) as a light-

[179] Z. Wang, D. Pei, C. Wang, J. Sun, A facile one-pot process for the formation of hindered tertiary amines. *Molecules* **2012**, *17*, 5151–5163.
[180] H. Chung, Y. K. Chung, Cobalt–rhodium heterobimetallic nanoparticle-catalyzed *N*-alkylation of amines with alcohols to secondary and tertiary amines. *J. Org. Chem.* **2018**, *83*, 8533–8542.

yellow oil (103.8 mg, 83% yield).

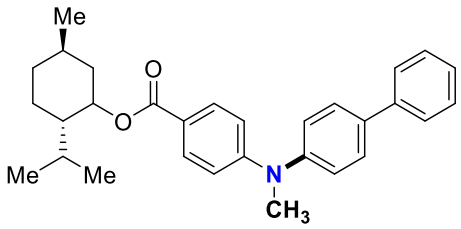
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.36 – 7.27 (m, 2H), 7.12 – 7.04 (m, 4H), 7.00 (tt, *J* = 7.4, 1.1 Hz, 1H), 4.65 (s, 2H), 3.36 (s, 3H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 1.92 – 1.75 (m, 2H), 1.65 – 1.52 (m, 3H), 1.51 – 1.37 (m, 4H), 1.35 – 1.23 (m, 12H), 1.21 – 1.05 (m, 7H), 0.94 – 0.84 (m, 12H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.1, 148.9, 148.2, 148.0, 130.7, 129.3, 129.2, 128.1, 126.1, 123.0, 121.5, 120.7, 120.4, 117.7, 74.9, 74.8, 40.4, 40.2, 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 31.4, 28.1, 25.0, 24.6, 24.0, 22.9, 22.8, 21.2, 20.8, 19.9, 19.8, 13.1, 12.2, 12.0.

IR (KBr): 3031, 2951, 2925, 2866, 1596, 1514, 1496, 1462, 1412, 1368, 1343, 1256, 1132, 1085, 993, 697 cm^{-1}.

HRMS (**ESI**) $[C_{43}H_{63}NO_2Na]$ $[M+Na]^+$ calculated: 648.4756, found: 648.4759.

(2*S*,5*R*)-2-*iso*-Propyl-5-methylcyclohexyl 4-([1,1'-biphenyl]-4-yl(methyl)amino)benzoate (14zzw)



Compound **14zzw** was prepared according to the **General procedure E** from **1a** (34.4 mg, 0.2 mmol) and **13v** (87.0 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 15/1) as a light-yellow oil (66.8 mg, 75% yield).

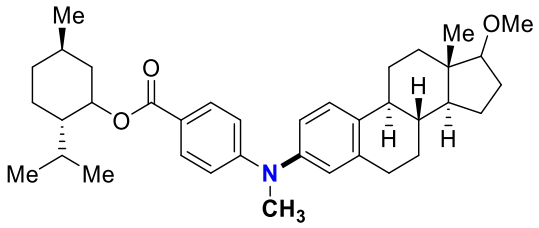
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 2H), 7.64 – 7.60 (m, 4H), 7.49 – 7.45 (m, 2H), 7.37 (ddt, *J* = 8.6, 7.0, 1.2 Hz, 1H), 7.30 – 7.27 (m, 2H), 6.94 – 6.79 (m, 2H), 4.92 (td, *J* = 10.9, 4.4 Hz, 1H), 3.41 (s, 3H), 2.17 – 2.12 (m, 1H), 2.02 – 1.97 (m, 1H), 1.76 – 1.71 (m, 2H), 1.61 – 1.52 (m, 2H), 1.18 – 1.06 (m, 2H), 0.93 (dd, *J* = 9.2, 6.8 Hz, 7H), 0.82 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.3, 152.4, 146.9, 140.5, 137.7, 131.1, 128.9, 128.4, 127.3, 127.0, 125.5, 120.5, 114.7, 74.2, 47.4, 41.2, 40.3, 34.5, 31.6, 26.6, 23.8, 22.2, 20.9, 16.7.

IR (KBr): 3032, 2954, 2869, 1704, 1599, 1513, 1487, 1347, 1275, 1181, 1115, 768, 697 cm^{-1}.

HRMS (ESI) $[C_{30}H_{35}NO_2Na]$ $[M+Na]^+$ calculated: 464.2565, found: 464.2568.

(2*S*,5*R*)-2-*iso*-Propyl-5-methylcyclohexyl-4-(((8*R*,9*S*,13*S*,14*S*)-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)(methyl)amino)benzoate (14zzx)



Compound **14zzx** was prepared according to the **General procedure E** from **1x** (57.6 mg, 0.2 mmol) and **13v** (87.0 mg, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a light-yellow oil (69.1 mg, 62% yield).

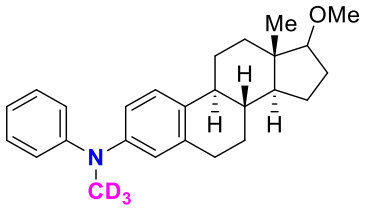
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 2H), 7.29 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.96 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.91 (dd, *J* = 2.4, 1.1 Hz, 1H), 6.78 – 6.70 (m, 2H), 4.86 (td, *J* = 10.8, 4.4 Hz, 1H), 3.38 (s, 3H), 3.32 (s, 3H), 3.32 (t, *J* = 8.4 Hz, 1H), 2.91 – 2.76 (m, 2H), 2.36 – 2.28 (m, 1H), 2.27 – 2.12 (m, 1H), 2.15 – 2.02 (m, 3H), 1.99 – 1.92 (m, 1H), 1.92 – 1.86 (m, 1H), 1.74 – 1.66 (m, 3H), 1.58 – 1.44 (m, 4H), 1.49 – 1.38 (m, 1H), 1.36 (tt, *J* = 12.7, 6.5 Hz, 2H), 1.28 – 1.16 (m, 1H), 1.17 – 1.06 (m, 1H), 1.11 – 1.00 (m, 1H), 0.92 – 0.86 (m, 8H), 0.81 (s, 3H), 0.77 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.4, 152.7, 145.1, 138.5, 137.9, 131.0, 126.8, 126.3, 123.3, 119.4, 113.5, 90.9, 74.0, 58.0, 50.5, 47.5, 44.4, 43.3, 41.2, 40.3, 38.5, 38.1, 34.5, 31.6, 29.7, 27.9, 27.2, 26.6, 26.4, 23.8, 23.2, 22.2, 20.9, 16.7, 11.7.

IR (KBr): 2953, 2924, 2870, 1704, 1600, 1514, 1498, 1355, 1274, 1180, 1119, 918, 768, 732 cm^{-1}.

HRMS (ESI) $[C_{37}H_{52}NO_3]$ $[M+H]^+$ calculated: 558.3947, found: 558.3929.

(8*R*,9*S*,13*S*,14*S*)-17-Methoxy-13-methyl-*N*-(methyl-*d*^{3})-*N*-phenyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-amine (*d*^{3}-14zzy)



Compound ***d*^{3}-4aea** was prepared according to the **General procedure E** from **1x** (57.6 mg, 0.2 mmol) and ***d*^{3}-13a** (70.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 4/1) as a white solid (58.3 mg, 77% yield).

m.p. = 110.3 – 111.2 ℃.

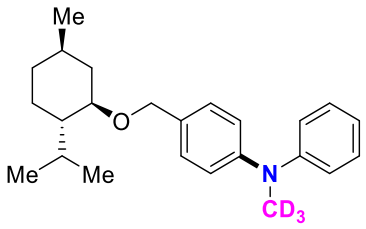
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 2H), 7.26 – 7.18 (m, 1H), 7.01 – 6.93 (m, 2H), 6.94 – 6.83 (m, 2H), 6.81 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.39 (s, 3H), 3.33 (t, *J* = 8.4 Hz, 1H), 2.88 – 2.77 (m, 2H), 2.30 (dq, *J* = 11.2, 4.0, 3.5 Hz, 1H), 2.22 (td, *J* = 11.3, 4.1 Hz, 1H), 2.11 – 2.04 (m, 2H), 1.91 – 1.85 (m, 1H), 1.49 – 1.30 (m, 1H), 1.58 – 1.49 (m, 2H), 1.49 – 1.30 (m, 4H), 1.26 – 1.19 (m, 1H), 0.81 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.3, 146.6, 137.8, 134.4, 129.1, 126.3, 122.1, 120.1, 119.5, 118.9, 90.9, 58.0, 50.4, 44.2, 43.4, 38.7, 38.2, 29.8, 27.9, 27.4, 26.4, 23.2, 11.7.

IR (KBr): 3058, 3031, 2931, 2867, 2193, 2060, 1610, 1592, 1494, 1429, 1337, 1298, 1264, 1193, 1133, 1103, 992, 812, 778, 702 cm^{-1}.

HRMS (ESI) $[C_{26}H_{31}D_3NO]$ $[M+H]^+$ calculated: 379.2829, found: 379.2820.

4-((((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)methyl)-*N*-(methyl-*d*^{3})-*N*-phenylaniline (*d*^{3}-14zzz)



Compound ***d*^{3}-14zzz** was prepared according to the **General procedure E** from **1zl** (53.0 mg, 0.2 mmol) and ***d*^{3}-13a** (70.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 20/1) as a light-yellow oil (62.5 mg, 88% yield).

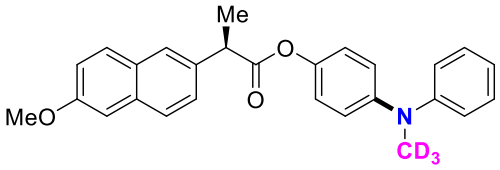
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 4H), 7.08 – 6.98 (m, 4H), 6.98 – 6.90 (m, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 3.20 (td, *J* = 10.6, 4.2 Hz, 1H), 2.40 – 2.27 (m, 1H), 2.23 (dtd, *J* = 12.2, 3.6, 2.0 Hz, 1H), 1.67 (ddq, *J* = 23.0, 13.0, 3.2 Hz, 2H), 1.46 – 1.34 (m, 1H), 1.35 – 1.25 (m, 1H), 1.02 – 0.87 (m, 9H), 0.75 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.2, 148.5, 132.3, 129.3, 129.2, 121.0, 120.9, 120.0, 78.6, 70.3, 48.4, 40.4, 34.7, 31.7, 25.6, 23.3, 22.5, 21.2, 16.2.

IR (KBr): 3030, 2953, 2920, 2868, 2198, 2064, 1595, 1513, 1495, 1513, 1494, 1334, 1272, 1068, 698 cm^{-1}.

HRMS (ESI) $[C_{24}H_{30}D_3NONa]$ $[M+Na]^+$ calculated: 377.2468, found: 377.2460.

4-((Methyl-*d*^{3})(phenyl)amino)phenyl (*R*)-2-(6-methoxynaphthalen-2-yl)propanoate (*d*^{3}-14zzza)



Compound ***d*^{3}-14zzza** was prepared according to the **General procedure E** from **1zm** (65.0 mg, 0.2 mmol) and ***d*^{3}-13a** (70.0 μL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a light-yellow oil (58.3 mg, 70% yield).

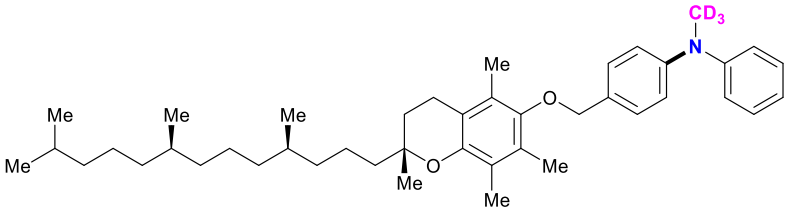
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 (dt, *J* = 2.0, 0.6 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.52 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.17 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 6.99 – 6.95 (m, 4H), 6.94 – 6.89 (m, 3H), 4.10 (q, *J* = 7.1 Hz, 1H), 3.93 (s, 3H), 1.70 (, *J* = 7.2 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 173.6, 157.8, 149.0, 146.8, 145.3, 135.4, 133.9, 129.4, 129.3, 129.1, 127.5, 126.3, 126.2, 122.1, 121.8, 121.1, 119.8, 119.2, 105.7, 55.4, 50.9, 45.7, 18.7.

IR (KBr): 3056, 2975, 2935, 2840, 2188, 2057, 1754, 1605, 1496, 1327, 1268, 1200, 1135, 852 cm^{-1}.

HRMS (ESI) $[C_{27}H_{22}D_3NO_3Na]$ $[M+Na]^+$ calculated: 437.1920, found: 437.1929.

_N_-(Methyl-_d_^{3})-_N_-phenyl-4-((((_R_)-2,5,7,8-tetramethyl-2-((4_R_,8_R_)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)aniline (_d_^{3}-14zzv)



Compound ***d*^{3}-14zzv** was prepared according to the **General procedure E** from **1zk** (110.0 mg, 0.2 mmol) and ***d*^{3}-13a** (70.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 3/1) as a light-yellow oil (99.0 mg, 79% yield).

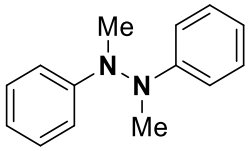
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51 – 7.39 (m, 2H), 7.36 – 7.27 (m, 2H), 7.12 – 7.06 (m, 4H), 7.01 (tt, *J* = 7.3, 1.2 Hz, 1H), 4.67 (s, 2H), 2.64 (t, *J* = 6.9 Hz, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 1.94 – 1.76 (m, 2H), 1.66 – 1.54 (m, 3H), 1.53 – 1.39 (m, 3H), 1.37 – 1.25 (m, 11H), 1.22 – 1.08 (m, 7H), 0.96 – 0.86 (m, 12H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 149.0, 148.8, 148.2, 148.0, 130.7, 129.3, 129.3, 128.1, 126.1, 123.0, 121.5, 120.7, 120.3, 117.7, 74.9, 74.8, 40.2, 39.5, 37.5, 37.4, 32.9, 32.8, 31.4, 28.1, 25.0, 24.6, 24.0, 22.9, 22.8, 21.2, 20.8, 19.9, 19.8, 19.7, 13.1, 12.2, 12.0.

IR (KBr): 3032, 2953, 2905, 2865, 2181, 2059, 1595, 1514, 1495, 1462, 1414, 1367, 1335, 1258, 1084, 993, 748, 699 cm^{-1}.

HRMS (ESI) $[C_{43}H_{60}D_3NO_2Na]$ $[M+Na]^+$ calculated: 651.4945, found: 651.4938.

1,2-Dimethyl-1,2-diphenylhydrazine (15)



Compound **15** was prepared according to the **General procedure E** from **3a** (64.0 µL, 0.6 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 10/1) as a light-yellow oil (17.0 mg, 27% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 4H), 6.96 – 6.68 (m, 6H), 3.01 (s, 6H).

MS(EI): *m/z* 212 $[M]^+$. The chemical shifts were consistent with those reported in the literature.[181]

3.7 General procedure for the scale-up reaction

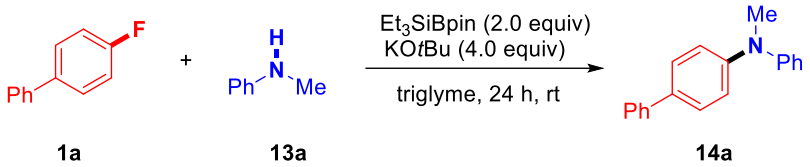
In a nitrogen-filled glovebox, to a flame-dried flask was added 4-fluorobiphenyl **1a** (0.86 g, 5.0 mmol), KO*t*Bu (2.25 g, 20.0 mmol), dry triglyme (20 mL), and *N*-methylaniline 1**3a** (1.62 mL, 15.0 mmol), sequentially. The flask was then sealed and moved out from the glovebox. After stirring for 5 min, a

[181] A. Bredihhin, M. Uno, Effective strategy for the systematic synthesis of hydrazine derivatives. *Tetrahedron* **2008**, *64*, 6788–6793.

triethylsilyl boronate (2.42 g, 10.0 mmol) solution in 5.0 mL dry triglyme was injected to the flask slowly over 30 minutes. The solution was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (100.0 mL), then extracted with Et_2O, washed with water and brine, dried over Na_2SO_4, then concentrated under vacuum to give the crude, which was purified by column chromatography on silica gel to give the corresponding amines **14a** (1.13 g, 87% yield).

4.4 Supplementary Discussion

4.4.1 The NMR spectroscopic studies



1a **13a** **14a**

Following the **General procedure E**, charging **1a** (17.2 mg, 0.1 mmol), **13a** (32.0 μL, 0.3 mmol), silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol), and then anhydrous triglyme (0.5 mL) sequentially into a flame-dried screw-capped test tube. And then stirred in glovebox at room temperature for 24 h. The reaction mixture was then subjected to ^{11}B NMR analysis using THF-d^8 as a solvent to show the details of the reaction. After that the reaction mixture was quenched by adding D_2O (2.0 mL) while stirring for 5 min, then the ^{19}F NMR analysis of the water system was conducted to show the details of the reaction. The organic system was extracted with Et_2O (5 mL), washed with water, dried over Na_2SO_4, and concentrated under vacuum, followed by 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. Then the ^1H NMR analysis and ^{19}F NMR analysis of the crude mixture were conducted to show the details of the model reaction.

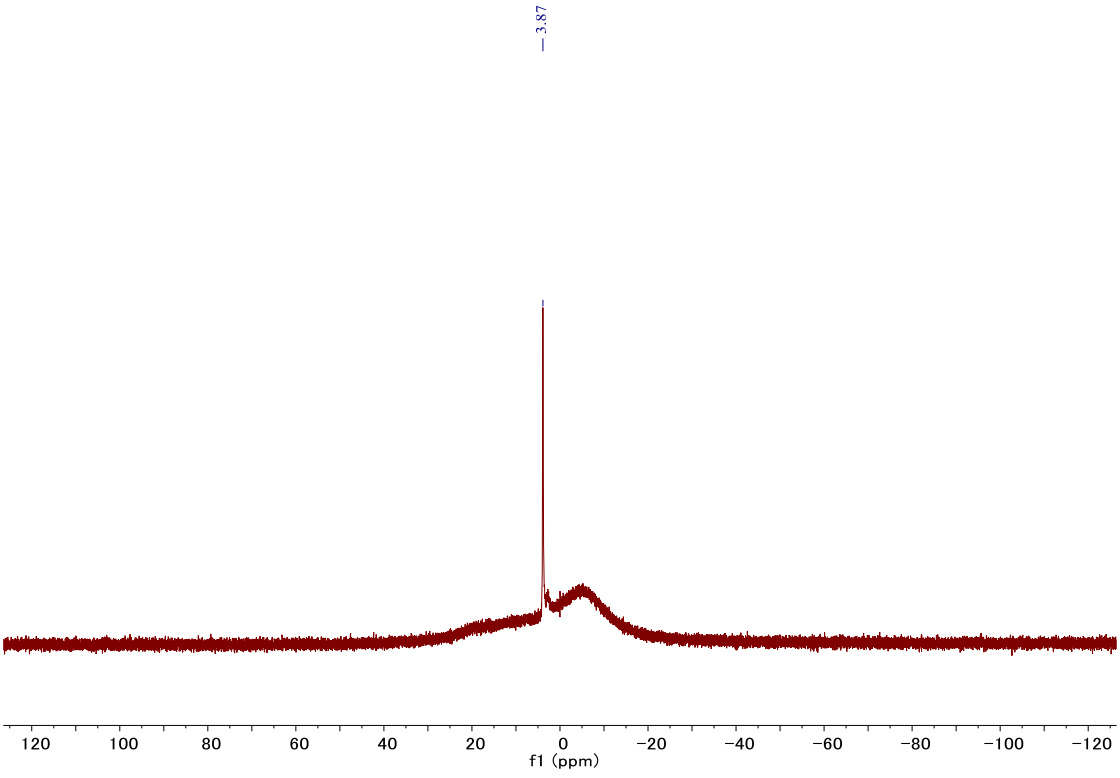


Figure S1.[11]B NMR (225 MHz, THF-d_8, 25 ℃) observation of the model reaction.

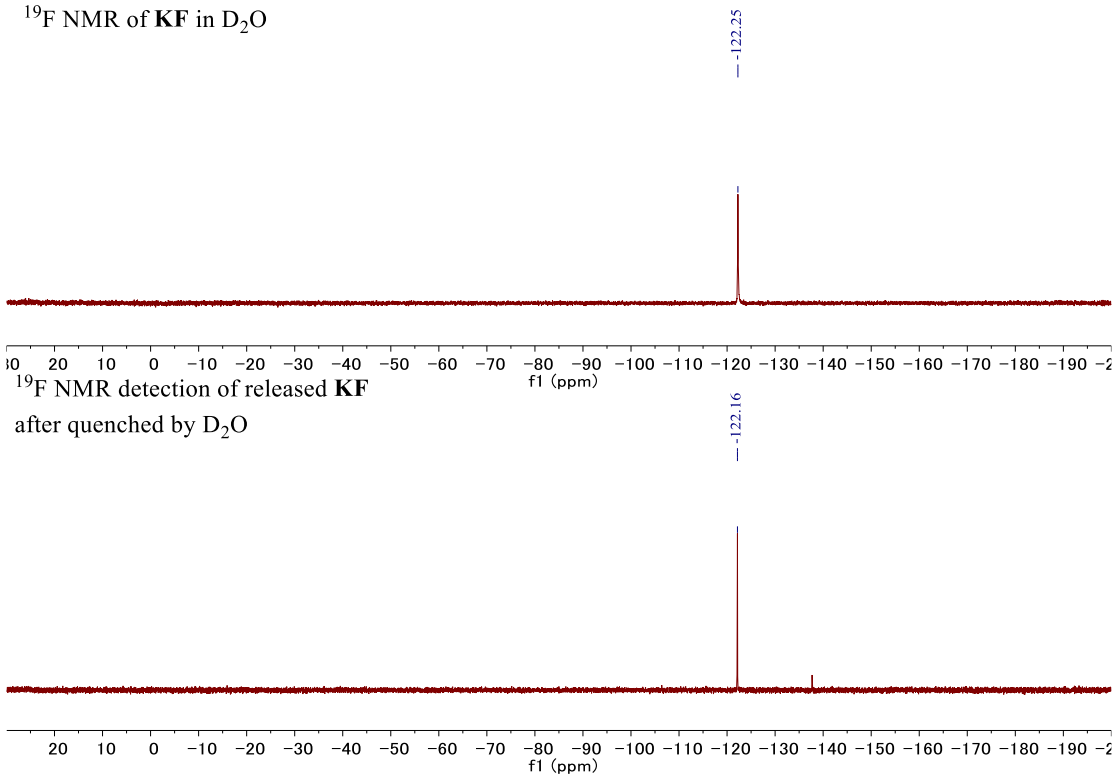


Figure S2. [19]F NMR (282 MHz, D_2O, 25 ℃) observation of KF in D_2O and KF released in the model reaction.

4.4.2 Reaction with radical scavenger TEMPO

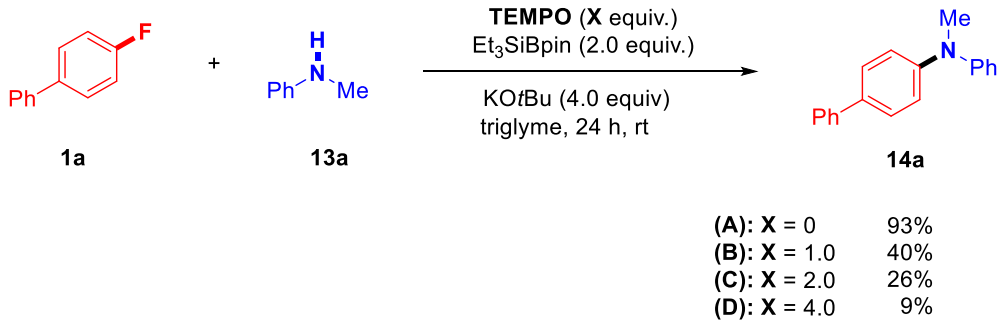


Figure S3. Effect of TEMPO to the silylboronate-mediated coupling reaction of aryl fluoride **1a** with **13a**.

Following the **General procedure E**, charging **1a** (17.2 mg, 0.1 mmol), **13a** (32.0 μL, 0.3 mmol), silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol), TEMPO, and then anhydrous triglyme (0.5 mL) sequentially into a flame-dried screw-capped test tube. Then move out from glovebox and stirred at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard, then [1]H NMR analysis was taken to show the reaction details.

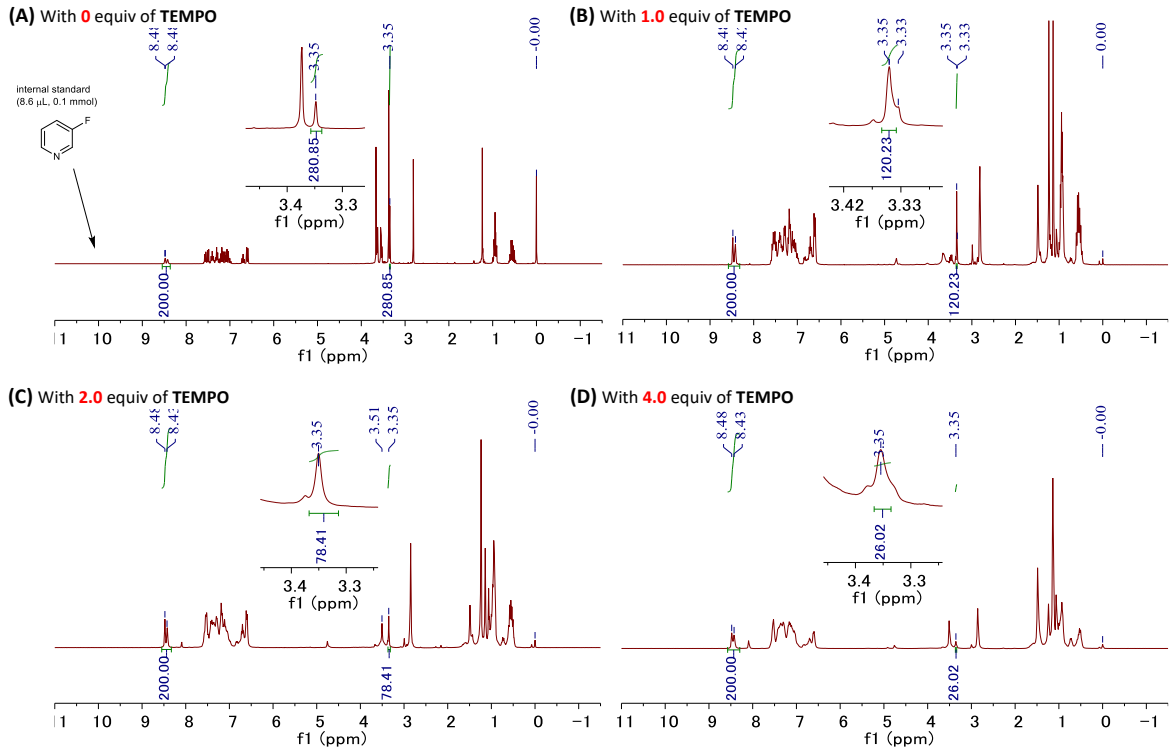


Figure S4. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) observation of the effect of TEMPO to the coupling reaction.

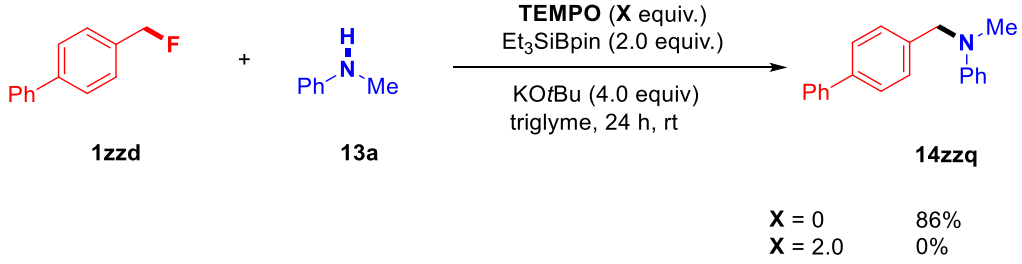


Figure S5. Effect of TEMPO to the silylboronate-mediated coupling reaction of benzyl fluoride **1zzd** with **13a**.

Following the **General procedure E**, charging **1zzd** (18.6 mg, 0.1 mmol), **13a** (32.0 μL, 0.3 mmol), silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol), TEMPO (32.0 mg, 0.2 mmol), and then anhydrous triglyme (0.5 mL) sequentially into a flame-dried screw-capped test tube. Then move out from glovebox and stir at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard, then ^{1}H NMR analysis was taken to show the reaction details.

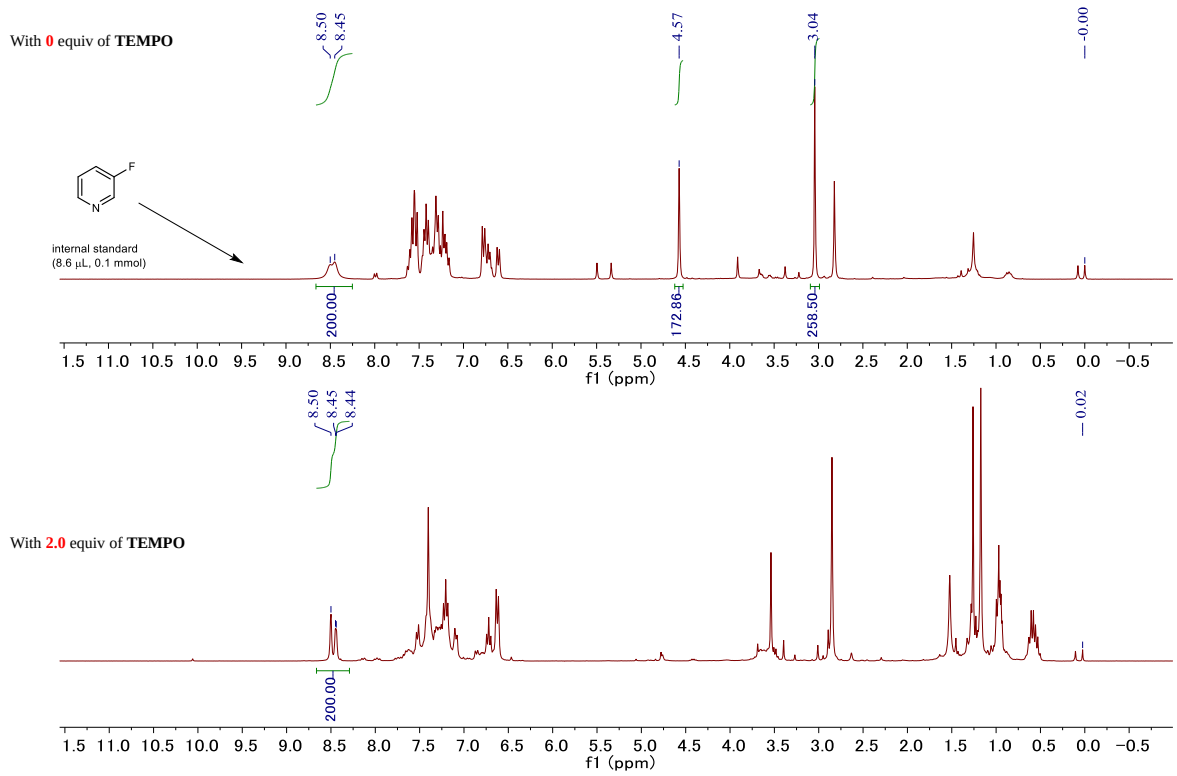
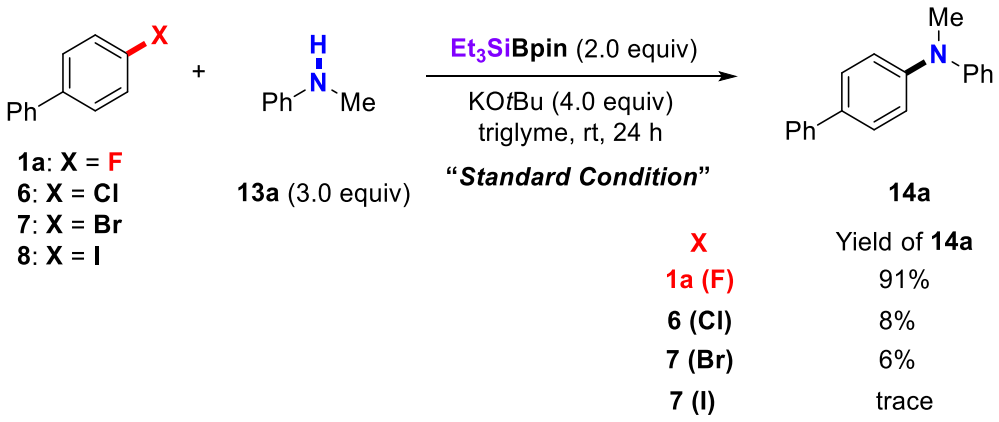


Figure S6. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) observation of the effect of TEMPO to the coupling reaction of benzyl fluoride **1zzd** with **13a**.

4.4.3 Chemoselectivity of organic halides

Evaluate aryl halides under the standard conditions:



X	Yield of **14a**
1a (F)	91%
6 (Cl)	8%
7 (Br)	6%
7 (I)	trace

Figure S7. Effect of aryl halides to the silylboronate-mediated coupling reaction.

Following the **General procedure E**, charging **8** (0.1 mmol), **3a** (32.0 μL, 0.3 mmol), silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.4 mmol), and then anhydrous triglyme (0.5 mL) sequentially into a flame-dried screw-capped test tube. Then move out from glovebox and stir at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1

mmol) as an internal standard, then ^{1}H NMR analysis was taken to show the reaction details.

Note: for the reaction using **8c**, after the reaction finished and work-up, the trace yield of **4aa** was observed by thin layer chromatography (TLC, eluent: *n*-hexane/DCM: 10/1).

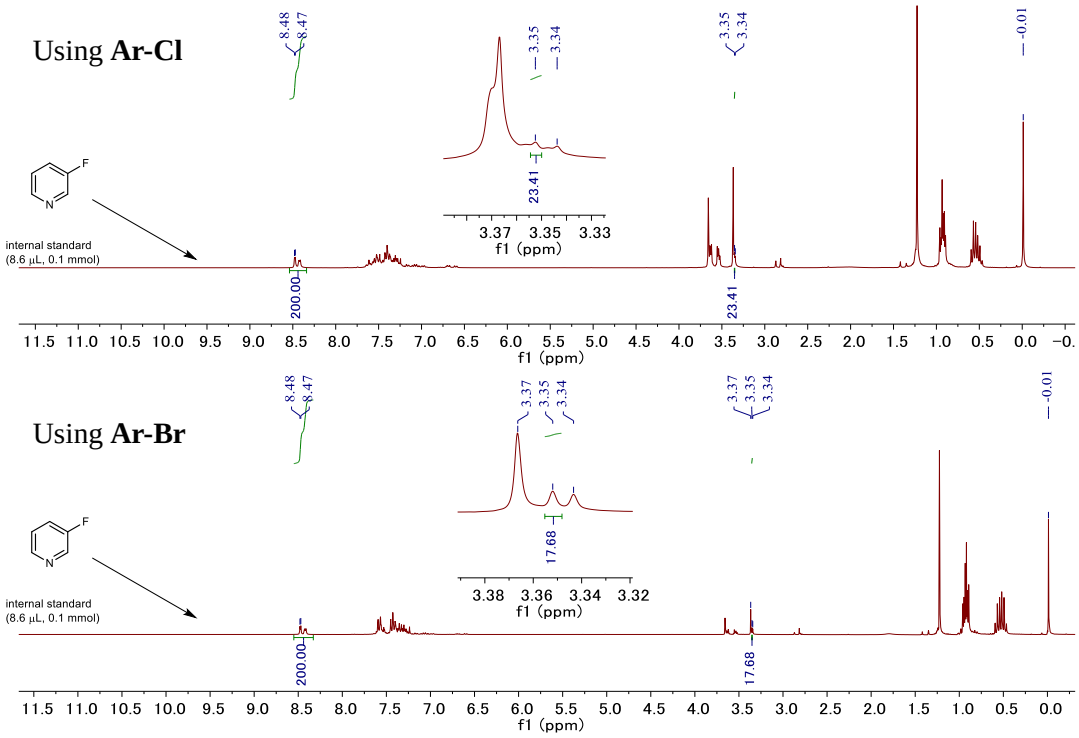


Figure S8. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) observation of the effect of aryl halides to the silylboronate-mediated coupling reaction

Evaluate alkyl halides under the standard conditions with/without silylboronate:

Firstly, we evaluated the reaction of alkyl bromide with *N*-Me-aniline 1**3a** under standard conditions, and desired amination product was obtained in 91% yield. However, even without silylboronate, the amination product formed quantitatively. Alkyl chloride also gave the desired amination product in high yield even without silylboronate. On the other hand, alkyl fluoride **1zzh** gave the product **14zzu** in a 26% NMR yield under standard conditions but no reaction without silylboronate. These results agree with the report.[2b]

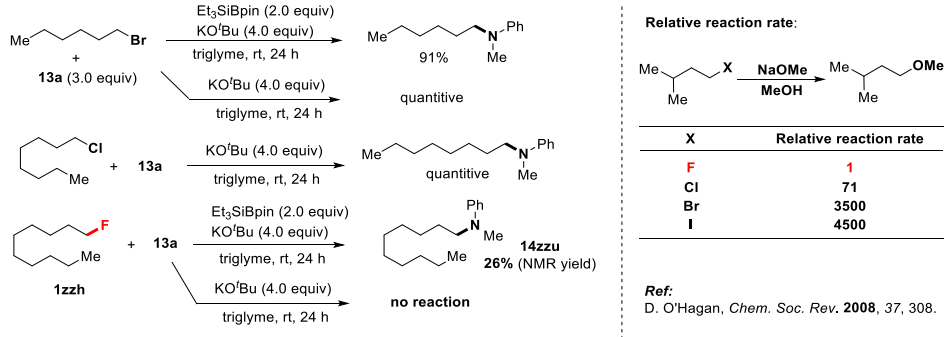


Figure S9. Evaluation of alkyl halides for this reaction

Evaluate allyl fluoride or cinnamyl fluoride under the standard conditions with/without silylboronate:

The reaction of allyl fluoride or cinnamyl fluoride under the standard conditions gave the complex mixtures, and we detected no desired products. Furthermore, allyl fluoride or cinnamyl fluoride also give the same result even under identical conditions but without silylboronate. This is presumably because of allyl fluoride and cinnamyl fluoride are too reactive and unstable.

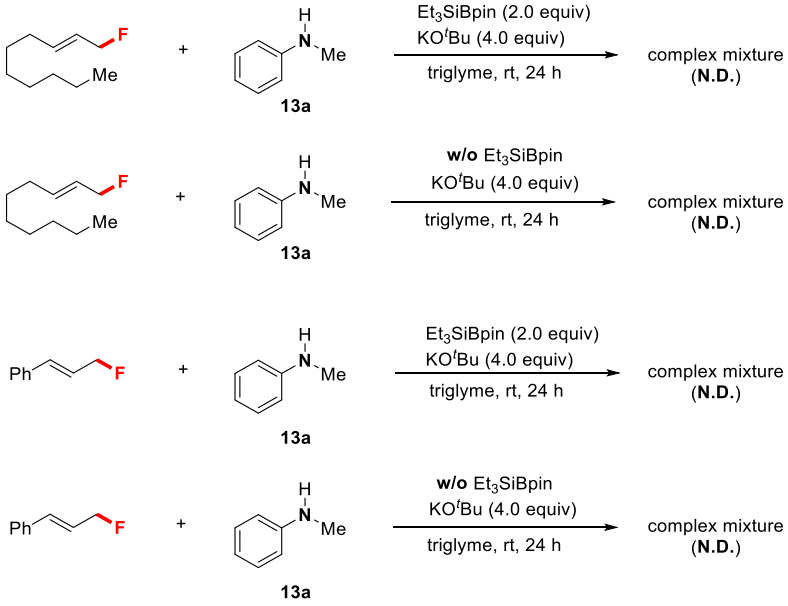


Figure S10. Evaluation of allyl fluoride or cinnamyl fluoride for this reaction.

4.4.4 Mechanism control experiments

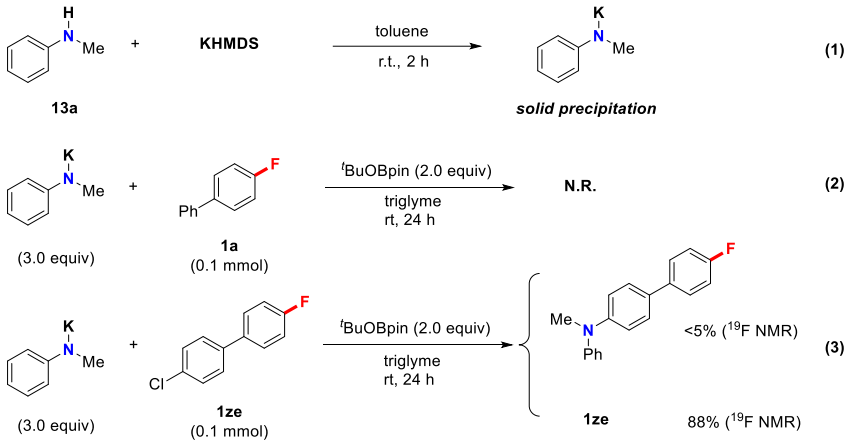


Figure S11. Mechanism control experiments.

Reaction (**1**): Synthetic procedure was followed to a previously reported method.[182] In a nitrogen-filled glovebox, to a flask were charged potassium hexamethyldisilazide (KHMDS, 600 mg, 3.0 mmol) and dry toluene (6 mL). Stir at room temperature until solid was fully dissolved. To this solution was added *N*-methylaniline **13a** (330 μL, 3.05 mmol) dropwise, and keep stirring while a precipitate of potassium salt (KNPhMe) was formed slowly. After stirring for 2 h, the product was filtered and washed twice with dry toluene (3 mL) and dry *n*-hexane (3 mL). The product was collected and moved out of glovebox, and then dried in vacuo to yield solvent-free K-salt of **13a** as a solid (411 mg, 95% yield).

Reaction (**2**) and (**3**): In a nitrogen-filled glovebox, to a flame-dried screw-capped test tube was added sequentially aryl fluorides **1a** (17.2 mg, 0.1 mmol) or **1ze** (20.6 mg, 0.1 mmol), KNPhMe (43.5 mg, 0.3 mmol), dry triglyme (0.5 mL), and ^{t}BuOBpin (40.0 mg, 0.2 mmol, freshly prepared). The tube was then sealed and moved out of glovebox and stirred at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard.

^{1}H NMR and **^{19}F NMR** analysis of reaction (**3**) are copied below:

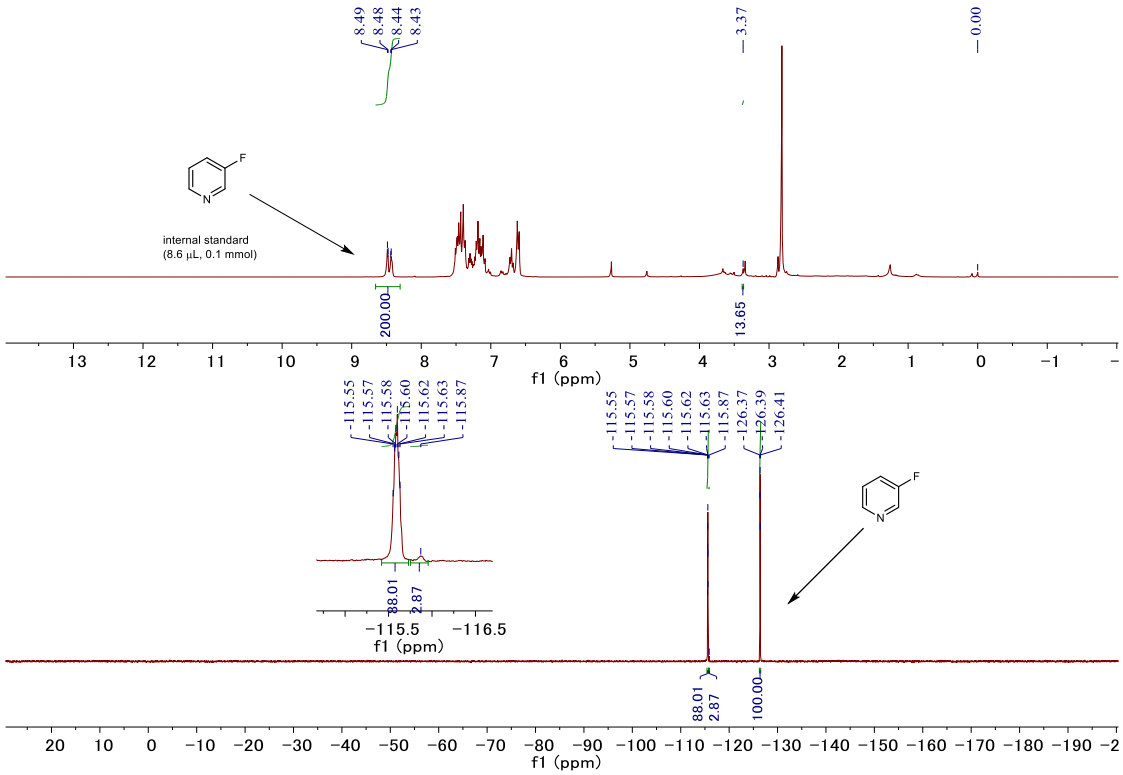


Figure S12. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) and ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C) analysis of reaction (**3**).

Note: After the reaction of (**2**) was work-up, no reaction (N.R.) was observed by TLC (eluent: *n*-hexane/DCM: 10/1).

4.4.5 Radical clock experiments

[182] C. Glock, H. Görls, M. Westerhausen, Electronic, steric, and ligand influence on the solid-state structures of substituted sodium and potassium anilides. *Eur. J. Inorg. Chem.* **2011**, *2011*, 5288–5298.

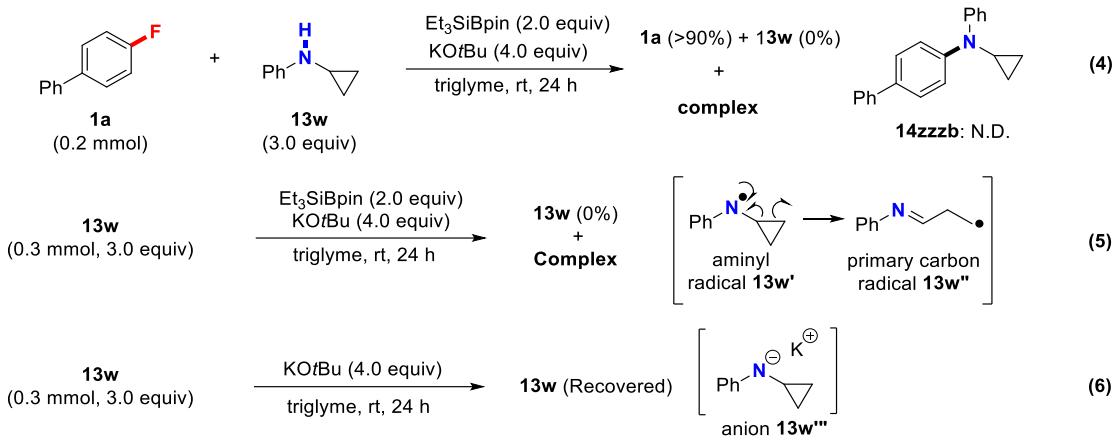
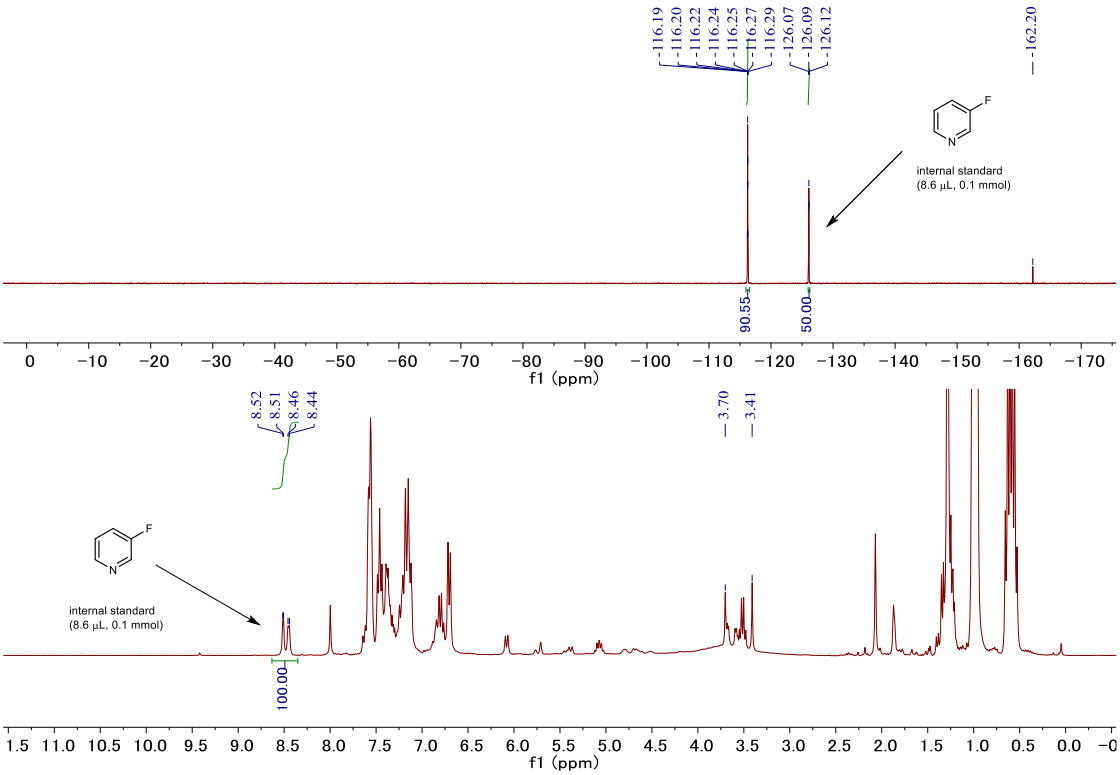


Figure S13. Evaluate allyl fluoride or cinnamyl fluoride for this reaction.

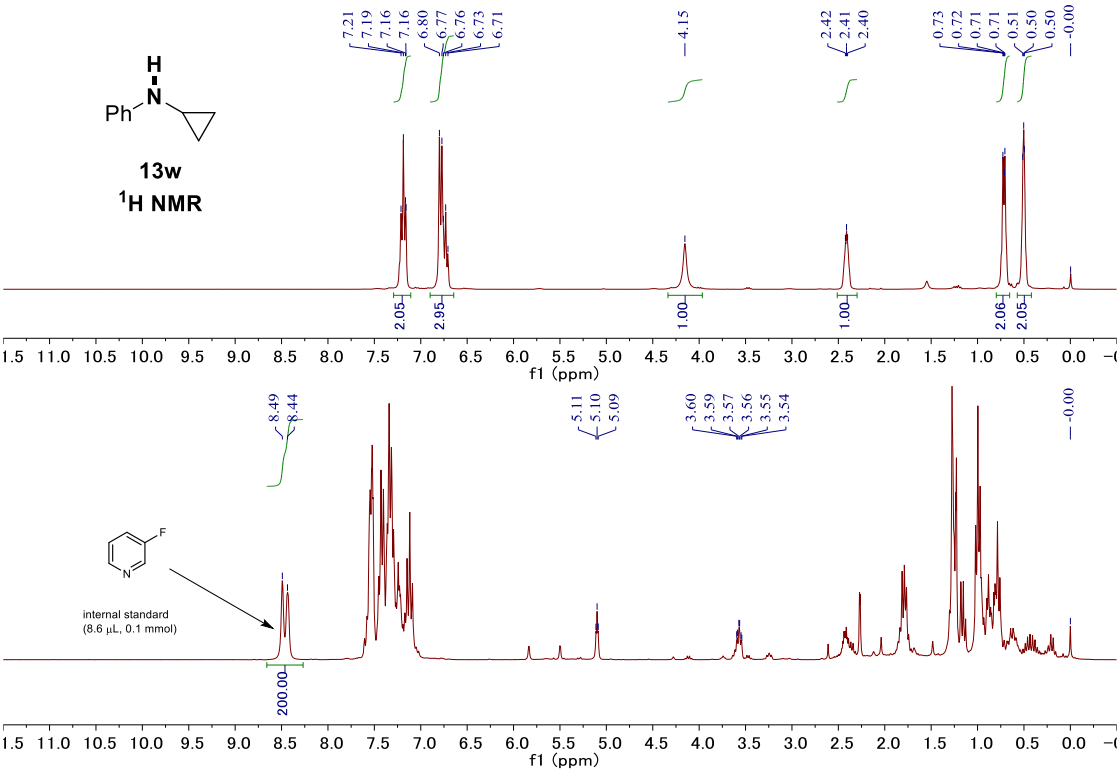
Reaction (**4**): Following the **General procedure E**, charging **1a** (0.2 mmol), **13w** (80.0 mg, 0.6 mmol), silyl boronate $Et_3SiBpin$ (96.8 mg, 0.4 mmol), KO*t*Bu (90.0 mg, 0.8 mmol), and then anhydrous triglyme (1.0 mL) sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stir at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard, then ^{19}F NMR and ^1H NMR analysis was taken to show the reaction details.

Reaction (**5**) and (**6**): Following the **General procedure E**, charging **13w** (40.0 mg, 0.3 mmol), with or without silyl boronate $Et_3SiBpin$ (48.4 mg, 0.2 mmol), KO*t*Bu (44.8 mg, 0.8 mmol), and then anhydrous triglyme (0.5 mL) sequentially into a flame-dried screw-capped test tube. And then move out from glovebox and stir at room temperature for 24 h. The reaction tube was diluted with Et_2O (5 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard, then ^1H NMR analysis was taken to show the reaction details.

Note: After the reaction of **(6)** was worked-up, starting material 1**3w** was observed by TLC (eluent: *n*-hexane/DCM: 10/1).



Supplementary Figure 14. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C) and ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) analysis of the reaction (**4**).



Supplementary Figure 15. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) of **13w** and the ^{1}H NMR (300 MHz, $CDCl_3$,

25 ℃) analysis details of reaction (**5**).

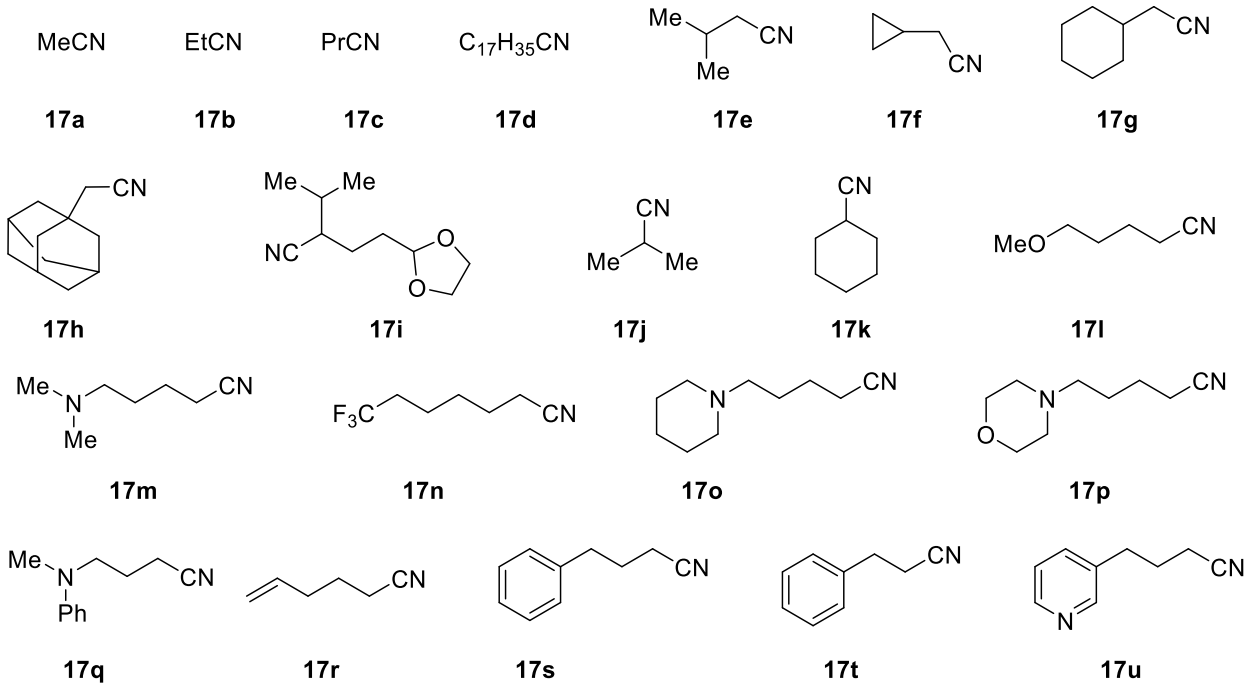
The reaction of **1a** with **13w** under standard conditions did not give the desired product 1**4zzzb**, and majority of **1a** were remains and recovered (around 90%, **^{19}F NMR** yield). **^{1}H NMR** spectrum shows complex mixtures, and no desired product **14zzzb** formed (Similar characteristic peak should be around 2.77 ppm, see *Tetrahedron*, **2006**, *62*, 4253–4261 and *Chem. Eur. J.* **2018**, *24*, 13744–13748 for the details.) However, 1**3w** disappeared completely. Thus, it is difficult to colorlessly assign the products in this reaction.

When treated only **13w** under standard conditions, resulting in the complex mixture and **13w** disappearing. This fact is consistent with the literature that the generated aminyl radical **13w'** spontaneously transforms into the ring-opening primary carbon radical **13w"** (*J. Am. Chem. Soc.* **1980**, *102*, 328–331; *Chem. Soc. Rev.* **2022**, *51*, 7344–7357; and *Acc. Chem. Res.* **2016**, *49*, 1957−1968). Thus, the amine radical **13w'** does not exist anymore, and the resulting ring-opening primary radical **13w"** is unstable and decomposes into the complex mixture.

Additionally, when treated only **13w** under standard conditions without $Et_3SiBpin$ for 24 h, and as a result, **13w** was recovered after work-up process. This is reasonable since the anion **13w"'** is stable.

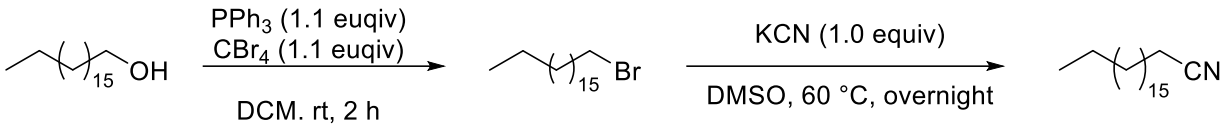
Chapter 5. An Innovative Approach to α-Arylation of acetonitrile

5.1 Preparation for alkylnitirles



17a, **17b**, **17c**, **17e**, **17f**, **17j**, **17k**, **17r**, **17s**, and **17t** were purchased from TCI or Sigma Aldrich.

Nonadecanenitrile (17d)



To a mixture of 1-octadecanol (2.7 g, 10.0 mmol) in DCM (30 mL) was added CBr_4 (3.6 g, 11.0 mmol), stir the reaction mixture for 5 minutes at rt, PPh_3 (2.9 g, 11.0 mmol) dissolved in minimum amount of DCM was drop wised into the mixture at 0 ℃, then stir the mixture at 0 ℃ for 2 h, quench the reaction with sat. $NaHCO_3$ aq.. The resulting mixture was extracted with DCM for three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/DCM 10/1) to give 1-bromooctadecane as white solid (3.1 g, yield: 94%).

To a mixture of 1-bromooctadecane (1.67 g, 5.0 mmol) in DMSO (10 mL) was added KCN (326 mg, 5.0 mmol), the reaction mixture was warned to 60 ℃ overnight, the mixture was poured into H_2O/NH_3 (pH 9) and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 20/1) to give 1-bromooctadecane as white solid (266 mg, yield: 19%).

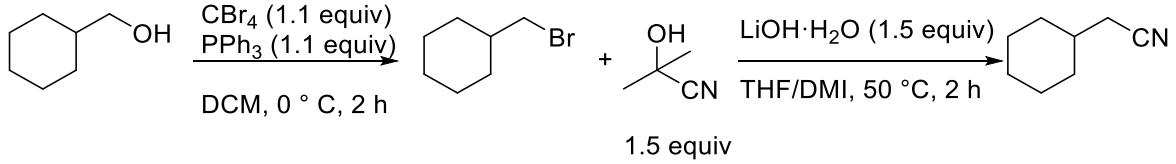
m. p. = 41.6 – 42.1 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (t, *J* = 7.2 Hz, 2H), 1.66 (dt, *J* = 15.0, 7.2 Hz, 2H), 1.48 – 1.40 (m, 2H), 1.26 (s, 28H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 119.93, 31.95, 29.72, 29.69, 29.66, 29.62, 29.53, 29.39, 29.33, 28.79, 28.69, 25.39, 22.72, 17.16, 14.16.

HRMS (ESI) $[C_{19}H_{37}NNa]$ $[M+Na]^+$ calculated: 302.2824, found: 302.2820.

2-cyclohexylacetonitrile (2g)



To a mixture of cyclohexylmethanol (1.14 g, 10.0 mmol) in DCM (30 mL) was added CBr4 (3.6 g, 11.0 mmol), stir the reaction mixture for 5 minutes at rt, PPh_3 (2.9 g, 11.0 mmol) dissolved in minimum amount of DCM was drop wised into the mixture at 0 ℃, then stir the mixture at 0 ℃ for 3 h, quench the reaction with sat. $NaHCO_3$ aq.. The resulting mixture was extracted with DCM 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane) to give (bromomethyl)cyclohexane as colorless oil (1.5 g, yield: 85%).

To a solution of 2-hydroxy-2-methylpropanenitrile (956 mg, 11.2 mmol) in THF/DMI (15 mL: 5 mL, v/v, 3/1) was added $LiOH·H_2O$ (470 mg, 11.2 mmol), The reaction mixture was heated to 50 ºC and stirred for 1 h, (bromomethyl)cyclohexane was added and stir the mixture for more 3 h. After the completion of the reaction, dilute the mixture with water and extract with EtOAc for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was

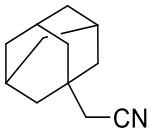
purified by column chromatography on silica gel (eluent: *n*-hexane/Et_2O 15/1) to give the title product as colorless oil (559 mg, yield: 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (d, *J* = 6.6 Hz, 2H), 1.86 – 1.64 (m, 6H), 1.31 – 1.05 (m, 5H).

MS (EI): *m/z* 123 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[183]

2-(adamantan-1-yl)acetonitrile (2h)



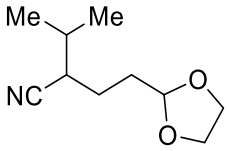
Conc. H_2SO_4 (2.7 mL, 100.0 mmol) was added dropwise at rt to a well-stirred suspension of 1-Adamantaneacetic acid (971 mg, 5.0 mmol) in MeCN (25 mL) and then the mixture was stirred under reflux overnight. The excess of acetonitrile was then evaporated, and DCM and H_2O were added. The layers were separated, and the water layer was extracted with a fresh portion of DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give the residue, which was purified by column chromatography on silica gel (eluent: EtOAc/*n*-hexane: 1/15) to give the title product as white solid (272 mg, yield: 31%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 2H), 2.01 (br, 3H), 1.73 – 1.57 (m, 12H).

MS (EI): *m/z* 175 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[184]

2-(2-(1,3-dioxolan-2-yl)ethyl)-3-methylbutanenitrile



To LDA (8.05 mmol) in THF (12 mL) was added 3-methylbutanenitrile (842 μL, 8.0 mmol) dropwise at 23 °C. The reaction mixture was allowed to stir at 23 °C for 2 hr. The solution was then cooled to 0 °C and 2-(2-bromoethyl)-1,3-dioxolane (1.26 mL, 9.6 mmol) was added dropwise. After stirring at 23 °C for 24 h, the reaction mixture was quenched by adding water (100 mL). The aqueous solution was extracted by ether three times. The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was then purified by chromatography on silica gel, eluting with hexane/ethyl acetate (95/5 then 75/25) to provide the title compound (946.0 mg, 65%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.91 – 4.89 (m, 1H), 4.08 – 3.84 (m, 4H), 2.53 – 2.46 (m, 1H), 1.99 – 1.63 (m,

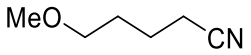
[183] T. Shen, T. Wang, C. Qin, N. Jiao, Silver-Catalyzed Nitrogenation of Alkynes: A Direct Approach to Nitriles through C-C Bond Cleavage, *Angew. Chem. Int. Ed*. **2013**, *52*, 6677 – 6680.
[184] K. Mlinarić-Majerski, R. Margeta, J. Veljković, A Facile and Efficient One-Pot Synthesis of Nitriles from Carboxylic Acids, *Synlett* **2005**, *13*, 2089 – 2091.

6H), 1.06 (d, *J* = 6.7 Hz, 6H).

MS (EI): *m/z* 183 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[185]

5-methoxypentanenitrile (2l)



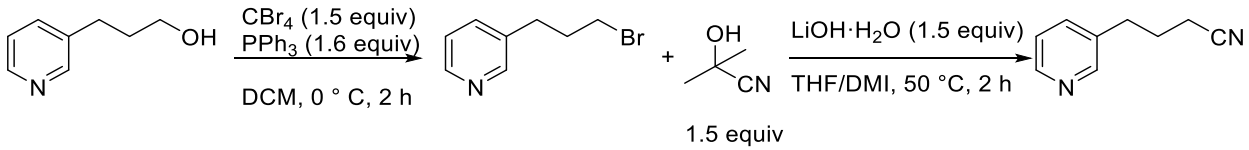
To an oven-dried flask charged with dry MeOH (20 mL) was added Na (460 mg, 20.0 mmol) at 0 ºC, the reaction was stirred at 0 ºC for 20 min, warm it up to rt followed by addition of 5-bromopentanenitrile. Reflux the mixture for 16 h, quench the reaction with NH_4Cl, then extract with Et_2O for 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give the residue, which was purified by column chromatography on silica gel (eluent: Et_2O/*n*-hexane: 1/4) to give the title product as pale-yellow oil (408 mg, yield: 36%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (t, *J* = 5.7 Hz, 2H), 3.33 (s, 3H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.79 – 1.70 (m, 4H).

MS (EI): *m/z* 113 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[186]

4-(pyridin-3-yl)butanenitrile (2u)



To a mixture of 3-(pyridin-3-yl)propan-1-ol (641 μL, 5.0 mmol) in DCM (20 mL) was added CBr_4 (2.5 g, 7.5 mmol), stir the reaction mixture for 5 min at rt, PPh_3 (2.1 g, 8.0 mmol) dissolved in minimum amount of DCM was drop wised into the mixture at 0 ℃, then stir the mixture at 0 ℃ for 2 h, quench the reaction with sat. $NaHCO_3$ aq.. The resulting mixture was extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 3/1) to give 3-(3-bromopropyl)pyridine as pale-yellow oil (801 mg, yield: 80%).

To a solution of 2-hydroxy-2-methylpropanenitrile (510 mg, 6.0 mmol) in THF/DMI (15 mL: 5 mL, v/v, 3/1) was added $LiOH·H_2O$ (252 mg, 6.0 mmol), The reaction mixture was heated to 50 ºC and stirred for 1 h, 3-(3-bromopropyl)pyridine was added and stir the mixture for more 2 h. After the completion of the reaction, dilute the mixture with water and extract with EtOAc for three times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column

[185] L. Wu, J. F. Hartwig, Mild Palladium-Catalyzed Selective Monoarylation of Nitriles, *J. Am. Chem. Soc.* **2005**, *127*, 15824–15832.
[186] World Intellectual Property Organization, WO2016041925 A1 2016-03-24

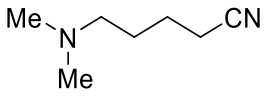
chromatography on silica gel (eluent: *n*-hexane/EA 2/1) to give the title product as a yellow oil (427 mg, yield: 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 – 8.48 (m, 2H), 7.53 (dt, *J* = 7.8, 2.1 Hz, 1H), 7.28 – 7.24 (m, 1H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 6.7 Hz, 2H), 2.02 (q, *J* = 8.1, 7.7 Hz, 2H).

MS (EI): *m/z* 146 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[187]

5-(dimethylamino)pentanenitrile (2m)



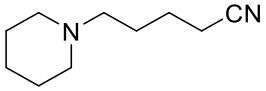
To a stirring solution of NaI (150 mg, 1.0 mmol) and dimethylamine (ca. 50% in Water, ca. 9.5mol/L, 6.3 mL, 60 mmol) was added 5-bromopentanenitrile (1.16 mL,10.0 mmol). The reaction mixture was stirred at rt for 24 h. after the reaction completed, extracted with DCM for 3 times, The combined organic layers were washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure, the residue was purified by column chromatography on alumina (eluent: MeOH/DCM 15/1) to give the title product as colorless oil (1.47 g, yield: quantitative).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (t, *J* = 6.9 Hz, 2H), 2.34 – 2.25 (t, *J* = 6.9 Hz, 2H), 2.22 (s, 6H), 1.76 – 1.57 (m, 4H).

MS (EI): *m/z* 126 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[188]

5-(piperidin-1-yl)pentanenitrile (2o)



To a stirring solution of NaI (75 mg, 0.5 mmol) and piperidine (6.3 mL, 30 mmol) was added 5-bromopentanenitrile (0.6 mL, 5 mmol). The reaction mixture was stirred at rt for 24 h. after the reaction completed, extracted with DCM for 3 times, The combined organic layers were washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure, the residue was purified by column chromatography on alumina (eluent: MeOH/DCM 1/15) to give the title product as colorless oil (816 mg, yield: 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 – 2.27 (m, 8H), 1.69 – 1.64 (m, 4H), 1.57 (p, *J* = 5.7 Hz, 4H), 1.45 – 1.42 (m, 2H).

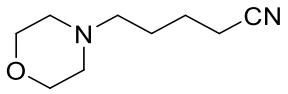
[187] S. Menghin, H. H. Pertz, K. Kramer, R. Seifert, W. Schunack, S. Elz, N(alpha)-imidazolylalkyl and pyridylalkyl derivatives of histaprodifen: synthesis and in vitro evaluation of highly potent histamine H(1)-receptor agonists, *J. Med. Chem.* **2003**, *46*, 5458–5470.

[188] S. Park, B. L. Hayes, F. Marankan, D. C. Mulhearn, L. Wanna, A. D. Mesecar, B. D. Santarsiero, M. E. Johnson, D. L. Venton, Regioselective Covalent Modification of Hemoglobin in Search of Antisickling Agents, *J. Med. Chem*. **2003**, *46*, 936–953.

^{13}C NMR (126 MHz, $CDCl_3$) δ 119.81, 58.23, 54.62, 26.01, 25.89, 24.44, 23.66, 17.13.

HRMS (ESI) [$C_7H_{10}NNaF_3$] $[M+Na]^+$ calculated: 189.1362, found: 189.1363.

5-morpholinopentanenitrile (2p)



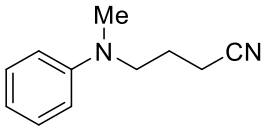
To a stirring solution of NaI (20 mg, 0.13 mmol) and morpholine (680 mg, 7.8 mmol) was added 5-bromopentanenitrile (0.16 mL, 1.3 mmol). The reaction mixture was stirred at rt for 24 h. after the reaction completed, extracted with DCM for 3 times, The combined organic layers were washed with brine, dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure, the residue was purified by column chromatography on alumina (eluent: MeOH/DCM 1/9) to give the title product as colorless oil (120 mg, yield: 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 – 3.70 (m, 4H), 2.44 – 2.35 (m, 8H), 1.78 – 1.59 (m, 4H).

MS (EI): *m/z* 168 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[189]

4-(methyl(phenyl)amino)butanenitrile (2q)



To a mixture of a *N*-methylaniline (268 mg, 2.5 mmol) KI (346 mg, 5.0 mmol) and K_2CO_3 (830 mg, 5.0 mmol) in DMF (3 mL) was added 4-bromobutanenitrile (370 mg, 2.5 mmol), heat the mixture to 100 ºC for 5 h, dilute the mixture with water and extract with EtOAc for 3 times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EA 5/1) to give the title product as yellow oil (449 mg, yield: quantitative).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 6.77 – 6.70 (m, 3H), 3.47 (t, *J* = 6.9 Hz, 2H), 2.96 (s, 3H), 2.40 (t, *J* = 7.0 Hz, 2H), 1.96 (p, *J* = 7.0 Hz, 2H).

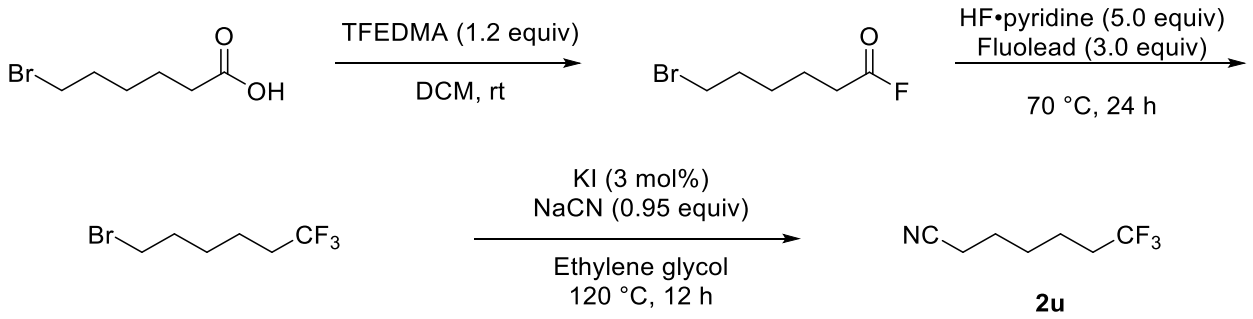
MS (EI): *m/z* 174 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[190]

7,7,7-trifluoroheptanenitrile (2n)

[189] T. J. Fyfe, B. Zarzycka, H. D. Lim, B. Kellam, S. N. Mistry, V. Katrich, P. J. Scammells, J. R. Lane, B, Capuano, A Thieno[2,3-*d*]pyrimidine Scaffold Is a Novel Negative Allosteric Modulator of the Dopamine D_2 Receptor, *J. Med. Chem.* **2019**, *62*, 174–206.

[190] M. C. Mollo, N. Gruber, J. E. Díaz, J. Á. Bisceglia, L. R. Orelli, An Efficient Synthesis of *N*-Alkyl-*N*-arylputrescines and Cadaverines, *Organic Preparations and Procedures International*, **2014**, *46*, 444-452.



To an oven-dried flask charged with 6-bromohexanoic acid (1.95 g, 10 mmol) in DCM (30 mL) was added *N*, *N*-Dimethyl-1,1,2,2-tetrafluoroethylamine (1.7 mL, 12 mmol) at rt. The reaction was stirred for 1 h at rt, quenching the reaction with sat. $NaHCO_3$ aq., then extracted it with DCM for 3 times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/Et_2O 9/1) to give 6-bromohexanoyl fluoride as colorless oil (1.84 g, 94%).

An oven-dried narrow-mouth FEP tube (Nalgene®, 50.0 mL) containing a magnetic stirring bar was charged with 6-bromohexanoyl fluoride (9.4 mmol), FLUOLEAD® (7.0 g, 28.2 mmol) and the *n*HF·pyridine complex (HF 70%, pyridine 30%, 6 mL, 47 mmol). The tube was tightly sealed, and the reaction mixture stirred at 70 °C for 24 h. Then the mixture was cooled to 0 °C and quenched with addition 20% $NaHCO_3$ at until no evolution of gas, extract the resulted mixture with DCM for 3 times, The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The product was purified by distillation (100 °C, 11 torr) to give pure 6-bromo-1,1,1-trifluorohexane as colorless oil (930 mg, 45%).

To a mixture of 6-bromo-1,1,1-trifluorohexane (794 mg, 3.6 mmol) in ethylene glycol (2 mL) was added NaCN (234 mg, 3.4 mmol) and KI (18 mg, 0.11 mmol), the reaction mixture was warmed to 120 °C for 12 h, the mixture was poured into H_2O/NH_3 (pH 9) and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-pentane/Et_2O 7/1) to give the title product as colorless oil (385 mg, yield: 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (t, *J* = 7.0 Hz, 2H), 2.16 – 2.06 (m, 2H), 1.73 – 1.67 (m, 2H), 1.65 – 1.59 (m, 2H), 1.57 – 1.53 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 126.95 (q), 119.39, 33.46 (q), 27.71, 25.06, 21.31 (q), 17.04.

HRMS (ESI) [$C_7H_{10}NNaF_3$] $[M+Na]^+$ calculated: 188.0663, found: 188.0664.

5.2 General procedure

5.2.1 General procedure for optimalizations the defluoroalkylation

General procedure A: In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added aryl fluorides **1** (17.2 mg, 0.1 mmol, 1.0 equiv), KO*t*Bu (56.1 mg, 0.5 mmol, 5.0 equiv), silyl boronates $Et_3SiBpin$ (0.5 mmol, 2.5 equiv), acetonitirle **17a** (0.2 mmol, 2.0 equiv), and dry tetraglyme (1.0 mL) sequentially. The tube was then sealed and removed from the glovebox. The solution was stirred at room temperature for 5 h. The reaction was diluted with Et_2O (5 mL), quenched with H_2O (1 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1

mmol) as an internal standard. After NMR analysis was conducted. The mixture was then concentrated again to give the crude, which was purified by column chromatography on silica gel to give 2-([1,1'-biphenyl]-4-yl)acetonitrile **18a**.

5.2.2 General procedure for defluoroalkylation

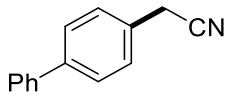
General procedure B: In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added aryl fluorides **1** (0.2 mmol, 1.0 equiv), KO*t*Bu (112.2 mg, 1.0 mmol, 5.0 equiv), silyl boronates $Et_3SiBpin$ (0.5 mmol, 2.5 equiv), alkyl nitirles **17** (0.4 mmol, 2.0 equiv), and dry tetraglyme (2.0 mL) sequentially. The tube was then sealed and removed from the glovebox. The solution was stirred at room temperature for 5 h. The reaction was diluted with Et_2O (5 mL), quenched with H_2O (2 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After NMR analysis was conducted. The mixture was then concentrated again to give the crude, which was purified by column chromatography on silica gel to give the corresponding α-aryl nitriles **18**.

5.2.3 General procedure for intramolecular defluoroalkylation

General procedure C: In a N_2 filled glovebox, to a flame-dried screw-capped test tube was added aryl fluorides **1** (0.2 mmol, 1.0 equiv), KO*t*Bu (112.2 mg, 1.0 mmol, 5.0 equiv), silyl boronates $Et_3SiBpin$ (0.5 mmol, 2.5 equiv), and dry tetraglyme (2.0 mL) sequentially. The tube was then sealed and removed from the glovebox. The solution was stirred at room temperature for 5 h. The reaction was diluted with Et_2O (5 mL), quenched with H_2O (2 mL), then extracted with Et_2O, washed with brine, dried over Na_2SO_4, then concentrated under vacuum, followed by adding 3-fluoropyridine (8.6 μL, 0.1 mmol) as an internal standard. After NMR analysis was conducted. The mixture was then concentrated again to give the crude, which was purified by column chromatography on silica gel to give the corresponding α-aryl nitriles **18**.

5.3 Characterization Data of α-aryl nitriles Products

2-([1,1'-biphenyl]-4-yl)acetonitrile (**18a**)



Compound **18a** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a pale yellow solid (35.6 mg, 92% yield).

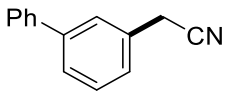
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, J = 7.7 Hz, 4H), 7.48 – 7.37 (m, 5H), 3.79 (s, 2H).

MS (EI): *m/z* 193 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[191]

2-([1,1'-biphenyl]-3-yl)acetonitrile (18b)

[191] Y. Chen, L. Xu, Y. Jiang, D. Ma, Assembly of α-(Hetero)aryl Nitriles via Copper-Catalyzed Coupling Reactions with (Hetero)aryl Chlorides and Bromides, *Angew. Chem. Int. Ed.* **2021**, *60*, 7082 –7086.



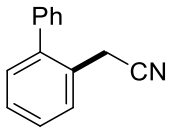
Compound **18b** was prepared according to the **General procedure B** from **1b** (34.4 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a colorless oil (28.2 mg, 75% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 4H), 7.46 (t, *J* = 7.3 Hz, 3H), 7.41 – 7.30 (m, 2H), 3.83 (s, 2H).

MS (EI): *m/z* 193 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[192]

2-([1,1'-biphenyl]-2-yl)acetonitrile (18c)



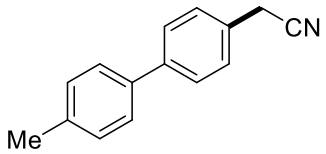
Compound **18c** was prepared according to the **General procedure B** from **1c** (34.4 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a colorless oil (28.1 mg, 73% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 1H), 7.49 – 7.37 (m, 5H), 7.32 – 7.28 (m, 3H), 3.64 (s, 2H).

MS (EI): *m/z* 193 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[193]

2-(4'-methyl-[1,1'-biphenyl]-4-yl)acetonitrile (18d)



Compound **18d** was prepared according to the **General procedure B** from **1f** (37.2 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (35.7 mg, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H),

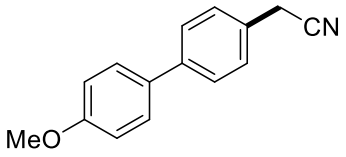
[192] D. Cartagenova, S. Bachmann, K. Püntener, M. Scalone, M. A. Newton, F. A. P. Esteves, T. Rohrbach, P. P. Zimmermann, J. A. van Bokhoven, M. Ranocchiari, Highly selective Suzuki reaction catalysed by a molecular Pd–P-MOF catalyst under mild conditions: role of ligands and palladium speciation, *Catal. Sci. Technol*. **2022**, *12*, 954-961.
[193] E. D. Mock, L. Kosogianni, W. P. F. Driever, C. S. Fonseca, J. M. Vooijs, H. den Dulk, C. A. A. van Boeckel, M. Van der Stelt, Structure–Activity Relationship Studies of Pyrimidine-4-Carboxamides as Inhibitors of N-Acylphosphatidylethanolamine Phospholipase D, *J. Med. Chem.* **2021**, *64*, 481–515.

7.26 (d, *J* = 6.8 Hz, 2H), 3.78 (s, 2H), 2.40 (s, 3H).

MS (EI): *m/z* 207 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[194]

2-(4'-methoxy-[1,1'-biphenyl]-4-yl)acetonitrile (18e)



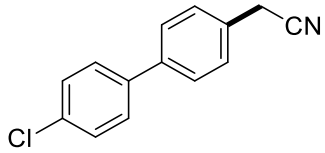
Compound **18e** was prepared according to the **General procedure B** from **1g** (40.4 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a white solid (36.2 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 2H).

MS (EI): *m/z* 223 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[195]

2-(4'-chloro-[1,1'-biphenyl]-4-yl)acetonitrile (18f)



Compound **18f** was prepared according to the **General procedure B** from **1ze** (41.2 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a white solid (37.7 mg, 83% yield).

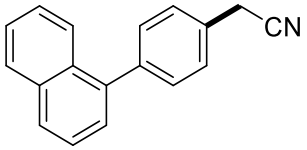
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.43 – 7.39 (m, 4H), 3.80 (s, 2H).

MS (EI): *m/z* 227 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[196]

2-(4-(naphthalen-1-yl)phenyl)acetonitrile (18g)

[194] B. An, S. Kwon, S. Jung, S. Y. Park, Enhanced Emission and Its Switching in Fluorescent Organic Nanoparticles, *J. Am. Chem. Soc.* **2002**, *124*, 14410 – 14415.
[195] C. Calvion, E. Henriet, L. F. Muff, S. Schrettl, C. Weder, Mechanochromic Polymers Based on Microencapsulated Solvatochromic Dyes, *Macromol. Rapid Commun*. **2020**, *41*, 1900654 – 1900654.
[196] M. Kienle, P. Knochel, *i*-PrI Acceleration of Negishi Cross-Coupling Reactions, *Org. Lett*. **2010**, *12*, 2702–2705.



Compound **18g** was prepared according to the **General procedure B** from **1e** (44.4 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a pale yellow solid (45.6 mg, 94% yield).

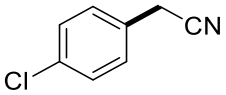
m.p. = 51.1 – 51.8 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 3H), 7.55 – 7.47 (m, 4H), 7.46 – 7.37 (m, 4H), 3.83 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.72, 139.24, 133.82, 131.47, 130.84, 128.92, 128.42, 128.03, 127.96, 127.01, 126.28, 125.95, 125.73, 125.42, 117.97, 23.51.

HRMS (ESI) $[C_{18}H_{13}NNa]$ $[M+Na]^+$ calculated: 266.0946, found: 266.0941.

2-(4-chlorophenyl)acetonitrile (18h)



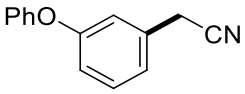
Compound **18h** was prepared according to the **General procedure B** from **1zc** (26.1 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a pale yellow oil (24.6 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 2H).

MS (EI): *m/z* 151 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[197]

2-(3-phenoxyphenyl)acetonitrile (18i)



Compound **18i** was prepared according to the **General procedure B** from **1zr** (37.6 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 5/1) as a pale yellow oil (36.8 mg, 88% yield).

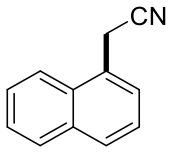
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 3H), 7.17 – 7.12 (m, 1H), 7.08 – 7.00 (m, 3H), 6.97 – 6.94 (m, 2H), 3.72 (s, 2H).

[197] G. Wu, Y. Deng, C. Wu, Y. Zhang, J. Wang, Synthesis of α-Aryl Esters and Nitriles: Deaminative Coupling of α-Aminoesters and α-Aminoacetonitriles with Arylboronic Acids, *Angew. Chem. Int. Ed*. **2014**, *53*, 10510 – 10514.

MS (EI): *m/z* 209 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[193]

2-(naphthalen-1-yl)acetonitrile (18j)



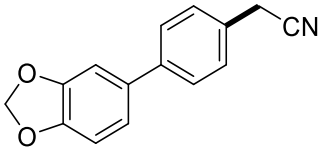
Compound **18j** was prepared according to the **General procedure B** from **1d** (29.2 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a pale yellow oil (27.5 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 3H), 7.64 – 7.54 (m, 3H), 7.50 – 7.45 (m, 1H), 4.13 (s, 2H).

MS (EI): *m/z* 167 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[191]

2-(4-(benzo[d][1,3]dioxol-5-yl)phenyl)acetonitrile (18k)



Compound **18k** was prepared according to the **General procedure B** from **1h** (43.2 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 4/1) as a pale yellow solid (31.7 mg, 67% yield).

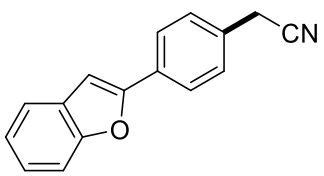
m.p. = 133.3 – 133.8 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.05 – 7.03 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.00 (s, 2H), 3.77 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.25, 147.39, 140.82, 134.54, 128.47, 128.37, 127.55, 120.66, 117.91, 108.70, 107.57, 101.28, 23.31.

HRMS (ESI) $[C_{15}H_{11}NO_2Na]$ $[M]^+$ calculated: 260.0687, found: 260.0692.

2-(4-(benzofuran-2-yl)phenyl)acetonitrile (18l)



Compound **18l** was prepared according to the **General procedure B** from **1u** (42.4 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 3/1) as a white solid (35.2 mg, 75% yield).

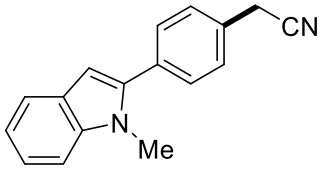
m.p. = 159.0 – 159.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.27 (m, 1H), 7.26 – 7.21 (m, 1H), 7.04 (s, 1H), 3.78 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.95, 130.40, 129.98, 129.06, 128.43, 125.58, 124.64, 123.13, 121.09, 117.66, 111.26, 101.97, 23.51 (one missing carbon).

HRMS (ESI) [$C_{16}H_{11}NONa$] $[M+Na]^+$ calculated: 256.0738, found: 256.0743.

2-(4-(1-methyl-1H-indol-2-yl)phenyl)acetonitrile (18m)



Compound **18m** was prepared according to the **General procedure B** from **1q** (45.0 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 4/1) as a pale yellow solid (44.4 mg, 90% yield).

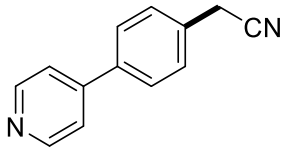
m.p. = 159.0 – 159.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.57 (s, 1H), 3.81 (s, 2H), 3.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.52, 138.49, 132.80, 130.02, 129.51, 128.20, 127.87, 122.01, 120.61, 120.06, 117.74, 109.72, 102.08, 31.26, 23.49.

HRMS (ESI) [$C_{20}H_{17}NO$] $[M+H]^+$ calculated: 247.1235, found: 247.1233.

2-(4-(pyridin-4-yl)phenyl)acetonitrile (18n)



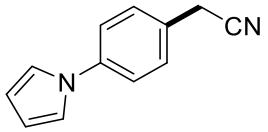
Compound **18b** was prepared according to the **General procedure B** from **1zq** (34.6 mg, 0.2 mmol) and acetonitrile (21.0 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 3/1) as a pale yellow solid (21.0 mg, 54% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, *J* = 6.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.46 (m, 4H), 3.83 (s, 2H).

MS (EI): *m/z* 167 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[198]

2-(4-(1H-pyrrol-1-yl)phenyl)acetonitrile (18o)



Compound **18o** was prepared according to the **General procedure B** from **1n** (32.2 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 4/1) as a white solid (24.8 mg, 68% yield).

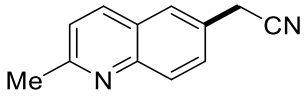
m.p. = 101.2 – 101.8 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 4H), 7.09 (t, *J* = 2.2 Hz, 2H), 6.36 (t, *J* = 2.2 Hz, 2H), 3.77 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.53, 129.21, 127.01, 120.91, 119.21, 117.72, 110.86, 23.13.

HRMS (ESI) $[C_{12}H_{11}N_2]$ $[M]^+$ calculated: 183.0922, found: 183.0920.

2-(2-methylquinolin-6-yl)acetonitrile (18p)



Compound **18p** was prepared according to the **General procedure B** from **1zs** (32.2 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 1/1) as a white solid (12.5 mg, 34% yield).

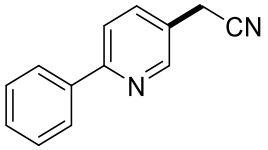
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (t, *J* = 7.9 Hz, 2H), 7.79 (s, 1H), 7.58 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 2H), 2.76 (s, 3H).

MS (EI): *m/z* 182 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[94g]

2-(6-phenylpyridin-3-yl)acetonitrile (18q)

[198] Y. You, H. Yang, J. W. Chung, J. H. Kim, Y. Jung, S. Y. Park, Micromolding of a Highly Fluorescent Reticular Coordination Polymer: Solvent-Mediated Reconfigurable Polymerization in a Soft Lithographic Mold, *Angew. Chem. Int. Ed.* **2010**, *49*, 3757 – 3761.



Compound **18q** was prepared according to the **General procedure B** from **1zzi** (34.6 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (20.8 mg, 54% yield).

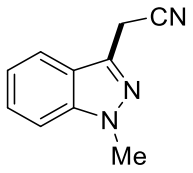
m.p. = 99.1 – 99.7 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.02 – 7.95 (m, 2H), 7.77 (s, 2H), 7.51 – 7.47 (m, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 3.80 (d, *J* = 0.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.48, 148.94, 138.45, 136.34, 129.44, 128.91, 126.95, 124.26, 120.67, 117.00, 21.01.

HRMS (ESI) $[C_{13}H_{10}N_2]$ $[M+H]^+$ calculated: 195.0922, found: 195.0923.

2-(1-methyl-1H-indazol-3-yl)acetonitrile (18r)



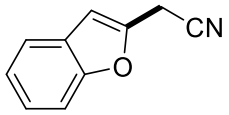
Compound **18r** was prepared according to the **General procedure B** from **1zn** (30.0 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (20.0 mg, 35% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.06 (s, 2H), 4.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.10, 133.11, 126.95, 121.75, 121.05, 119.57, 116.61, 109.41, 35.58, 16.59.

HRMS (ESI) $[C_{10}H_{10}N_3]$ $[M+H]^+$ calculated: 172.0875, found: 172.0873.

2-(benzofuran-2-yl)acetonitrile (18s)



Compound **18s** was prepared according to the **General procedure B** from **1b** (27.2 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a yellow solid (19.2 mg, 62% yield).

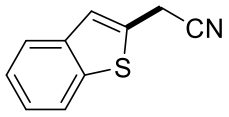
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 1H), 7.48 – 7.45 (m, 1H), 7.34 – 7.25 (m, 2H), 6.75 (d, *J* =

1.1 Hz, 1H), 3.92 (s, 2H).

MS (EI): *m/z* 157 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[199]

2-(benzo[b]thiophen-2-yl)acetonitrile (18t)



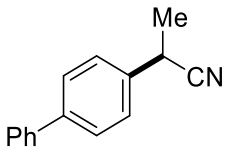
Compound **18t** was prepared according to the **General procedure B** from **1b** (30.4 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a yellow solid (16.8 mg, 48% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 2H), 7.41 – 7.32 (m, 2H), 7.32 (s, 1H), 4.00 (s, 2H).

MS (EI): *m/z* 173 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[199]

2-([1,1'-biphenyl]-4-yl)propanenitrile (18u)



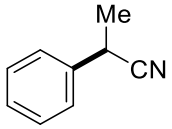
Compound **18u** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17b** (27.8 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 5/1) as a white solid (37.0 mg, 89% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 4H), 7.48 – 7.42 (m, 4H), 7.40 – 7.34 (m, 1H), 3.95 (q, *J* = 7.3 Hz, 1H), 1.69 (d, *J* = 7.3 Hz, 3H).

MS (EI): *m/z* 207 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[199]

2-phenylpropanenitrile (18v)



[199] J. Zhang, J. Liu, D. Hu, J. Song, G. Zhu, H. Ren, Rapid and Simple Access to α-(Hetero)arylacetonitriles from Gem-Difluoroalkenes, *Org. Lett*. **2022**, *24*, 786–790.

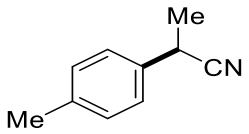
Compound **18v** was prepared according to the **General procedure B** from **1i** (19.2 mg, 0.2 mmol) and **17b** (27.8 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a colorless oil (25.3 mg, 96% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 3.91 (q, J = 7.3 Hz, 1H), 1.65 (d, J = 7.3 Hz, 3H).

MS (EI): *m/z* 131 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[94g]

2-(p-tolyl)propanenitrile (18w)



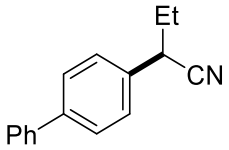
Compound **18w** was prepared according to the **General procedure B** from **1s** (22.0 mg, 0.2 mmol) and **17b** (27.8 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a colorless oil (27.9 mg, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 4H), 3.87 (q, *J* = 7.3 Hz, 1H), 2.35 (s, 3H), 1.63 (d, *J* = 7.3 Hz, 3H).

MS (EI): *m/z* 145 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[94g]

2-([1,1'-biphenyl]-4-yl)butanenitrile (18x)



Compound **18x** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17c** (34.8 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a white solid (40.5 mg, 92% yield).

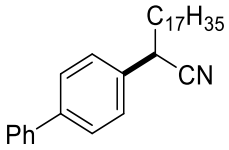
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 4H), 7.48 – 7.37 (m, 5H), 3.79 (t, *J* = 7.2 Hz, 1H), 1.99 (p, *J* = 7.0 Hz, 2H), 1.12 (t, *J* = 7.4 Hz, 3H).

MS (EI): *m/z* 221 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[200]

2-([1,1'-biphenyl]-4-yl)nonadecanenitrile (18y)

[200] Z. Li, G. Zhang, Y. Song, M. Li, Z. Li, W. Ding, J. Wu, Copper-Catalyzed Enantioselective Decarboxylative Cyanation of Benzylic Acids Promoted by Hypervalent Iodine(III) Reagents, *Org. Lett*. **2023**, *25*, 3023–3028.



Compound **18y** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17d** (111.8 mg, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 3/1) as a white solid (74.8 mg, 87% yield).

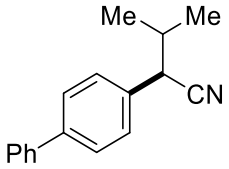
m.p. = 56.6 – 57.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (t, *J* = 8.5 Hz, 4H), 7.45 (t, J = 7.6 Hz, 2H), 7.41 – 7.34 (m, 3H), 3.81 (dd, *J* = 8.6, 6.2 Hz, 1H), 2.00 – 1.82 (m, 2H), 1.56 – 1.41 (m, 2H), 1.25 (s, 28H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.01, 140.31, 135.07, 128.89, 127.76, 127.70, 127.61, 127.11, 120.96, 37.13, 35.94, 31.97, 29.73, 29.65, 29.55, 29.41, 29.35, 29.02, 27.11, 22.74, 14.18 (10 missing carbons).

HRMS (ESI) $[C_{31}H_{45}NNa]$ $[M+Na]^+$ calculated: 454.3450, found: 454.3456.

2-([1,1'-biphenyl]-4-yl)-3-methylbutanenitrile (18z)



Compound **18z** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17e** (42.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (41.8 mg, 89% yield).

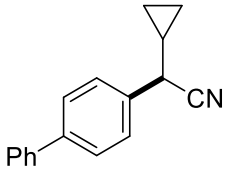
m.p. = 46.9 – 47.7 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.33 (m, 3H), 3.70 (d, *J* = 6.2 Hz, 1H), 2.16 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.08 (dd, *J* = 12.4, 6.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.95, 140.30, 133.92, 128.90, 128.34, 127.62, 127.53, 127.10, 119.89, 44.83, 33.84, 20.87, 18.89.

HRMS (ESI) $[C_{17}H_{17}NNa]$ $[M+Na]^+$ calculated: 258.1259, found: 258.1255.

2-([1,1'-biphenyl]-4-yl)-2-cyclopropylacetonitrile (18za)



Compound **18za** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17f**

(33.7 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a white solid (38.4 mg, 82% yield).

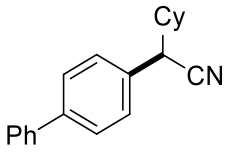
m.p. = 55. – 55.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 4H), 7.47 – 7.43 (m, 4H), 7.38 – 7.35 (m, 1H), 3.54 (d, *J* = 7.6 Hz, 1H), 1.36 – 1.29 (m, 1H), 0.80 – 0.66 (m, 2H), 0.62 – 0.57 (m, 1H), 0.56 – 0.49 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.23, 140.32, 134.56, 128.91, 127.82, 127.76, 127.65, 127.14, 119.87, 40.76, 15.58, 4.90, 3.99.

HRMS (ESI) $[C_{17}H_{15}NNa]$ $[M+Na]^+$ calculated: 256.1102, found: 256.1105.

2-([1,1'-biphenyl]-4-yl)-2-cyclohexylacetonitrile (18zb)



Compound **18zb** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17g** (48.6 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc/DCM: 15/1/1) as a white solid (47.8 mg, 86% yield).

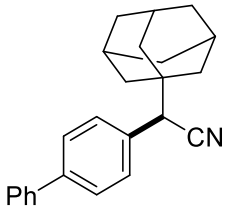
m.p. = 159.3 – 160.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.34 (m, 3H), 3.68 (d, *J* = 6.6 Hz, 1H), 1.90 – 1.87 (m, 1H), 1.81 – 1.75 (m, 3H), 1.73 – 1.66 (m, 2H), 1.24 – 1.16 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.90, 140.32, 133.67, 128.88, 128.44, 127.59, 127.50, 127.10, 120.16, 44.06, 42.81, 31.27, 29.61, 25.98, 25.85.

HRMS (ESI) $[C_{20}H_{21}NNa]$ $[M+Na]^+$ calculated: 298.1572, found: 298.1568.

2-([1,1'-biphenyl]-4-yl)-2-(adamantan-1-yl)acetonitrile (18zc)



Compound **18zc** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17h** (70.1 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 3/1) as a white solid (43.7 mg, 67% yield).

m.p. = 174.6 – 175.3 ℃

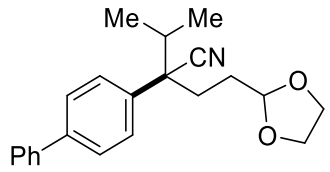
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.30 (d,

J = 8.2 Hz, 2H), 3.47 (s, 1H), 2.05 – 2.02 (m, 3H), 1.72 – 1.67 (m, 6H), 1.63 – 1.58 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.88, 140.32, 131.02, 129.96, 128.88, 127.59, 127.09, 126.88, 119.92, 50.37, 39.82, 36.51, 36.37, 28.39.

HRMS (ESI) $[C_{24}H_{25}NNa]$ $[M+Na]^+$ calculated: 350.1885, found: 350.1883.

2-(2-(1,3-dioxolan-2-yl)ethyl)-2-([1,1'-biphenyl]-4-yl)-3-methylbutanenitrile (18zd)



Compound **18zd** was prepared according to the **General procedure B** from **1b** (34.4 mg, 0.2 mmol) and **17i** (74.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (31.1 mg, 46% yield).

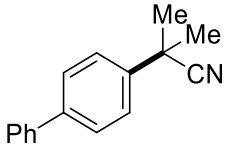
m.p. = 38.9 – 39.7 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 4.80 (t, *J* = 4.8 Hz, 1H), 3.94 – 3.90 (m, 2H), 3.85 – 3.78 (m, 2H), 2.31 (ddd, J = 11.4, 7.6, 4.1 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.85 (dq, J = 13.3, 6.8 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.49 – 1.44 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.18, 141.15, 138.71, 128.92, 128.71, 126.96, 126.77, 104.72, 64.84, 52.68, 33.55, 32.33, 27.15, 20.90.

HRMS (ESI) $[C_{22}H_{26}NO_2]$ $[M+H]^+$ calculated: 336.1964, found: 336.1960.

2-([1,1'-biphenyl]-4-yl)-2-methylpropanenitrile (18ze)



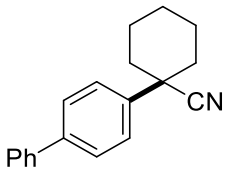
Compound **18ze** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17j** (36.6 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 9/1) as a white solid (15.2 mg, 34% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.53 (m, 6H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 1.77 (s, 6H).

MS (EI): *m/z* 221 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[94g]

1-([1,1'-biphenyl]-4-yl)cyclohexane-1-carbonitrile (18zf)



Compound **18zf** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17k** (47.5 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 15/1) as a white solid (24.5 mg, 47% yield).

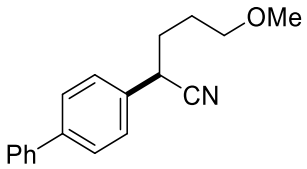
m.p. = 109.7 – 110.2 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.1 Hz, 3H), 7.57 (d, *J* = 13.8 Hz, 3H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 2.21 – 2.17 (m, 2H), 1.92 – 1.77 (m, 7H), 1.34 – 1.26 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.78, 140.47, 140.31, 128.87, 127.58, 127.11, 126.06, 122.74, 44.15, 37.40, 25.02, 23.64 (one missing carbon).

HRMS (ESI) $[C_{19}H_{19}NNa]$ $[M+Na]^+$ calculated: 284.1415, found:284.1412.

2-([1,1'-biphenyl]-4-yl)-5-methoxypentanenitrile (18zg)



Compound **18zg** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17l** (50.1 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (47.0 mg, 89% yield).

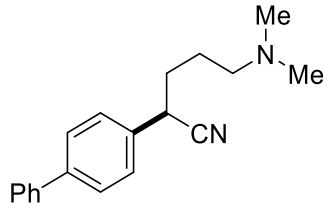
m.p. = 56.8 – 57.3 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 4H), 7.46 – 7.43 (m, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 3.89 (t, *J* = 7.4 Hz, 1H), 3.47 – 3.39 (m, 2H), 3.32 (s, 3H), 2.06 – 2.01 (m, 2H), 1.83 – 1.73 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.10, 140.30, 134.78, 128.90, 127.80, 127.76, 127.63, 127.12, 120.81, 71.66, 58.70, 36.86, 32.88, 27.08.

HRMS (ESI) $[C_{18}H_{19}NONa]$ $[M+Na]^+$ calculated: 288.1364, found: 288.1361.

2-([1,1'-biphenyl]-4-yl)-5-(dimethylamino)pentanenitrile (18zh)



Compound **18zh** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17m** (57.9 µL, 0.4 mmol), and purified by silica gel column chromatography (DCM/MeOH: 20/1) as a white solid (35.8 mg, 64% yield).

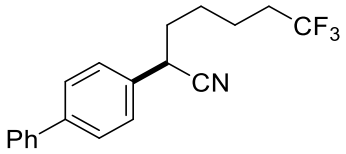
m.p. = 66.9 – 67.6 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.41 – 7.35 (m, 3H), 3.89 (dd, *J* = 8.3, 6.4 Hz, 1H), 2.36 (d, *J* = 1.8 Hz, 2H), 2.23 (s, 6H), 2.02 – 1.94 (m, 2H), 1.76 – 1.61 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.11, 140.28, 134.72, 128.89, 127.79, 127.71, 127.63, 127.11, 120.78, 58.64, 45.35, 36.93, 33.62, 24.88.

HRMS (ESI) $[C_{19}H_{23}N_2]$ $[M+H]^+$ calculated: 279.1861, found: 279.1866.

2-([1,1'-biphenyl]-4-yl)-7,7,7-trifluoroheptanenitrile (18zi)



Compound **18zi** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17n** (66.1 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (19.7 mg, 31% yield).

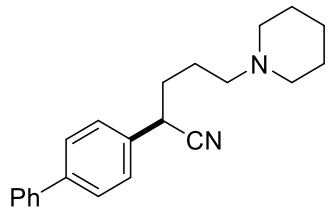
m.p. = 50.3 – 51.2 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.8, 6.0 Hz, 4H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.32 (m, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.97 – 6.91 (m, 1H), 6.85 – 6.76 (m, 2H), 4.36 – 4.31 (m, 2H), 3.79 – 3.76 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 145.2, 140.7, 136.2, 132.0, 128.9, 128.1, 127.1, 126.9, 123.3, 121.0, 120.7, 117.4, 117.3, 64.5, 48.6.

HRMS (ESI) $[C_{19}H_{18}NNaF_3]$ $[M+Na]^+$ calculated: 340.1289, found: 340.1282.

2-([1,1'-biphenyl]-4-yl)-5-(piperidin-1-yl)pentanenitrile (18zj)



Compound **18zj** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17o** (71.2 µL, 0.4 mmol), and purified by silica gel column chromatography (DCM/MeOH: 20/1) as a white solid (59.2 mg, 93% yield).

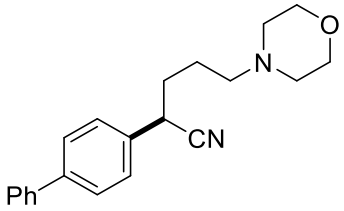
m.p. = 48.4 – 49.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 8.4 Hz, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.41 (s, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 3.91 (dd, *J* = 8.3, 6.4 Hz, 1H), 2.40 – 2.35 (m, 6H), 2.00 – 1.91 (m, 2H), 1.75 – 1.67 (m, 2H), 1.62 – 1.58 (m, 4H), 1.46 – 1.42 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.08, 140.30, 134.80, 128.89, 127.80, 127.72, 127.62, 127.11, 120.84, 58.23, 54.56, 36.89, 33.91, 25.80, 24.29, 24.10.

HRMS (ESI) $[C_{22}H_{26}N_2Na]$ $[M+Na]^+$ calculated: 341.1994, found: 341.1986.

2-([1,1'-biphenyl]-4-yl)-5-morpholinopentanenitrile (18zk)



Compound **18zk** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17p** (67.6 µL, 0.4 mmol), and purified by silica gel column chromatography (DCM/MeOH: 20/1) as a white solid (60.0 mg, 94% yield).

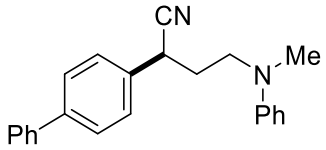
m.p. = 76.2 – 77.2 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.39 – 7.35 (m, 1H), 3.91 (dd, J = 8.3, 6.3 Hz, 1H), 3.70 (t, J = 4.7 Hz, 4H), 2.45 – 2.40 (m, 3H), 2.38 (t, J = 7.4 Hz, 3H), 2.07 – 1.91 (m, 2H), 1.75 – 1.60 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.14, 140.24, 134.72, 128.91, 127.82, 127.69, 127.10, 120.77, 66.99, 57.89, 53.70, 36.90, 33.69, 23.81 (one missing carbon).

HRMS (EI) $[C_{21}H_{25}N_2O]$ $[M+H]^+$ calculated: 321.1967, found: 321.1970.

2-([1,1'-biphenyl]-4-yl)-4-(methyl(phenyl)amino)butanenitrile (18zl)



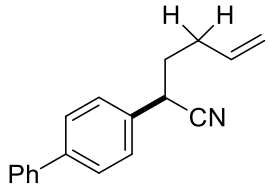
Compound **18zl** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17q** (68.2 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 5/1) as a colorless oil (58.3 mg, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.35 (m, 3H), 7.25 – 7.22 (m, 3H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 2H), 3.90 (t, *J* = 7.4 Hz, 1H), 3.55 – 3.47 (m, 2H), 2.95 (s, 3H), 2.21 (q, *J* = 7.3 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.26, 129.39, 128.94, 127.92, 127.73(2), 127.13, 120.59, 117.17, 112.78, 50.08, 38.80, 34.51, 32.92.

HRMS (EI) $[C_{23}H_{22}N_2Na]$ $[M+Na]^+$ calculated: 349.1681, found: 349.1677.

2-([1,1'-biphenyl]-4-yl)hex-5-enenitrile (18zm)



Compound **18zm** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17r** (45.3 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 20/1) as a white solid (43.1 mg, 83% yield).

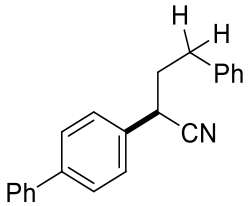
m.p. = 48.4 – 48.8 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 5.79 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.13 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.09 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.85 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.31 – 2.25 (m, 2H), 2.12 – 2.05 (m, 1H), 2.02 – 1.94 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.16, 140.26, 136.12, 134.69, 128.91, 127.84, 127.79, 127.66, 127.12, 120.71, 116.78, 36.23, 34.91, 30.98.

HRMS (ESI) $[C_{18}H_{17}NNa]$ $[M+Na]^+$ calculated: 270.1259, found: 270.1255.

2-([1,1'-biphenyl]-4-yl)-4-phenylbutanenitrile (18zn)



Compound **18zn** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17s** (58.0 mg, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 9/1) as a white solid (27.2 mg, 48% yield).

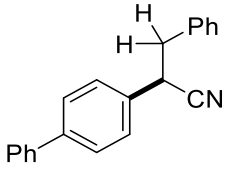
m.p. = 83.9 – 84.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.37 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 3H), 3.78 (dd, *J* = 9.0, 6.1 Hz, 1H), 2.90 – 2.79 (m, 2H), 2.35 – 2.18 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.20, 140.25, 139.80, 134.58, 128.91, 128.75, 128.50, 127.85, 127.76, 127.66, 127.12, 126.57, 120.66, 37.36, 36.26, 33.08.

HRMS (ESI) $[C_{22}H_{19}NNa]$ $[M+Na]^+$ calculated: 320.1415, found: 320.1415.

2-([1,1'-biphenyl]-4-yl)-3-phenylpropanenitrile (18zo)



Compound **18zo** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17t** (52.4 mg, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (20.0 mg, 35% yield).

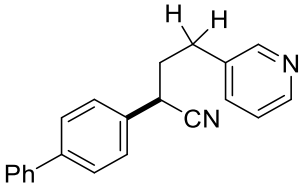
m.p. = 109.9 – 110.3 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.58 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.31 (m, 3H), 7.30 – 7.28 (m, 2H), 7.18 (d, *J* = 6.3 Hz, 2H), 4.05 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.25 – 3.15 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.19, 140.21, 136.27, 134.18, 129.28, 128.91, 128.70, 127.95, 127.70, 127.46, 127.11, 120.37, 42.21, 39.56.

HRMS (ESI) $[C_{21}H_{17}NNa]$ $[M+Na]^+$ calculated: 306.1259, found: 306.1250.

2-([1,1'-biphenyl]-4-yl)-4-(pyridin-3-yl)butanenitrile (18zp)



Compound **18p** was prepared according to the **General procedure B** from **1a** (34.4 mg, 0.2 mmol) and **17u** (57.0 μL, 0.4 mmol), and purified by silica gel column chromatography (EtOAc only) as a white solid (49.0 mg, 82% yield).

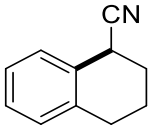
m.p. = 109.9 – 110.3 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.1 Hz, 2H), 7.62 – 7.57 (m, 4H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.47 – 7.44 (m, 3H), 7.25 – 7.23 (m, 1H), 3.83 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.90 – 2.79 (m, 2H), 2.34 – 2.18 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.91, 148.17, 141.40, 140.12, 135.93, 135.19, 134.05, 128.93, 127.96, 127.73, 127.11, 123.60, 120.31, 36.93, 36.39, 30.28.

HRMS (EI) $[C_{20}H_{17}N_2Na]$ $[M+Na]^+$ calculated: 321.1368, found: 321.1362.

1,2,3,4-tetrahydronaphthalene-1-carbonitrile (18zq)



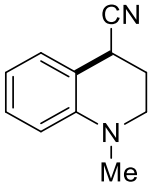
Compound **18zq** was prepared according to the **General procedure C** from **1zu** (35.4 mg, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a colorless oil (21.9 mg, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.24 – 7.19 (m, 2H), 7.14 – 7.11 (m, 1H), 3.99 (t, *J* = 6.3 Hz, 1H), 2.92 – 2.74 (m, 2H), 2.19 – 2.13 (m, 2H), 2.07 – 1.98 (m, 1H), 1.91 – 1.80 (m, 1H).

MS (EI): *m/z* 145 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[201]

1-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (18zr)



Compound **18zr** was prepared according to the **General procedure C** from **1zv** (38.4 mg, 0.2 mmol, and purified by silica gel column chromatography (*n*-hexane/EtOAc: 7/1) as a pale-yellow oil (18.8 mg, 55% yield).

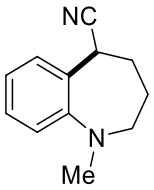
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 6.69 (td, *J* = 7.4, 1.1 Hz, 1H), 6.63 (dd, *J* = 8.7, 1.1 Hz, 1H), 3.97 – 3.95 (m, 1H), 3.45 – 3.40 (m, 1H), 3.31 – 3.26 (m, 1H), 2.91 (s, 3H), 2.29 – 2.25 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.65, 129.62, 128.89, 121.19, 116.84, 115.05, 111.89, 48.16, 38.92, 29.38, 26.00.

HRMS (ESI) $[C_{11}H_{13}N_2]$ $[M+H]^+$ calculated: 173.1079, found: 173.1075.

[201] L. Song, N. Fu, B. G. Ernst, W. Lee, M. O. Frederick, R. A. Distasio, S. Lin, Dual electrocatalysis enables enantioselective hydrocyanation of conjugated alkenes, *Nat. Chem.* **2020**, *12*, 747–754.

1-methyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine-5-carbonitrile (18zs)



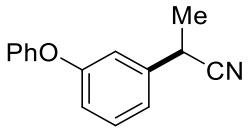
Compound **18zs** was prepared according to the **General procedure C** from **1zw** (41.2 µL, 0.2 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 5/1) as a colorless oil (25.3 mg, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.01 – 6.98 (m, 2H), 4.22 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.86 (s, 3H), 2.86 – 2.78 (m, 1H), 2.10 – 2.04 (m, 1H), 1.90 – 1.82 (m, 1H), 1.81 – 1.7 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.70, 128.88, 128.13, 127.76, 121.90, 121.11, 117.60, 55.41, 42.35, 34.41, 29.13, 26.37.

HRMS (ESI) $[C_{12}H_{15}N_2]$ $[M+H]^+$ calculated: 187.1235, found: 187.1235.

2-(3-phenoxyphenyl)propanenitrile (18zt)



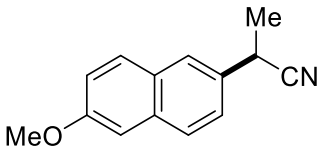
Compound **18zt** was prepared according to the **General procedure B** from **1zr** (32.8 µL, 0.2 mmol) and **17b** (27.8 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 5/1) as a colorless oil (38.8 mg, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (q, *J* = 7.7 Hz, 3H), 7.17 – 7.09 (m, 2H), 7.04 – 6.92 (m, 4H), 3.87 (q, *J* = 7.3 Hz, 1H), 1.64 (d, *J* = 6.8 Hz, 3H).

MS (EI): *m/z* 223 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[191]

2-(6-methoxynaphthalen-2-yl)propanenitrile (18zu)



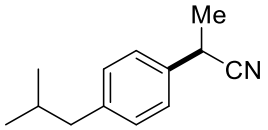
Compound **18zu** was prepared according to the **General procedure B** from **1zx** (35.2 mg, 0.2 mmol) and **17b** (27.8 µL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 5/1) as a white solid (34.6 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (t, *J* = 8.4 Hz, 3H), 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.20 – 7.13 (m, 2H), 4.03 (q, *J* = 7.3 Hz, 1H), 3.93 (s, 3H), 1.71 (d, *J* = 7.3 Hz, 3H).

MS (EI): *m/z* 197 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[100]

2-(4-isobutylphenyl)propanenitrile (18zv)



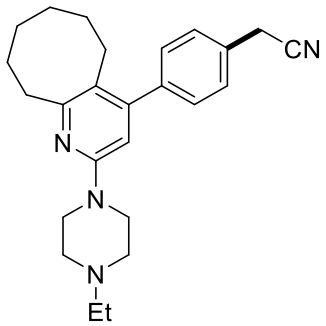
Compound **18zv** was prepared according to the **General procedure B** from **1zzb** (32.0 μL, 0.2 mmol) and **2b** (27.8 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a white solid (33.5 mg, 89% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 3.87 (q, *J* = 7.3 Hz, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.85 (dp, *J* = 13.5, 6.8 Hz, 1H), 1.63 (d, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 6H).

MS (EI): *m/z* 173 $[M]^+$.

The chemical shifts were consistent with those reported in the literature.[199]

2-(4-(2-(4-ethylpiperazin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-4-yl)phenyl)acetonitrile (18zw)



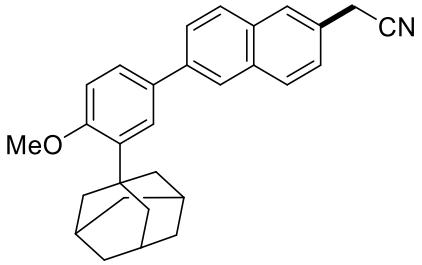
Compound **18zw** was prepared according to the **General procedure B** from **1zz** (73.5 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (DCM/MeOH: 30/1) as a clear viscous oil (55.0 mg, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.29 (s, 1H), 3.80 (s, 2H), 3.54 (dd, *J* = 6.4, 4.1 Hz, 4H), 2.92 – 2.85 (m, 2H), 2.57 (q, *J* = 6.2, 5.6 Hz, 6H), 2.48 (q, *J* = 7.2 Hz, 2H), 1.81 – 1.76 (m, 2H), 1.45 – 1.42 (m, 2H), 1.39 – 1.34 (m, 4H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.01, 157.27, 150.46, 141.46, 129.30, 128.84, 127.64, 122.76, 117.86, 105.76, 52.73, 52.48, 45.48, 35.54, 31.55, 30.62, 26.52, 25.80, 24.88, 23.45, 11.96.

HRMS (ESI) $[C_{25}H_{33}N_4]$ $[M+H]^+$ calculated: 389.2705, found: 389.2709.

2-(6-(3-(adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)acetonitrile (18zx)



Compound **18zx** was prepared according to the **General procedure B** from **1zza** (77.2 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/DCM: 2/1) as a white solid (65.8 mg, 81% yield).

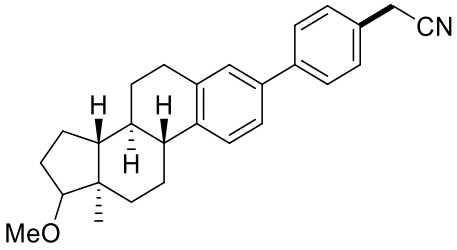
m.p. = 192.6 – 193.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.88 (dd, *J* = 14.2, 8.5 Hz, 2H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.77 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 2H), 3.90 (s, 3H), 2.19 (s, 6H), 2.10 (s, 3H), 1.80 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.72, 139.68, 138.95, 133.11, 132.76, 132.12, 129.71, 129.21, 128.08, 126.75, 126.65, 125.92, 125.78, 125.63, 124.82, 117.96, 112.10, 55.20, 40.62, 37.21, 37.15, 29.12, 23.88.

HRMS (ESI) $[C_{29}H_{29}NONa]$ $[M+Na]^+$ calculated: 430.2147, found: 430.2142.

2-(4-((8S,9R,13R,14R)-17-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)phenyl)acetonitrile (18zy)



Compound **18zy** was prepared according to the **General procedure B** from **1zy** (72.8 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc/DCM: 9/1/1) as a white solid (56.7 mg, 74% yield).

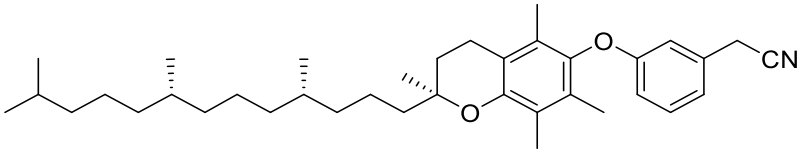
m.p. = 147.6 – 148.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.37 (m, 4H), 7.31 (s, 1H), 3.78 (s, 2H), 3.39 (s, 3H), 3.35 – 3.32 (m, 1H), 2.95 – 2.93 (m, 2H), 2.38 – 2.26 (m, 2H), 2.11 – 2.05 (m, 2H), 1.96 – 1.91 (m, 1H), 1.75 – 1.69 (m, 1H), 1.57 – 1.35 (m, 6H), 1.27 – 1.21 (m, 1H), 0.81 (s, 3H)..

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.05, 140.09, 137.51, 137.33, 128.48, 128.31, 127.67, 126.02, 124.33, 117.93, 90.77, 57.95, 50.41, 44.35, 43.23, 38.40, 38.06, 29.71, 27.77, 27.20, 26.29, 23.35, 23.08, 11.57(one missing carbon).

HRMS (ESI) [$C_{27}H_{31}NONa$] $[M+Na]^+$ calculated: 408.2303, found: 408.2307.

2-(3-(((S)-2,5,7,8-tetramethyl-2-((4S,8S)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)phenyl)acetonitrile (18zz)



Compound **18zz** was prepared according to the **General procedure B** from **1zzc** (104.8 mg, 0.2 mmol) and acetonitrile (21.0 μL, 0.4 mmol), and purified by silica gel column chromatography (*n*-hexane/EtOAc: 10/1) as a colorlee oil (20.0 mg, 35% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.92 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.72 (s, 1H), 6.66 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.67 (s, 2H), 2.61 (t, *J* = 6.9 Hz, 2H), 2.12 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.89 – 1.75 (m, 2H), 1.64 – 1.56 (m, 2H), 1.55 – 1.48 (m, 2H), 1.44 – 1.35 (m, 3H), 1.34 – 1.18 (m, 12H), 1.16 – 1.11 (m, 3H), 1.07 – 1.03 (m, 2H), 0.88 – 0.83 (m, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.39, 148.91, 143.02, 131.45, 130.31, 128.05, 126.18, 123.43, 120.41, 118.01, 117.86, 114.53, 114.31, 75.14, 40.06, 39.39, 37.59, 37.49, 37.42, 37.32, 32.82, 32.71, 31.22, 28.01, 24.85, 24.48, 23.86, 23.59, 22.76, 22.66, 21.07, 20.64, 19.71, 12.90, 12.04, 11.87.

HRMS (ESI) [$C_{37}H_{55}NO_2Na$] $[M+Na]^+$ calculated: 568.4130, found: 568.4136.

Chapter 6. Mechanochemical Deoxyfluorination of Carboxylic Acids to Acyl Fluorides and Successive Mechanochemical Amide Bond Formation

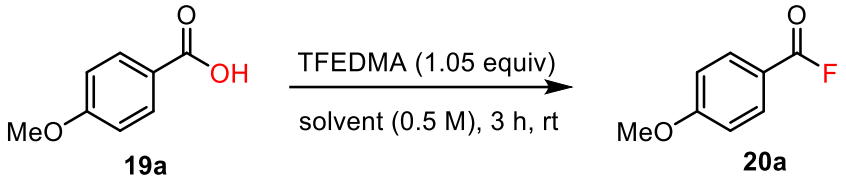
6.1 Information of Information of mechanochemical device

All ball-milling reactions were conducted in a mixer mill (MM400, Retsch Gmbh, Hann, Germany) using a 1.5 mL or 5.0 mL (SUS440B) stainless-steel grinding jar with a stainless-steel ball (φ5.0 mm or φ7.0 mm).

Figure S1. MM400, Retsch and stainless jar as well as ball used in this study.

6.2 Reaction condition optimization

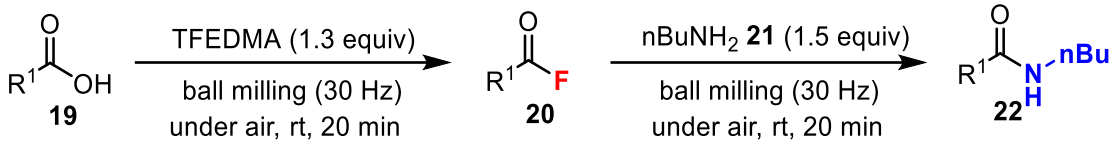
Table S1. Batch reaction of deoxyfluorination mediated by TFEDMA



Entry	Solvent	^{19}F NMR yield(%)[a]
1	**DCM**	**>99%(93%)**[b]
2	Toluene	97%
3	MeCN	68%
4	-	97%

[a]^{19}F NMR yield of the crude product was determined by C_6H_5F as an internal standard in chloroform-*d*; [b]The isolated yield was shown in the parentheses.

Table S2. Mechanochemical one-pot amidation from carboxylic acids

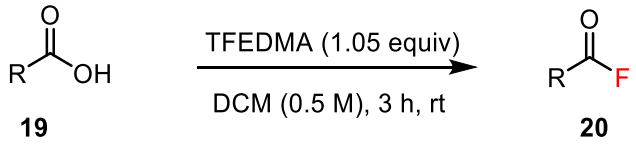


Entry	TFEDMA (equiv)	*n*BuNH$_2$ (equiv)	Time (min)	^{1}H NMR yield(%)[a]
1	1.05	1.2	20	63
2	1.05	1.2	30	51
3	1.05	1.2	60	54
4	1.05	1.3	20	67
5	1.05	1.4	20	68
6	1.05	1.5	20	68
7	1.05	2.0	20	75
8	1.20	1.5	20	78
9	**1.30**	**1.5**	**20**	**82(76)**[b]
10	1.40	1.5	20	78
11	1.50	1.5	20	77
12	1.50	2.0	20	64

[a]^{1}H NMR yield of the crude product was determined by 3-fluoropyridine as an internal standard in chloroform-*d*; [b]The isolated yield was shown in the parentheses.

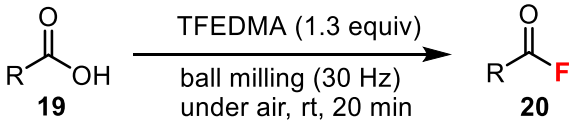
6.3 Experimental procedures

3.1 The general procedure of deoxyfluorination for batch reaction



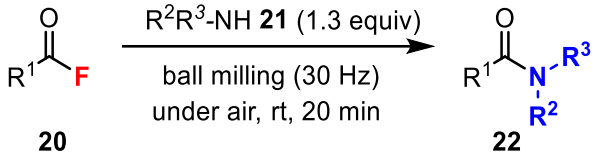
To narrow-mouth FEP tube (Nalgene®) (10.0 mL) containing a magnetic stir bar was charged with **19** (0.1 mmol), DCM (0.5 M), and TFEDMA (1.05 equiv.) successively, stir the reaction mixture for 3 h at room temperature. Concentrate the reaction mixture under reduced pressure and purify through a short pad of silica gel to give products **20.**

3.2 The general procedure A for acyl fluorides



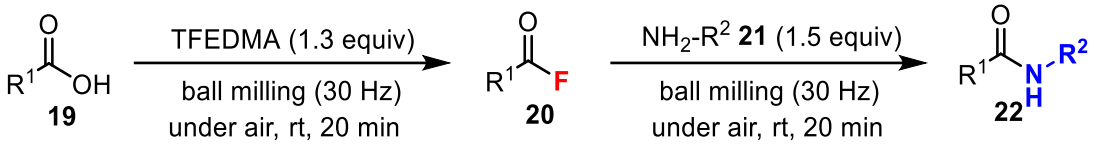
A grinding jar with a stainless-steel ball containing **19** (0.1 mmol) was charged with TFEDMA (19.0 μL, 1.3 equiv, 80 wt%, 1.24 g/mL, measured by a micropipette). The grinding jar was set in the mixer mill, vibrated it at 30 Hz for 20 min, and then washed it with DCM. Thereafter, sat. $NaHCO_3$ aq. (1.0 mL) was added, and the reaction mixture was extracted with DCM (5.0 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **20**.

3.3 The general procedure B for amide compounds from acyl fluorides



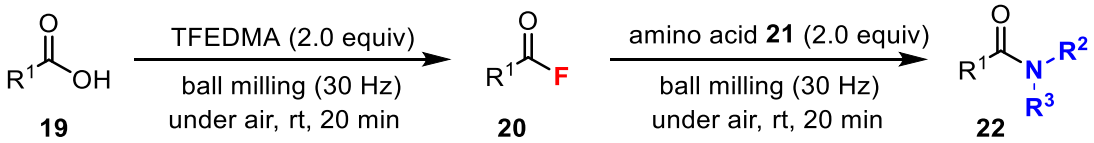
A grinding jar with a stainless-steel ball containing **20** (0.2 mmol) was charged with amine **21**. The grinding jar was set in the mixer mill, vibrated it at 30 Hz for 20 min, and then washed it with DCM. Thereafter, sat. $NaHCO_3$ aq. (1.0 mL) was added, and the reaction mixture was extracted with DCM (5.0 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure to give products **22**.

3.4 The general procedure C for amide compounds by one-pot synthesis



A grinding jar with a stainless-steel ball containing **19** (0.2 mmol) was charged with TFEDMA (38.0 μL, 1.3 equiv, 80 wt%, 1.24 g/mL, measured by a micropipette). The grinding jar was set in the mixer mill, vibrated it at 30 Hz for 20 min, and then amine **21** was added, vibrated it at 30 Hz for more 20 min. and then washed it with DCM. Thereafter, sat. $NaHCO_3$ aq. (1.0 mL) was added, and the reaction mixture was extracted with DCM (5.0 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **22**.

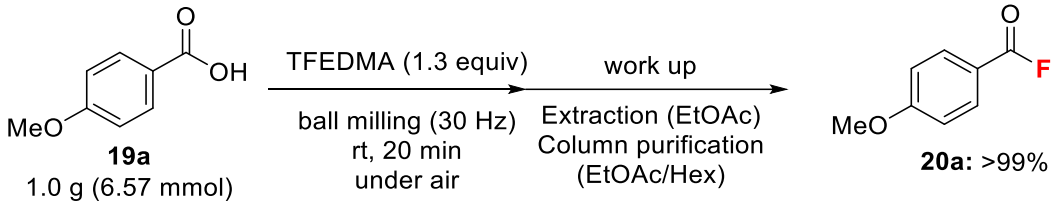
3.5 The general procedure D for dipeptide compounds by one-pot synthesis



A grinding jar with a stainless-steel ball containing **19** (0.2 mmol) was charged with TFEDMA (58.5 μL, 2.0 equiv., 80 wt%, 1.24 g/mL, measured by a micropipette). The grinding jar was set in the mixer mill, vibrated it

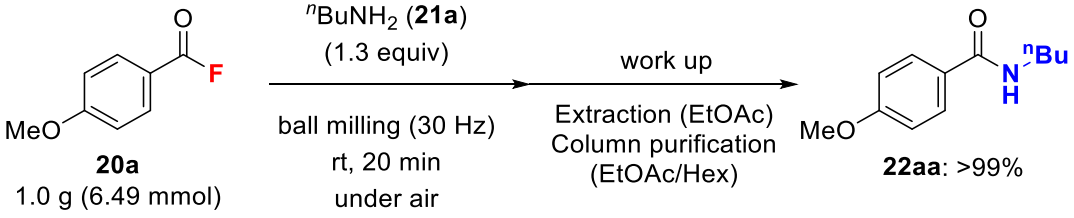
at 30 Hz for 20 min, and then amine **21** was added, vibrated it at 30 Hz for more 20 min. and then washed it with DCM. Thereafter, sat. $NaHCO_3$ aq. (1.0 mL) was added, and the reaction mixture was extracted with DCM (5.0 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **22**. (**note: All amino esters we used are the form of hydrochloride salts**)

3.6 The procedure for gram-scale ball-milling deoxyfluorination



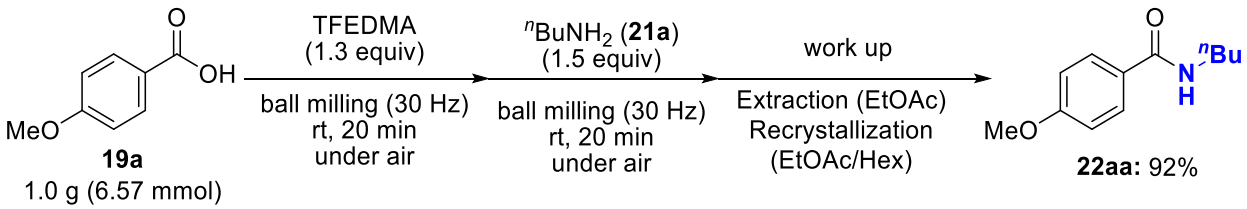
A grinding jar with a stainless-steel ball containing **19a** (1.0 g, 1.0 equiv., 6.57 mmol) was charged with TFEDMA (1.15 mL, 1.3 equiv, 87 wt%, 1.24 g/mL). The grinding jar was set in the mixer mill, vibrated it at 30 Hz for 20 min. and then washed it with Ethyl acetate. Thereafter, sat. $NaHCO_3$ aq. (10 mL) was added, and the reaction mixture was extracted with Ethyl acetate (20 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **20a** (yield: 1.03 g, >99%) as pale-yellow oil.

3.7 The procedure for gram-scale ball-milling coupling reaction



A grinding jar with a stainless-steel ball containing **20a** (1.0 g, 6.49 mmol) was charged with $^nBuNH_2$ (0.83 mL, 1.3 equiv., 0.74 g/mL). The grinding jar was set in the mixer mill, vibrated it at 30 Hz for 20 min, and then washed it with Ethyl acetate. Thereafter, sat. $NaHCO_3$ aq. (10 mL) was added, and the aqueous layer was extracted with Ethyl acetate (20 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by recrystallization (*n*-hexane/Ethyl acetate) to give products **22aa** (yield: 1.36 g, >99%**)** as a white solid.

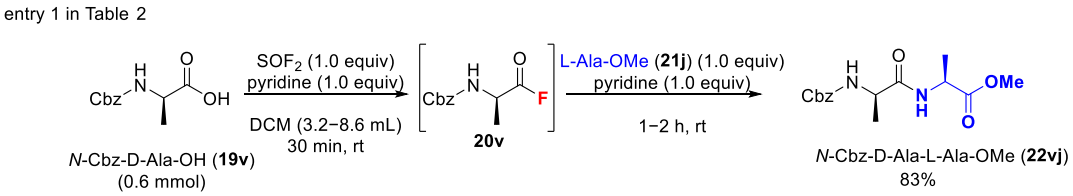
3.8 The procedure for gram-scale ball-milling one-pot deoxyfluorination/coupling



A grinding jar with a stainless-steel ball containing **19a** (1.0 g, 6.57 mmol) was charged with TFEDMA (1.15 mL, 1.3 equiv., 87 wt%, 1.24 g/mL, measured by a micropipette). The grinding jar was set in the mixer mill,

vibrated it at 30 Hz for 20 min, and then $^{n}BuNH_2$ (0.97 mL, 1.5 equiv., 0.74 g/mL) was added, vibrated it at 30 Hz for more 20 min. and then washed it with Ethyl acetate. Thereafter, sat. $NaHCO_3$ aq. (10 mL) was added, and the aqueous layer was extracted with Ethyl acetate (20 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by recrystallization (n-hexane/Ethyl acetate) to give products **22aa** (yield: 1.25 g, 92%) as a white solid.

6.4 Evaluation of green chemistry metrics of 22vj and 22th



Atom Economy (%) = $\frac{\text{Mol. wt. of product}}{\text{Mol. wt. of all reactants}} \times 100 = \frac{308.3340 \times 100}{223.2280 + 145.1006 \times 2 + 139.579 \times 2} =$ **38.9%**

Atom Effciency (%) = (yield of product x atom economy) x 100 = (83% x 54.04%) x 100 = **44.85%**

Carbon Efficiency (%) = $\frac{\text{moles of 22vj x no. of carbon in 22vj x 100}}{\text{(moles of 19v x carbon in 19v) + (moles of pyridine x carbon in pyridine) + (moles of 21j x carbon in 21j)}} = \frac{(15 \times 0.6 \times 0.83) \times 100}{11 \times 0.6 + 5 \times 1.2 + 4 \times 0.6} =$ **49.80%**

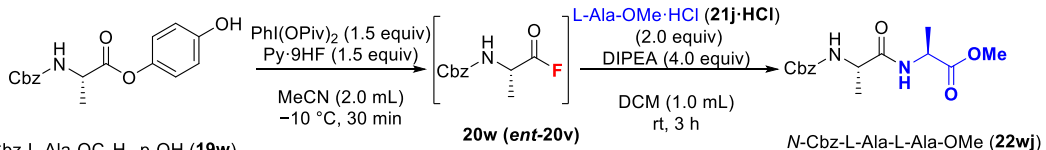
N-Cbz-D-Ala-OH (**19v**)	134 mg	0.6 mmol	Molecular Weight: 223.2280
SOF_2	52 mg	0.6 mmol	Molecular Weight: 86.0558
L-Ala-OMe (**21j**)	62 mg	0.6 mmol	Molecular Weight: 103.1210
pyridine	95 mg	0.6 x 2 mmol	Molecular Weight: 79.1020
DCM (solvent)	7847 mg	92.4 mmol on average	Molecular Weight: 84.9270
Product (**22vj**)	154 mg	0.5 mmol	Molecular Weight: 308.3340

Reaction Mass Efficiency (%) = $\frac{\text{mass of isolated 22vj}}{\text{mass of all reactants}} \times 100 \quad \frac{154 \times 100}{134 + 52 + 62 + 95} =$ **44.90%**

E-factor = $\frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{(134 + 52 + 62 + 7847) - 154}{154} =$ **52.18** mg waste/mg prodcut

Scheme S5. Calculations of green chemistry metrics for entry 1 in table 2

entry 2 in Table 2



N-Cbz-L-Ala-OC$_6$H$_4$-p-OH (**19w**) (0.1 mmol)

20w (*ent*-20v)

N-Cbz-L-Ala-L-Ala-OMe (**22wj**) 87%

Atom Economy (%) = $\frac{\textbf{Mol. wt. of product}}{\textbf{Mol. wt. of all reactants}}$ **x 100** = $\frac{308.3340 \times 100}{315.325 + 406.2605 \times 1.5 + 139.579 \times 2 + 59.1596 \times 1.5 + 129.247 \times 4}$ = **14.62%**

Atom Effciency (%) = (yield of product x atom economy) x 100 = (87% x 14.62%) x 100 = **12.72%**

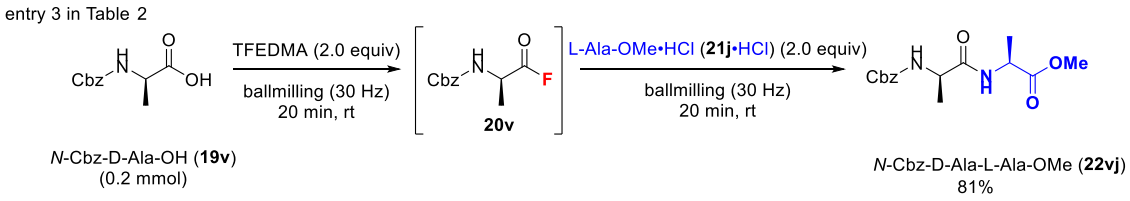
Carbon Efficiency (%) = $\frac{\textbf{moles of 22wj x no. of carbon in 22wj x 100}}{\textbf{(moles of 19w x carbon in 19w) + (moles of PhI(OPiv)}_2\textbf{ x carbon in PhI(OPiv)}_2\textbf{) + (moles of 21j·HCl x carbon in 21j·HCl) + (moles of Py·9HF x carbon in Py·9HF) + (moles of DIPEAF x carbon in DIPEA)}}$ = $\frac{(15 \times 0.1 \times 0.87) \times 100}{17 \times 0.1 + 16 \times 0.15 + 4 \times 0.2 + 5 \times 0.15 + 8 \times 0.4}$ = **14.75%**

N-Cbz-L-Ala-OC$_6$H$_4$-p-OH (**19w**)	31 mg	0.1 mmol	Molecular Weight: 315.3250
PhI(OPiv)$_2$	61 mg	0.15 mmol	Molecular Weight: 406.2605
L-Ala-OMe·HCl (**21j**·HCl)	28 mg	0.2 mmol	Molecular Weight: 139.5790
Py·9HF	39 mg	0.15 mmol	Molecular Weight: 259.1596
DIPEA	52 mg	0.4 mmol	Molecular Weight: 129.2470
DCM (solvent)	1330 mg	15.7 mmol	Molecular Weight: 84.9270
MeCN (solvent)	1572 mg	38.3 mmol	Molecular Weight: 41.0530
Product (**22wj**)	27 mg	0.087 mmol	Molecular Weight: 308.3340

Reaction Mass Efficiency (%) = $\frac{\textbf{mass of isolated 22wj}}{\textbf{mass of all reactants}}$ **x 100** $\frac{27 \times 100}{31 + 61 + 28 + 39 + 52}$ = **12.80%**

E-factor = $\frac{\textbf{total waste (mg)}}{\textbf{total product (mg)}}$ = $\frac{(31 + 61 + 28 + 39 + 52 + 1572 + 1330) - 27}{27}$ = **114.30** mg waste/mg prodcut

Scheme S2. Calculations of green chemistry metrics for entry 2 in table 2



N-Cbz-D-Ala-OH (**19v**)
(0.2 mmol)

N-Cbz-D-Ala-L-Ala-OMe (**22vj**)
81%

$$\textbf{Atom Economy (\%)} = \frac{\textbf{Mol. wt. of product}}{\textbf{Mol. wt. of all reactants}} \times 100 = \frac{308.3340 \times 100}{223.2280 + 145.1006 \times 2 + 139.579 \times 2} = \textbf{38.9\%}$$

$$\textbf{Atom Effciency (\%)} = \textbf{(yield of product x atom economy) x 100} = (81\% \times 38.9\%) \times 100 = \textbf{31.51\%}$$

$$\textbf{Carbon Efficiency (\%)} = \frac{\textbf{moles of 22vj x no. of carbon in 22vj x 100}}{\textbf{(moles of 19v x carbon in 19v) + (moles of TFEDMA x carbon in TFEDMA) + (moles of 21j x carbon in 21j)}} = \frac{(15 \times 0.162) \times 100}{11 \times 0.2 + 4 \times 0.4 + 4 \times 0.4} = \textbf{45.00\%}$$

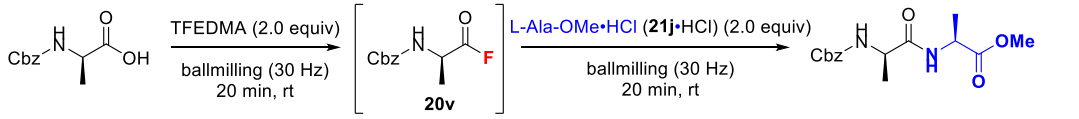
N-Cbz-D-Ala-OH (**19v**)	45 mg	0.2 mmol	Molecular Weight: 223.2280
TFEDMA	58 mg	0.4 mmol	Molecular Weight: 145.1006
L-Ala-OMe (**21j**)	56 mg	0.4 mmol	Molecular Weight: 139.579
Product (**22vj**)	50 mg	0.162 mmol	Molecular Weight: 308.3340

$$\textbf{Reaction Mass Efficiency (\%)} = \frac{\textbf{mass of isolated 22vj}}{\textbf{mass of all reactants}} \times 100 \quad \frac{50 \times 100}{45 + 58 + 56} = \textbf{31.45\%}$$

$$\textbf{E-factor} = \frac{\textbf{total waste (mg)}}{\textbf{total product (mg)}} = \frac{\textbf{(45 + 58 + 56) - 50}}{\textbf{50}} = \textbf{2.18} \text{ mg waste/mg prodcut}$$

Scheme S3. Calculations of green chemistry metrics for entry 3 in table 2

entry 4 in Table 2



N-Cbz-D-Ala-OH (**19v**)
(0.2 mmol)

N-Cbz-D-Ala-L-Ala-OMe (**22vj**)
72%

Atom Economy (%) = $\frac{\text{Mol. wt. of product}}{\text{Mol. wt. of all reactants}} \times 100 = \frac{308.3340 \times 100}{223.2280 + 145.1006 \times 2 + 139.579 \times 2} =$ **38.9%**

Atom Effciency (%) = (yield of product x atom economy) x 100 = (72% x 38.9%) x 100 = **28.01%**

Carbon Efficiency (%) = $\frac{\text{moles of 22vj x no. of carbon in 22vj x 100}}{\text{(moles of 19v x carbon in 19v) + (moles of TFEDMA x carbon in TFEDMA) + (moles of 21j x carbon in 21j)}} = \frac{(15 \times 0.144) \times 100}{11 \times 0.2 + 4 \times 0.4 + 4 \times 0.4} =$ **40.00%**

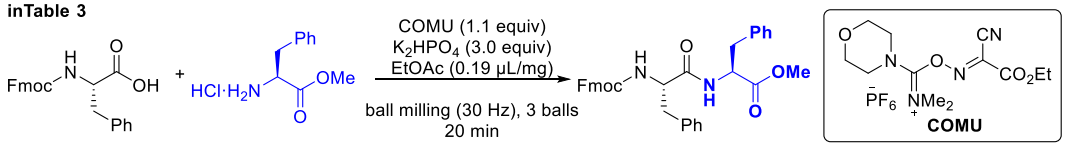
N-Cbz-D-Ala-OH (**19v**)	45 mg	0.2 mmol	Molecular Weight: 223.2280
TFEDMA	58 mg	0.4 mmol	Molecular Weight: 145.1006
L-Ala-OMe (**21j**)	56 mg	0.4 mmol	Molecular Weight: 139.579
Product (**22vj**)	44 mg	0.144 mmol	Molecular Weight: 308.3340

Reaction Mass Efficiency (%) = $\frac{\text{mass of isolated 22vj}}{\text{mass of all reactants}} \times 100 \frac{44 \times 100}{45 + 58 + 56} =$ **27.67%**

E-factor = $\frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{(45 + 58 + 56) - 44}{44} =$ **2.61** mg waste/mg prodcut

Scheme S4. Calculations of green chemistry metrics for entry 4 in table 2

entry 1 inTable 3



N-Fmoc-L-Phe-OH (**1t**) L-Phe-OMe·HCl (**3h·HCl**) (1.0 equiv)

4th: 94 %, >99: 1 dr

Atom Economy (%) = $\frac{\textbf{Mol. wt. of product}}{\textbf{Mol. wt. of all reactants}}$ **x 100** = $\frac{548.639 \times 100}{387.435 + 428.2722 \times 1.1 + 215.677 + 174.1744 \times 3}$ = **34.36%**

Atom Efficicency (%) =(yield of product x atom economy) x 100 = (94% x 34.36%) x 100 = **32.30%**

Carbon Efficiency (%) = $\frac{\textbf{moles of 4th x no. of carbon in 4th x 100}}{\textbf{(moles of 1t x carbon in 1t) + (moles of COMU x carbon in COMU) + (moles of 3h·HCl x carbon in 3h·HCl)}}$ = $\frac{(34 \times 0.4 \times 0.94) \times 100}{24 \times 0.4 + 12 \times 4.4 + 10 \times 0.4}$ = **67.71%**

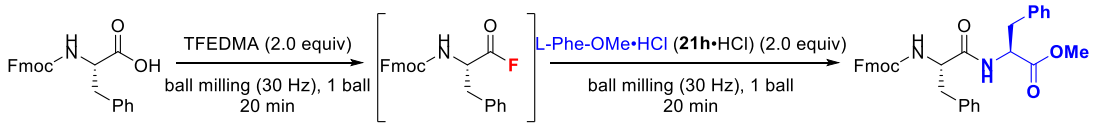
N-Fmoc-L-Phe-OH (**1t**)	155 mg	0.4 mmol	Molecular Weight: 387.4350
COMU	189 mg	0.44 mmol	Molecular Weight: 428.2722
L-Phe-OMe•HCl (**3h**•HCl)	86 mg	0.4 mmol	Molecular Weight: 215.6770
K_2HPO_4	209 mg	1.2 mmol	Molecular Weight: 174.1744
EtOAc (solvent)	110 mg	1.24 mmol	Molecular Weight: 88.1060
Product (**4th**)	206 mg	3.76 mmol	Molecular Weight: 548.6390

Reaction Mass Efficiency (%) = $\frac{\textbf{mass of isolated 4th}}{\textbf{mass of all reactants}}$ **x 100** $\frac{206 \times 100}{155 + 189 + 86 + 209}$ = **32.24%**

E-factor = $\frac{\textbf{total waste (mg)}}{\textbf{total product (mg)}}$ = $\frac{\textbf{(155 + 189 + 86 + 209 + 110) - 206}}{\textbf{206}}$ = **2.6** mg waste/mg prodcut

Scheme S5. Calculations of green chemistry metrics for entry 1 in table 3

entry 2 inTable 3



N-Fmoc-L-Phe-OH (**19t**) **20t** **22th**: 79%, >99: 1 dr

Atom Economy (%) = $\frac{\text{Mol. wt. of product}}{\text{Mol. wt. of all reactants}} \times 100 = \frac{548.639 \times 100}{387.435 + 145.1006 \times 2 + 215.667 \times 2} =$ **49.47%**

Atom Efficicency (%) =(yield of product x atom economy) x 100 = (79% x 49.47%) x 100 = **39.08%**

Carbon Efficiency (%) = $\frac{\text{moles of 22th x no. of carbon in 22th x 100}}{\text{(moles of 19t x carbon in 19t) + (moles of TFEDMA x carbon in TFEDMA) + (moles of 21h x carbon in 21h)}} = \frac{(34 \times 0.2 \times 0.79) \times 100}{24 \times 0.2 + 4 \times 0.4 + 10 \times 0.4} =$ **51.65%**

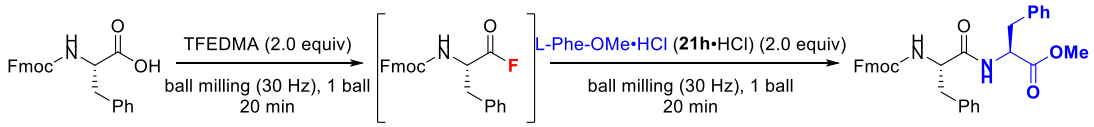
N-Fmoc-L-Phe-OH (**19t**)	77 mg	0.2 mmol	Molecular Weight: 387.4350
TFEDMA	58 mg	0.4 mmol	Molecular Weight: 145.1006
L-Phe-OMe•HCl (**21h**•HCl)	86 mg	0.4 mmol	Molecular Weight: 215.6770
Product (**22th**)	87 mg	0.158 mmol	Molecular Weight: 548.6390

Reaction Mass Efficiency (%) = $\frac{\text{mass of isolated 22th}}{\text{mass of all reactants}} \times 100 \quad \frac{87 \times 100}{77 + 58 + 86} =$ **39.37%**

E-factor = $\frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{(77 + 58 + 86) - 87}{87} =$ **1.5** mg waste/mg prodcut

Scheme S6. Calculations of green chemistry metrics for entry 2 in table 3

entry 3 inTable 3



N-Fmoc-L-Phe-OH (**19t**) **20t** **22th**: >99%, >99: 1 dr

Atom Economy (%) = $\frac{\text{Mol. wt. of product}}{\text{Mol. wt. of all reactants}}$ **x 100** = $\frac{548.639 \times 100}{387.435 + 145.1006 \times 2 + 215.667 \times 2}$ = **49.47%**

Atom Efficicency (%) =(yield of product x atom economy) x 100 = (99% x 49.47%) x 100 = **48.98%**

Carbon Efficiency (%) = $\frac{\text{moles of 22th x no. of carbon in 22th x 100}}{\text{(moles of 19t x carbon in 19t) + (moles of TFEDMA x carbon in TFEDMA) + (moles of 22h x carbon in 21h)}}$ = $\frac{(34 \times 0.2 \times 0.99) \times 100}{24 \times 0.2 + 4 \times 0.4 + 10 \times 0.4}$ = **64.73%**

N-Fmoc-L-Phe-OH (**1t**)	77 mg	0.2 mmol	Molecular Weight: 387.4350
TFEDMA	58 mg	0.4 mmol	Molecular Weight: 145.1006
L-Phe-OMe•HCl (**3h**•HCl)	86 mg	0.4 mmol	Molecular Weight: 215.6770
Product (**4th**)	109 mg	0.198 mmol	Molecular Weight: 548.6390

Reaction Mass Efficiency (%) = $\frac{\text{mass of isolated 22th}}{\text{mass of all reactants}}$ **x 100** $\frac{109 \times 100}{77 + 58 + 86}$ = **49.32%**

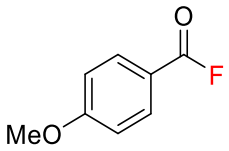
E-factor = $\frac{\text{total waste (mg)}}{\text{total product (mg)}}$ = $\frac{(77 + 58 + 86) - 109}{109}$ = **1.0** mg waste/mg prodcut

Scheme S7. Calculations of green chemistry metrics for entry 3 in table 3

Note: Evaluation method of green chemistry metrics was followed reference 202.[202]

6.5 Experimental data for products

4-Methoxybenzoyl fluoride (20a)



[202] A. N. V. Satyanarayana, N. Mukherjee, T. Chatterjee, 100% atom-economical and highly regio- and stereoselective iodosulfenylation of alkynes: a reagentless and sustainable approach to access (*E*)-β-iodoalkenyl sulfides and (*Z*)-tamoxifen. *Green Chem*. **2023**, *25*, 779-788.

Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 10/1) to give **20a** (13.1 mg, 85% yield) as a pale yellow oil. Following the general procedure for batch reaction, giving **20a** (14.3 mg, 93% yield).

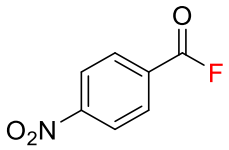
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 11.7 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H) ppm;

^{19}F NMR (282 MHz, $CDCl_3$) δ: 15.5 (s, 1F) ppm.

MS (EI): *m/z* 154 $[M+H]^+$

Spectroscopic data was agreement with the literature.[203]

4-Nitrobenzoyl fluoride (20b)



Following the general procedure A on a 0.2 mmol scale without quenching, collect the reaction mixture via washing with DCM, concentrate the solution under reduced pressure, purified through a short pad of silica gel (*n*-hexane/Ethyl acetate = 1/5) to give product (14.5 mg, 43% yield) as a pale yellow solid; **Following the general procedure for batch reaction on a 0.2 mmol scale**, giving **20b** (27.1 mg, 80% yield) (**note**: 4-Nitrobenzoyl fluoride is highly sensitive to moisture)

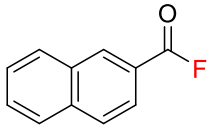
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (d, *J* = 7.9 Hz, 2H), 8.27 (d, *J* = 7.0 Hz, 2H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 20.5 (s, 1F) ppm.

MS (EI): *m/z* 169 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

2-Naphthoyl fluoride (20c)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 50/1) to give **20c** (15.9 mg, 90% yield) as a white solid; **Following the general procedure for batch reaction**, giving **20c** (11.1 mg, 64% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.02-7.91 (m, 4H), 7.71-7.59 (m, 2H) ppm.

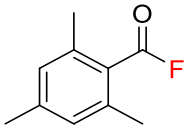
^{19}F NMR (282 MHz, $CDCl_3$) δ: 17.5 (s, 1F) ppm.

[203] Y. Liang, Z. Zhao, A. Taya N. Shibata, Acyl fluorides from carboxylic acids, aldehydes, or alcohols under oxidative fluorination. *Org. lett.* **2021**, *23*, 847-852.

MS (EI): *m/z* 174 $[M]^+$

Spectroscopic data was agreement with the literature.[204]

2,4.6-Trimethylbenzoyl fluoride (20d)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane only) to give **20d** (12.0 mg, 72% yield) as a white solid. **Following the general procedure for batch reaction on 0.2 mmol scale**, giving **20d** (8.2 mg, 25% yield).

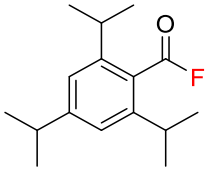
^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.93 (s, 2H), 2.44 (s, 6H), 2.32 (s, 3H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 52.0 (s, 1F) ppm.

MS (EI): *m/z* 166 $[M]^+$

Spectroscopic data was agreement with the literature.[205]

2,4,6-Triisopropylbenzoyl fluoride (20e)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane only) to give **20e** (18.1 mg, 72% yield) as a white solid. **Following the general procedure for a batch reaction on a 0.2 mmol scale**, the reaction time was set to 6 hours, giving in a yield of **20e** (13.9 mg, 28% yield). **m.p.**: 43.5-44.3 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (s, 2H), 3.04-2.86 (m, 3H), 1.29-1.25 (m, 18H) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ: 62.5 (s, 1F) ppm.

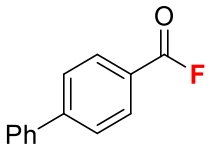
^{13}C NMR (176 MHz, $CDCl_3$) δ: 160.8, 159.8 (d, *J* = 358.0 Hz), 152.3, 146.3, 124.9 (d, *J* = 50.2 Hz), 121.3, 34.5, 31.8, 24.1, 23.8 ppm.

IR (KBr): 2975, 1829, 1607, 1463, 1365, 1221, 1099, 985, 878, 731, 607 cm^{-1}**.**

HRMS (ESI): The acyl fluoride **20e** readily converted into its corresponding methyl ester during analysis: *m/z* $[M+H]^+$ Calculated for $C_{16}H_{27}O_2H^+$ 263.2006; Found 263.2003**.**

[204] S. Mao, J. H. Kramer, S. Haoran, Deoxyfluorination of carboxylic acids with KF and highly electron-deficient fluoroarenes. *J. Org. Chem.* **2021**, *86*, 6066-6074.
[205] M. Mitterbauer, P. Knaack, S. Naumov, M. Markovic, A. Ovsianikov N. Moszner R. Liska, Acylstannanes: cleavable and highly reactive photoinitiators for radical photopolymerization at wavelengths above 500 nm with excellent photobleaching behavior. *Angew. Chem. Int. Ed.* **2018**, *57*, 12146-12150.

[1,1-Biphenyl]-4-carbonyl fluoride (20f)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Et_2O = 50/1) to give **20f** (16.5 mg, 82% yield) as a white solid.

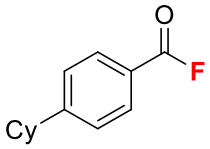
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.52-7.44 (m, 3H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 17.6 (s, 1F) ppm.

MS (EI): *m/z* 200 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

4-Cyclohexylbenzoyl fluoride (20g)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane only) to give **20g** (16.7 mg, 81% yield) as a white solid.

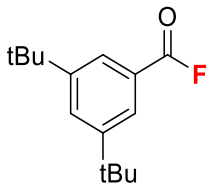
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.60 (s, 1H), 1.89-1.76 (m, 5H), 1.50-1.26 (m, 5H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 17.0 (s, 1F) ppm.

MS (EI): *m/z* 206 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

3,5-Di-*tert*-butylbenzoyl fluoride (20h)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane only) to give **20h** (17.1 mg, 72% yield) as a white solid.

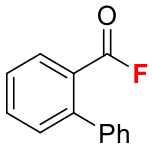
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (s, 2H), 7.76 (s, 1H), 1.36 (s, 18H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 17.4 (s, 1F) ppm.

MS (EI): *m/z* 236 $[M]^+$

Spectroscopic data was agreement with the literature.[206]

[1,1'-Biphenyl]-2-carbonyl fluoride (20i)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Et_2O = 50/1) to give **20i** (17.1 mg, 85% yield) as a pale yellow oil.

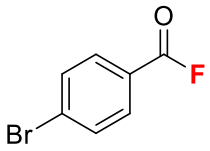
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.53-7.43 (m, 5H), 7.33 (s, 2H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 34.4 (s, 1F) ppm.

MS (EI): *m/z* 200 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

4-Bromobenzoyl fluoride (20j)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Et_2O = 10/1) to give **20j** (10.4 mg, 51% yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H) ppm.

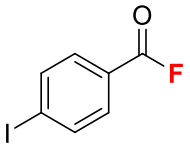
^{19}F NMR (282 MHz, $CDCl_3$) δ: 17.9 (s, 1F) ppm.

MS (EI): *m/z* 202 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

4-Iodobenzoyl fluoride (20k)

[206] Y. Liang, A. Taya, Z. Zhao, N. Saito, N. Shibata, Deoxyfluorination of acyl fluorides to trifluoromethyl compounds by FLUOLEAD®/Olah's reagent under solvent-free conditions. *Beilstein J. Org. Chem.* **2020**, *16*, 3052-3058.



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Et_2O = 50/1) to give **20k** (19.4 mg, 78% yield) as a white solid.

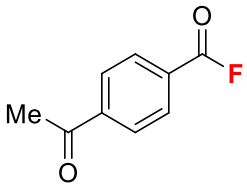
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 17.7 (s, 1F) ppm.

MS (EI): *m/z* 250 $[M]^+$

Spectroscopic data was agreement with the literature.[204]

4-Acetylbenzoyl fluoride (20l)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Et_2O = 10/1) to give **20l** (12.9 mg, 78% yield) as a white solid.

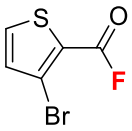
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 8.2 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 2H), 2.68 (s, 3H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 19.7 (s, 1F) ppm.

MS (EI): *m/z* 166 $[M]^+$

Spectroscopic data was agreement with the literature.[204]

3-Bromothiopnene-2-carbonyl fluoride (20m)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/ ethyl acetate = 20/1) to give **20m** (14.6 mg, 70% yield) as a white solid.

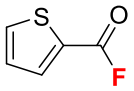
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 5.0 Hz, 1H), 7.26-7.22 (dd, *J* = 3.0, 3.0 Hz, 1H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 32.6 (s, 1F) ppm.

MS (EI): *m/z* 208 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

Thiophene-2-carbonyl fluoride (20n)



Following the general procedure A (Starting material used with 0.3 mmol scale.), the mixture was purified by column chromatography on silica gel (pentane/ Et_2O= 9/1) to give **20n** (27.8 mg, 72% yield) as a colorless oil.

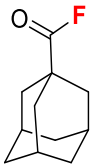
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.81 (s, 1H), 7.21 (s, 1H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 23.8 (s, 1F) ppm.

MS (EI): *m/z* 130 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

Adamantane-1-carbonyl fluoride (20o).



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Et_2O = 50/1) to give **20o** (12.0 mg, 66% yield) as a white solid.

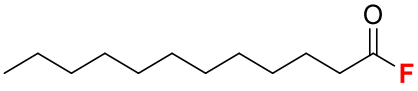
^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 1.97 (s, 6H), 1.79-1.69 (m, 6H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 23.4 (s, 1F) ppm.

MS (EI): *m/z* 182 $[M]^+$

Spectroscopic data was agreement with the literature.[204]

Dodecanoyl fluoride (20p)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/ Et_2O = 50/1) to give **20p** (14.6 mg, 72% yield) as a colorless oil.

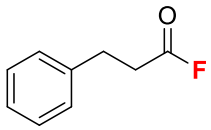
^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.50 (t, *J* = 7.3 Hz, 2H), 1.72-1.63 (m, 2H), 1.26 (m, 16H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 44.9 (s, 1F) ppm.

MS (EI): *m/z* 202 $[M]^+$.

Spectroscopic data was agreement with the literature.[203]

cinnamoyl fluoride (20q)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (pentane/ Et_2O= 9/1) to give **20q** (11.9 mg, 79% yield) as a colorless oil.

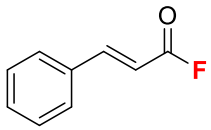
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.30 (m, 2H), 7.27-7.20 (m, 3H), 3.00 (t, *J* = 7.5 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H) ppm;

^{19}F NMR (282 MHz, $CDCl_3$) δ: 44.8 (s, 1F) ppm.

MS (EI): *m/z* 152 $[M]^+$

Spectroscopic data was agreement with the literature.[207]

1-fluoro-3-phenylpropane (20r)



Following the general procedure A, the mixture was purified by column chromatography on silica gel (pentane/Et_2O= 9/1) to give **20r** (13.5 mg, 89% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 16.1 Hz, 1H), 7.57 (m, 2H), 7.47-7.41 (m, 3H), 6.42-6.34 (m, 1H) ppm.

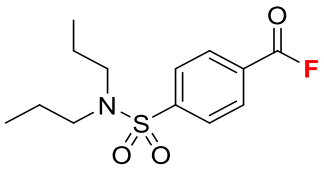
^{19}F NMR (282 MHz, $CDCl_3$) δ: (s, 1F) 25.1 ppm.

MS (EI): *m/z* 150 $[M]^+$

Spectroscopic data was agreement with the literature.[208]

4-(*N*,*N*-Dipropylsulfamoyl)benzoyl fluoride (20s)

[207] J. A. Vogel, R. Hammami, A. Ko, H. Datta, Y. N. Eiben, K. J. Labenne, E. C. McCarver, E. Yilmaz, P. R. Melvin, Synthesis of highly reactive sulfone iminium fluorides and their use in deoxyfluorination and sulfur fluoride exchange chemistry. *Org. lett.* **2022**, *24*, 5962-5966.
[208] S. B. Munoz, H. Dang, X. I. Rodriguez, T. Mathew, G. K. Surya Prakash, Direct access to acyl fluorides from carboxylic acids using a phosphine/fluoride deoxyfluorination reagent system. *Org. lett*. **2019**, *21*, 1659-1663.



Following the general procedure A, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 10/1) to give **20s** (16.4 mg, 57% yield) as a white solid.

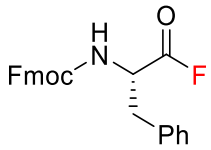
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 7.9 Hz, 2H), 3.13 (t, *J* = 7.6 Hz, 4H), 1.62-1.50 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 19.7 (s, 1F) ppm.

MS (EI): *m/z* 287 $[M]^+$

Spectroscopic data was agreement with the literature.[203]

Fmoc-L-Phe-F (20t)



Following the general procedure A, By omitting the quenching process, the reaction mixture is directly collected by washing with anhydrous diethyl ether in a nitrogen gas-filled glovebox. The solution is concentrated under reduced pressure and purified through recrystallization from anhydrous Et2O/*n*-hexane, giving **20t** (73.1 mg, 94% yield) as a white solid.

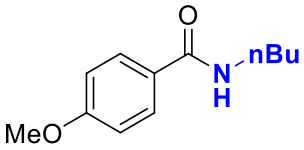
^{1}H NMR (700 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 6.4 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.34-7.31 (m, 5H), 7.13 (d, *J* = 6.8 Hz, 2H), 5.08 (d, *J* = 7.2 Hz, 1H), 4.83 (s, 1H), 4.44 (ddd, *J* = 36.2, 10.5, 6.9 Hz, 2H), 4.20 (t, *J* = 6.6 Hz, 1H), 3.19-3.17 (m, 2H) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ: 30.3 (s, 1F) ppm.

MS (ESI): The acyl fluoride **20t** readily converted into its corresponding methyl ester during analysis: *m/z* 424 $(M+Na)^+$.(**note**: **20t** is highly sensitive to moisture)

Spectroscopic data was agreement with the literature.[207]

***N*-Butyl-4-methoxybenzamide (22aa)**



Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 3/1) to give **22aa** (38.6 mg, 93% yield) as a white solid. **Following the general**

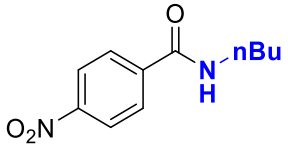
procedure C, to give **22aa** (31.3 mg, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.12 (brs, 1H), 3.84 (s, 3H), 3.44 (dd, *J* = 12.9, 7.0 Hz, 2H), 1.64-1.54 (m, 2H), 1.47-1.37 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm.

MS (ESI): *m/z* 208 $[M+H]^+$.

Spectroscopic data was agreement with the literature.[209]

***N*-butyl-4-nitrobenzamide (22ba)**



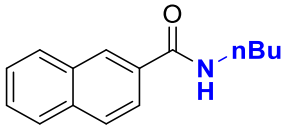
Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 2/1) to give **22ba** (40.2 mg, 90% yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 6.16 (brs, 1H), 3.53-3.46 (dd, *J* = 13.0 Hz, 7.2 Hz, 2H), 1.65 (m, 2H), 1.47-1.36 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 206 $[M+H]^+$.

Spectroscopic data was agreement with the literature.[209]

***N*-Butyl-2-naphthamide (22ca)**



Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 3/1) to give **22ca** (39.5 mg, 87 % yield) as a white solid. **Following the general procedure C,** to give **22ca** (39.3 mg, 86 % yield).

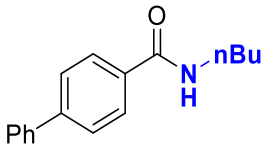
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 7.94-7.80 (m, 4H), 7.59-7.51 (m, 2H), 6.22 (brs, 1H), 3.56-3.48 (dd, *J* = 12.9, 6.4 Hz, 2H), 1.71-1.61 (m, 2H), 1.50-1.40 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 228 $[M+H]^+$

Spectroscopic data was agreement with the literature.[209]

***N*-Butyl-[1,1'-biphenyl]-4-carboxamide (22fa)**

[209] K. S. Goh, C. Tan, Metal-free pinnick-type oxidative amidation of aldehydes. *RSC Adv*. **2012**, *2*, 5536-5538.

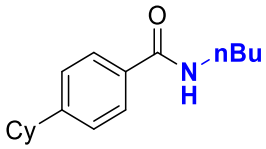


Following the general procedure C, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 3/1) to give **22fa** (41.3 mg, 82 % yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.2 Hz, 2H), 7.67-7.60 (m, 4H), 7.49-7.36 (m, 3H), 6.13 (brs, 1H), 3.49 (dd, *J* = 12.9, 7.0 Hz, 2H), 1.68-1.57 (m, 2H), 1.50-1.38 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 254 $[M+H]^+$ Spectroscopic data was agreement with the literature.[209]

***N*-Butyl-4-Cyclohexylbenzamide (22ga)**



Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/ Ethyl acetate = 5/1) to give **22ga** (42.1 mg, 81% yield) as a white solid. **Following the general procedure C,** to give **22ga** (38.9 mg, 75 % yield).

m.p.: 133.2-134.1 ℃.

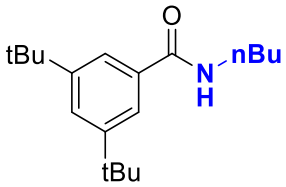
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 8.2 Hz, 2H), 7.25 (s, 2H), 6.04 (brs, 1H), 3.45 (dd, *J* = 12.9, 7.0 Hz, 2H), 2.54 (s, 1H), 1.85-1.74 (m, 5H), 1.64-1.59 (m, 2H), 1.47-1.33 (m, 6H), 1.29-1.20 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ: 167.6, 151.7, 132.5, 127.0 (d, *J* = 7.0 Hz), 44.6, 39.8, 34.3, 31.9, 26.8, 26.1, 20.2, 13.9 ppm.

IR (KBr): 3317, 2925, 1633, 1536, 1446, 1306, 836, 769, 680, 631 cm^{-1}**.**

HRMS (ESI): $[M+Na]^+$ Calculated for $C_{15}H_{25}NONa^+$ 282.1834; Found 282.1833.

***N*-Butyl-3,5-di-*tert*-butylbenzamide (22ha)**



Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 5/1) to give **22ha** (50.3 mg, 87% yield) as a white solid.

m.p.: 193.6-194.2 ℃.

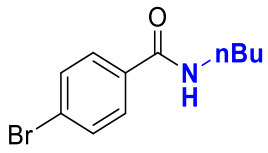
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (s, 2H), 7.26-7.29 (s, 1H), 6.05 (brs, 1H), 3.47 (dd, *J* = 12.9, 7.0 Hz, 2H), 1.67-1.60 (m, 2H), 1.46-1.39 (m, 2H), 1.35 (s, 18H), 0.97 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ: 168.8, 151.2, 134.6, 125.5, 120.9, 39.9, 35.0, 31.9, 31.5, 20.3, 13.9 ppm.

IR (KBr): 3257, 2957, 1686, 1633, 1363, 1276, 889, 709 cm^{-1}**.**

HRMS (ESI): $[M+Na]^+$ Calculated for $C_{19}H_{31}NONa^+$ 312.2303; Found 312.2299**.**

***N*-Butyl-4-bromobenzamide (22ja)**



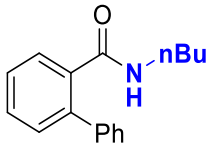
Following the general procedure C, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 3/1) to give **22ja** (41.3 mg, 81 % yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H), 6.03 (brs, 1H), 3.45 (dd, *J* = 13.0, 6.0 Hz, 2H), 1.65-1.56 (m, 2H), 1.48-1.36 (m, 2H), 0.99-0.94 (t, *J* = 7.6 Hz, 3H) ppm.

MS (ESI): *m/z* 256 $[M+H]^+$

Spectroscopic data was agreement with the literature.[209]

***N*-Butyl-[1,1'-biphenyl]-2-carboxamide (22ia)**



Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 3/1) to give **22ia** (42.1 mg, 87% yield) as a white solid. **Following the general procedure C**, to give **22ia** (39.5 mg, 78 % yield)**.**

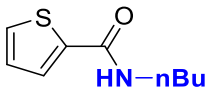
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.2 Hz, 1H), 7.47-7.34 (m, 8H), 5.07-5.21 (brs, 1H), 3.14 (dd, *J* = 12.9, 6.8 Hz, 2H), 1.19-1.09 (m, 2H), 1.06-0.94 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H) ppm.

MS (ESI): *m/z* 254 $[M+H]^+$

Spectroscopic data was agreement with the literature.[210]

***N*-butylthiophene-2-carboxamide (22ma)**

[210] A. Verma, L. S. Banjara, R. Meena, S. Kumar, C(sp2)−N and C(sp2)−O Coupling through Radical Pathway. *Asian J. Org. Chem.* **2020**, *9*, 105-110.



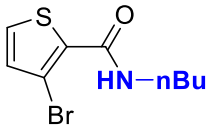
Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 5/1) to give **22ma** (39.0 mg, 85 % yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48-7.44 (m, 2H), 7.08-7.05 (m, 1H), 5.93 (brs, 1H), 3.44 (dd, *J* = 12.9, 7.0 Hz, 2H), 1.65-1.57 (m, 2H), 1.41 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 184 $[M+H]^+$

Spectroscopic data was agreement with the literature.[211]

3-Bromo-*N*-butylthiophene-2-carboxamide (22na)



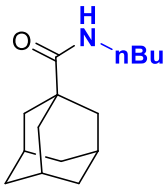
Following the general procedure C, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 5/1) to give **22na** (46.7 mg, 89 % yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 5.3 Hz, 1H), 7.02 (d, *J* = 5.3 Hz, 1H), 3.47 (dd, *J* = 12.9 Hz, 6.5 Hz, 2H), 1.67-1.60 (m, 2H), 1.50-1.38 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 262 $[M+H]^+$

Spectroscopic data was agreement with the literature.[212]

(3*r*,5*r*,7*r*)-N-butyladamantane-1-carboxamide (22oa)



Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 5/1) to give **22oa** (37.5 mg, 80% yield) as a white solid. **Following the general procedure C** (36.3 mg, 77% yield)**.**

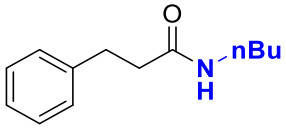
^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.55 (brs, 1H), 3.24 (dd, *J* = 12.8, 6.9 Hz, 2H), 2.04 (s, 3H), 1.85-1.84 (m, 6H), 1.77-1.67 (m, 6H), 1.52-1.43 (m, 2H), 1.40-1.28 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm.

[211] K. Singha, S. C. Ghosh, A. B. Panda, Visible Light-Driven Efficient Synthesis of Amides from Alcohols using Cu−N−TiO_2 Heterogeneous Photocatalyst. *Eur. J. Org. Chem.* **2021**, *4*, 657-662.
[212] G. Infante, S. Eisler, Genesis Infante, Sara Eisler. Accessing pyrrolones and pyridinones: controlling 5-exo and 6-endo ring closures in heterocyclic alkynylamides. *Can. J. Chem*. **2017**, *95*, 415-423.

MS (ESI): *m/z* 236 $[M+H]^+$

Spectroscopic data was agreement with the literature.[213]

***N*-butyl-3-phenylpropanamide (22qa)**



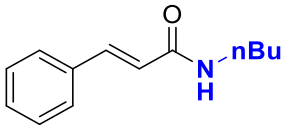
Following the general procedure B, the mixture was purified by column chromatography on silica gel (n-hexane/Ethyl acetate = 3/2) to give **22qa** (33.8 mg, 82% yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.26 (m, 2H), 7.22-7.18 (m, 3H), 5.42 (brs, 1H), 3.20 (dd, *J* = 12.9, 7.0 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 7.6 Hz, 2H), 1.45-1.35 (m, 2H), 1.31-1.19 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 206 $[M+H]^+$.

Spectroscopic data was agreement with the literature.[214]

***N*-Butyl-3-phenyl-acrylamide (22ra)**



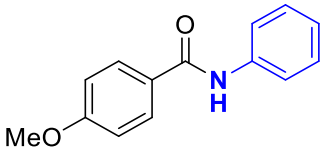
Following the general procedure B, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 5/1) to give **22ra** (33.5 mg, 82 % yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 15.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.40-7.35 (m, 3H), 6.40-6.35 (m, 1H), 5.56 (brs, 1H), 3.40 (dd, *J* = 12.9, 7.0 Hz, 2H), 1.61-1.56 (m, 2H), 1.46-1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm.

MS (ESI): *m/z* 204 $[M+H]^+$

Spectroscopic data was agreement with the literature.[214]

4-methoxy-*N*-pnenylbenzamide (22ab)



[213] E. Busseron, J. Lux, M. Degardin, J. Rebek, Synthesis and recognition studies with a ditopic, photoswitchable deep cavitand. *Chem. Commun*. **2013**, *49*, 4842-4844.
[214] Y. Yang, J. Liu, F. S. Kamounah, G. Ciancaleoni, J. W. Lee, A CO_2-Catalyzed Transamidation Reaction. *J. Org. Chem*. **2021**, *86*, 16867-16881.

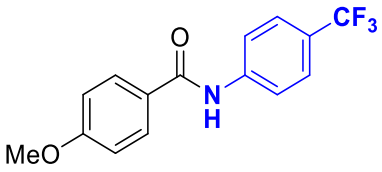
Following the general procedure B, without further purification, the mixture gives **22ab** (50.6 mg, quant) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 8.8 Hz, 2H), 7.76 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 7.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H) ppm.

MS (ESI): *m/z* 228 $[M+H]^+$

Spectroscopic data was agreement with the literature.[215]

4-methoxy-*N*-4-trifluoromethylphenyl -benzamide (22ac)

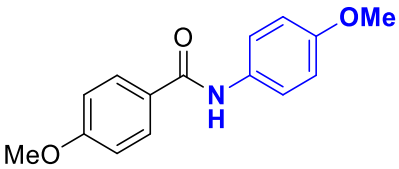


Following the general procedure B, without further purification, the mixture gives **22ac** (49.1 mg, 83%) as a white solid. **^{1}H NMR** (700 MHz, DMSO-d_6) δ: 10.42 (s, 1H), 7.99 (d, *J* = 3.2 Hz, 4H), 7.71 (d, *J* = 6.8 Hz, 2H), 7.08 (s, 2H), 3.85 (s, 3H) ppm.

MS (ESI): *m/z* 296 $[M+H]^+$.

Spectroscopic data was agreement with the literature.[216]

4-methoxy-*N*-4-methoxyphenyl -benzamide (22ad)



Following the general procedure B, without further purification, the mixture gives **22ad** (60.8 mg, quant) as a white solid.

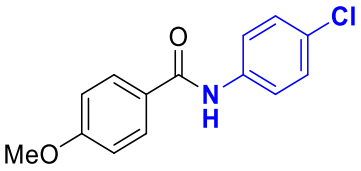
^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.02 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 9.1 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 9.1 Hz, 2H), 3.89 (s, 3H), 3.79 (s, 3H) ppm.

MS (ESI): *m/z* 258 $[M+H]^+$

Spectroscopic data was agreement with the literature.[217]

4-methoxy-*N*-4-chlorophenyl-benzamide (22ae)

[215] A. Ojeda-Porras, A. Hernández-Santanaa, D. Gamba-Sánchez, D. Gamba-Sanchez, Direct amidation of carboxylic acids with amines under microwave irradiation using silica gel as a solid support. *Green Chem*. **2015**, *17*, 3157-3163.
[216] Y. Yan, Z. Zhang, Y. Wan, G. Zhang, N. Ma, Q. Liu, Hypervalent Iodine(III)-Promoted Phenyl Transfer Reaction from Phenyl Hydrazides to Nitriles. *J. Org. Chem*. **2017**, *82*, 7957-7963.
[217] T. Fang, X. Gao, R. Tang, X. Zhang, C. Deng, A novel Pd-catalyzed N-dealkylative carbonylation of tertiary amines for the preparation of amides. *Chem. Commun*. **2014**, *50*, 14775-14777.



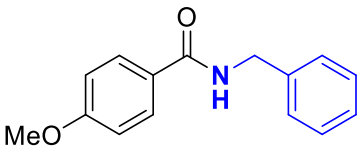
Following the general procedure B, without further purification, the mixture gives **22ae** (53.0 mg, quant) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.8 Hz, 2H), 7.71 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H) ppm.

MS (ESI): *m/z* 262 $[M+H]^+$

Spectroscopic data was agreement with the literature.[215]

***N*-benzylbenzamide (22af)**



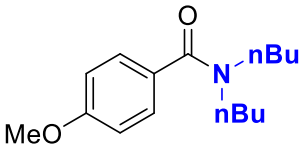
Following the general procedure B, without further purification, the mixture gives **22af** (54.5 mg, quant) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.3 Hz, 2H), 7.35-7.26 (m, 5H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.29 (s, 1H), 4.63-4.65 (m, 2H), 3.85 (s, 3H) ppm.

MS (ESI): *m/z* 242 $[M+H]^+$

Spectroscopic data was agreement with the literature.[218]

***N*,*N*-Di-butyl-4-methoxybenzamide (22ag)**



Following the general procedure B, without further purification, the mixture gives **22ag** (49.0 mg, 93 % yield) as a white solid.

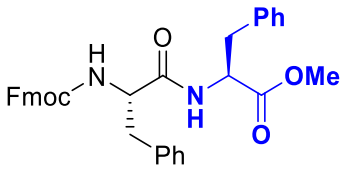
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.44 (s, 2H), 3.25 (s, 2H), 1.63-1.45 (m, 4H), 1.36-1.15 (m, 4H), 0.94-0.84 (m, 6H) ppm.

MS (ESI): *m/z* 264 $[M+H]^+$

[218] Y. Teo, F. Yong, I. K. Ithnin, S. T. Yio, Z. Lin, Efficient Manganese/Copper Bimetallic Catalyst for N-Arylation of Amides and Sulfonamides Under Mild Conditions in Water. *Eur. J. Org. Chem*., **2013**, *2013*, 515-524.

Spectroscopic data was agreement with the literature.[219]

_N_-[(9_H_-Fluoren-9-ylmethoxy)carbonyl]-L-phenylalanyl-L-phenylalanine methyl ester (22th) (Fmoc-Phe-Phe-OMe)

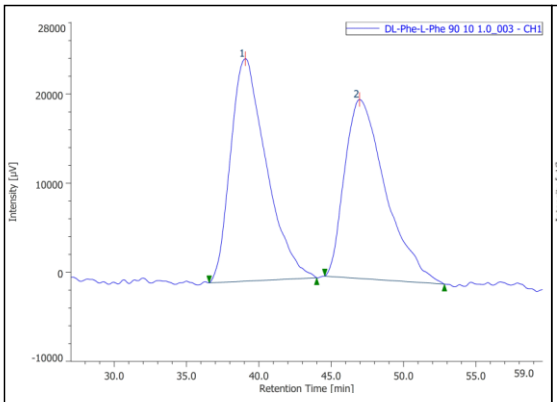


Following the general procedure D, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 2/1) to give **22th** (86.8 mg, 79% yield) as a white solid. When reaction completed, diluted it with Ethyl acetate, Thereafter, sat. $NaHCO_3$ aq. (1.0 mL) was added, and the aqueous layer was extracted with Ethyl acetate (5.0 mL × 3). The combined organic layer was washed with 1N HCl and brine successively, dried over Na_2SO_4, concentrated under reduced pressure to give pure **22th** (109.2 mg, >99%) as a white solid.

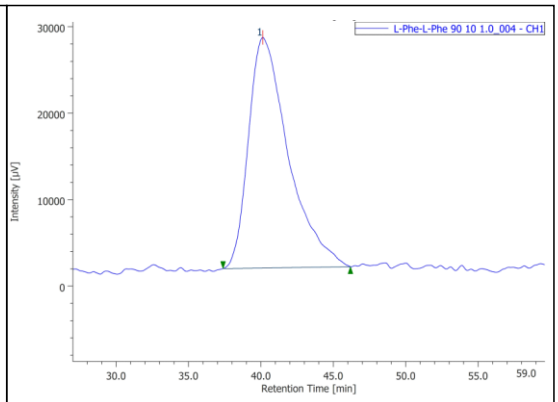
^{1}H NMR (700 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 6.8 Hz, 2H), 7.52 (t, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 2H), 7.32-7.27 (m, 4H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 6.8 Hz, 5H), 6.95 (d, *J* = 5.2 Hz, 2H), 6.17 (s, 1H), 5.25 (s, 1H), 4.77 (q, *J* = 6.3 Hz, 1H), 4.44-4.41 (m, 2H), 4.29 (s, 1H), 4.18 (t, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 3.09-2.98 (m, 4H) ppm.

MS (ESI): *m/z* 571 $[M+Na]^+$.

HPLC condition: Chiralcel OD-3 column, *n*-hexane/i-PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm).



NO.	t_R (min)	Area (%)	Hight (%)
1	39.167	51.950	55.430
2	46.950	48.050	44.570

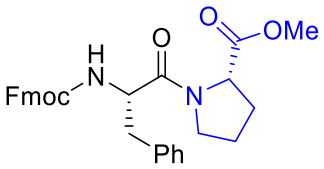


NO.	t_R (min)	Area (%)	Hight (%)
1	40.070	100.000	100.000

Spectroscopic data was agreement with the literature.[220]

[219] G. C. Y. Choo, H. Miyamura, S. Kobayashi, Synergistic cascade catalysis by metal nanoparticles and Lewis acids in hydrogen autotransfer. *Chem. Sci*. **2015**, *6*, 1719-1727.
[220] J. Chandra, S. R. Manne, S. Mondal, B. Mandal, (E)-Ethyl-2-cyano-2-(((2,4,6-trichlorobenzoyl)oxy)imino)acetate: A Modified Yamaguchi Reagent for Enantioselective Esterification, Thioesterification, Amidation, and Peptide Synthesis. *ACS Omega*. **2018**, *3*, 6120-6133.

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-phenylalanyl-L-proline methyl ester (22ti). (Fmoc-Phe-Pro-OMe)**

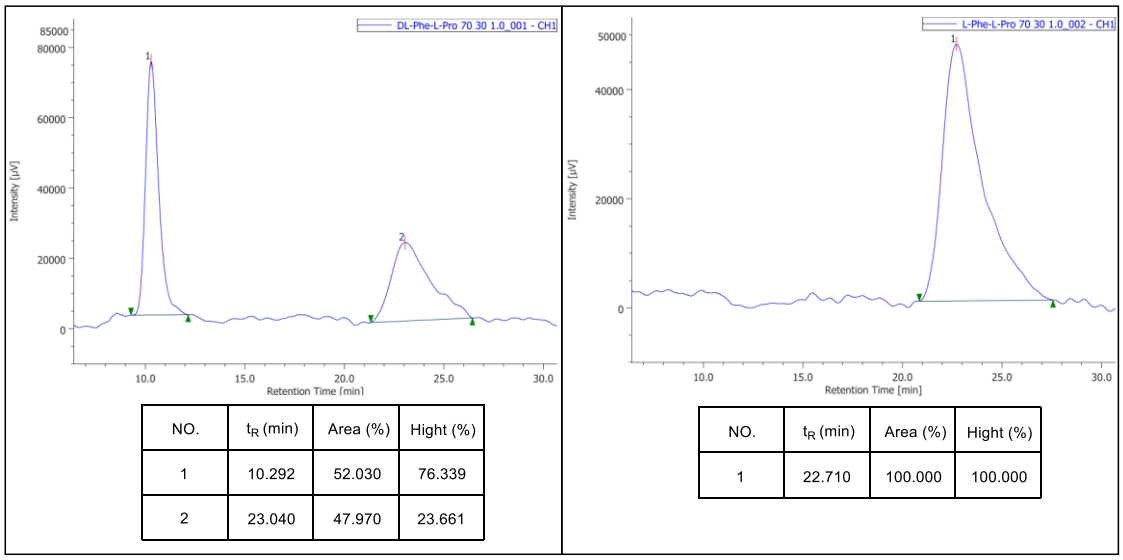


Following the general procedure D, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 2/1) to give **22ti** (76.8 mg, 77% yield) as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 7.76 (m, 2H), 7.54 (t, *J* = 8.6 Hz, 2H), 7.39 (m, 2H), 7.30-7.28 (m, 5H), 7.25-7.22 (m, 2H), 5.60 (d, *J* = 7.6 Hz, 1H), 4.73 (dd, *J* = 15.2, 6.8 Hz, 1H), 4.50 (m, 1H), 4.34 (m, 1H), 4.25 (m, 1H), 4.17 (t, *J* = 7.4 Hz, 1H), 3.76 (s, 3H), 3.64-3.58 (m, 1H), 3.14 (m, 1H), 2.98 (m, 1H), 2.20-2.15 (m, 1H), 1.97-1.89 (m, 2H), 1.26-1.24 (m, 1H), 0.88 (t, *J* = 7.2 Hz, 1H).

MS (ESI): *m/z* 521 $[M+Na]^+$.

HPLC condition: Chiralcel OD-3 column, *n*-hexane/i-PrOH = 70:30, flow rate = 1.0 mL/min, wavelength = 254 nm).



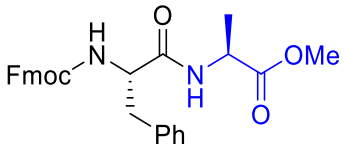
NO.	t_R (min)	Area (%)	Hight (%)
1	10.292	52.030	76.339
2	23.040	47.970	23.661

NO.	t_R (min)	Area (%)	Hight (%)
1	22.710	100.000	100.000

Spectroscopic data was agreement with the literature.[221]

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-phenylalanyl-L-alanine methyl ester (22tj). (Fmoc-Phe-Ala-OMe)**

[221] A. Temperini, F. Piazzolla, L. Minuti, M. Curini, C. Siciliano, General, Mild, and Metal-Free Synthesis of Phenyl Selenoesters from Anhydrides and Their Use in Peptide Synthesis. *J. Org. Chem.* **2017**, *82*, 4588-4603.

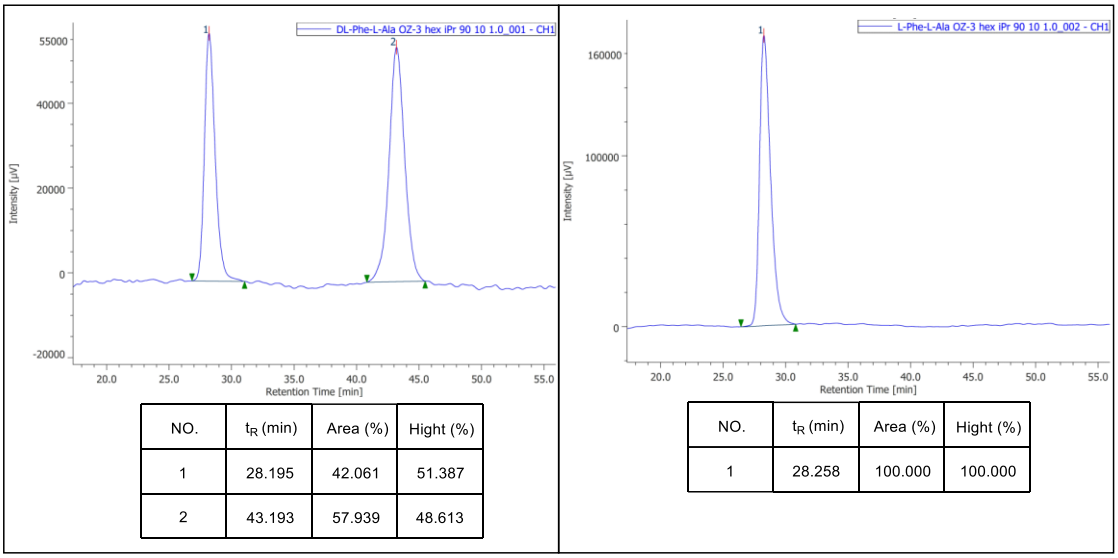


Following the general procedure D, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 3/2) to give **22tj** (78.5 mg, 83% yield) as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 7.6 Hz, 2H), 7.54 (dd, *J* = 11.2, 7.6 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32-7.29 (m, 4H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.21 (s, 2H), 6.27 (s, 1H), 5.34 (s, 1H), 4.52-4.43 (m, 3H), 4.34 (s, 1H), 4.20 (t, *J* = 7.0 Hz, 1H), 3.72 (s, 3H), 3.13 (s, 1H), 3.05 (s, 1H), 1.35 (d, *J* = 6.8 Hz, 3H) ppm.

MS (ESI): *m/z* 495 $[M+Na]^+$.

HPLC condition: Chiralcel OZ-3 column, *n*-hexane/i-PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm).

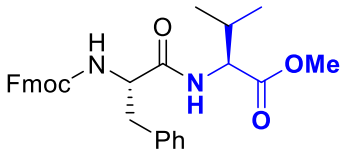


NO.	t_R (min)	Area (%)	Hight (%)
1	28.195	42.061	51.387
2	43.193	57.939	48.613

NO.	t_R (min)	Area (%)	Hight (%)
1	28.258	100.000	100.000

Spectroscopic data was agreement with the literature.[220]

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-phenylalanyl-L-valine methyl ester (22tk). (Fmoc-Phe-Val-OMe)**



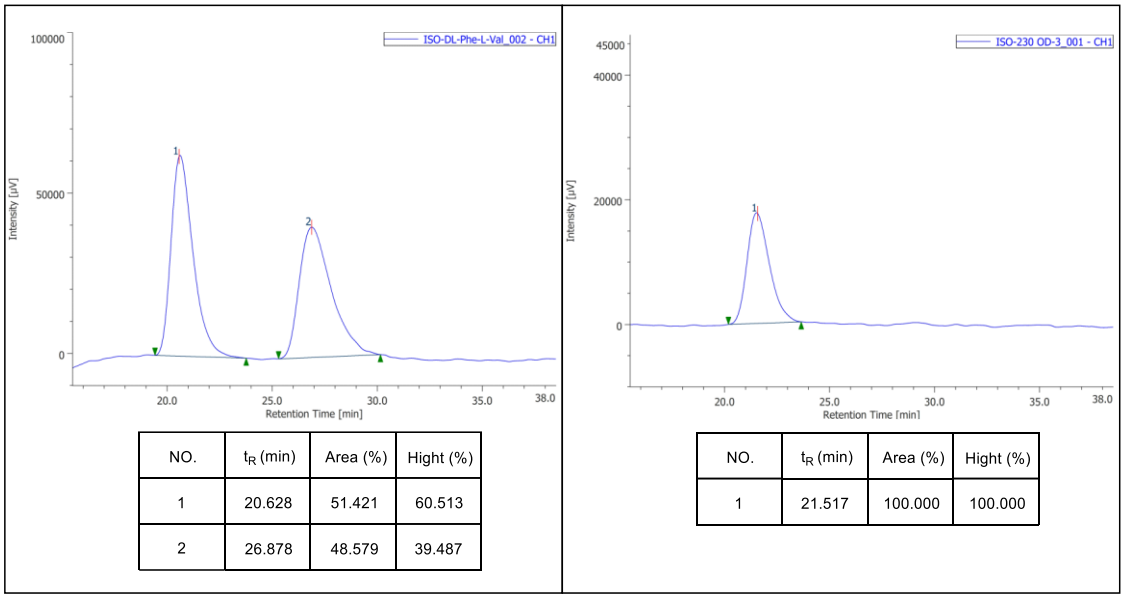
Following the general procedure D, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 2/1) to give **22tk** (102.1 mg, quant) as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.30 (dd, *J* = 16.8, 7.6 Hz, 4H), 7.25-7.20 (m, 3H), 6.21 (s, 1H), 5.38 (s, 1H), 4.46-4.41 (m, 3H), 4.34 (s, 1H), 4.20 (t, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 3.13 (s, 1H), 3.06 (s, 1H), 2.09 (q, *J* = 6.0 Hz, 1H), 0.85 (d, *J* = 6.8 Hz,

3H), 0.81 (d, *J* = 6.4 Hz, 3H) ppm.

MS (ESI): *m/z* 523 $[M+Na]^+$.

HPLC condition: Chiralcel OD-3 column, *n*-hexane/i-PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm).

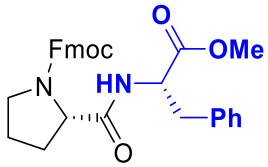


NO.	t_R (min)	Area (%)	Hight (%)
1	20.628	51.421	60.513
2	26.878	48.579	39.487

NO.	t_R (min)	Area (%)	Hight (%)
1	21.517	100.000	100.000

Spectroscopic data was agreement with the literature.[222]

1-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-prolyl-L-phenylalanine methyl ester (Fmoc-Pro-Phe-OMe) (22uh)



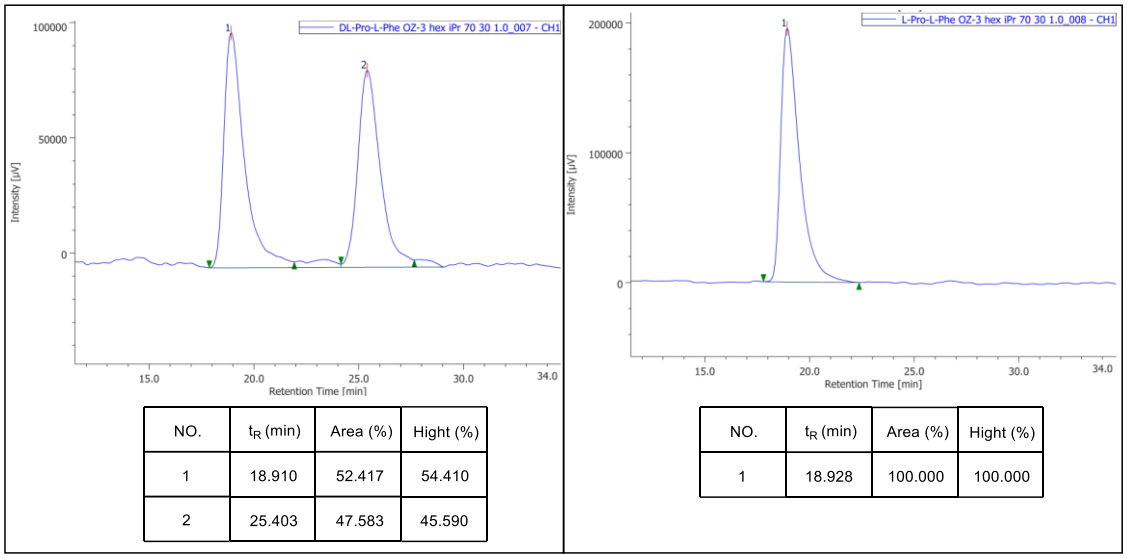
Following the general procedure D, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 2/1) to give **22uh** (96.3 mg, 96% yield) as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 27.2 Hz, 2H), 7.56 (d, *J* = 64.1 Hz, 2H), 7.42-7.32 (m, 4H), 7.22-7.06 (m, 5H), 6.40 (s, 1H), 4.86 (m, 1H), 4.36 (m, 3H), 4.19 (m, 1H), 3.71 (s, 3H), 3.54-3.38 (m, 2H), 3.18 (m, 1H), 3.00 (q, *J* = 6.9 Hz, 1H), 2.32 (s, 1H), 2.08 (d, *J* = 62.1 Hz, 1H), 1.86-1.64 (m, 2H) ppm.

MS (ESI): *m/z* 521 $[M+Na]^+$.

HPLC condition: Chiralcel OZ-3 column, *n*-hexane/i-PrOH = 70:30, flow rate = 1.0 mL/min, wavelength = 254 nm).

[222] W. Gong, G. Zhang, T. Liu, J. Giri, J. Yu, Site-Selective C(sp3)–H Functionalization of Di-, Tri-, and Tetrapeptides at the N-Terminus. *J. Am. Chem. Soc*. **2014**, *136*, 16940-16946.

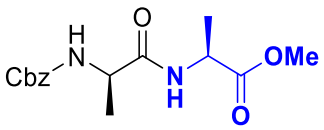


NO.	t_R (min)	Area (%)	Hight (%)
1	18.910	52.417	54.410
2	25.403	47.583	45.590

NO.	t_R (min)	Area (%)	Hight (%)
1	18.928	100.000	100.000

Spectroscopic data was agreement with the literature.[223]

methyl ((benzyloxy)carbonyl)-D-alanyl-L-alaninate (*N*-Cbz-D-Ala-L-Ala-OMe) (22vj)



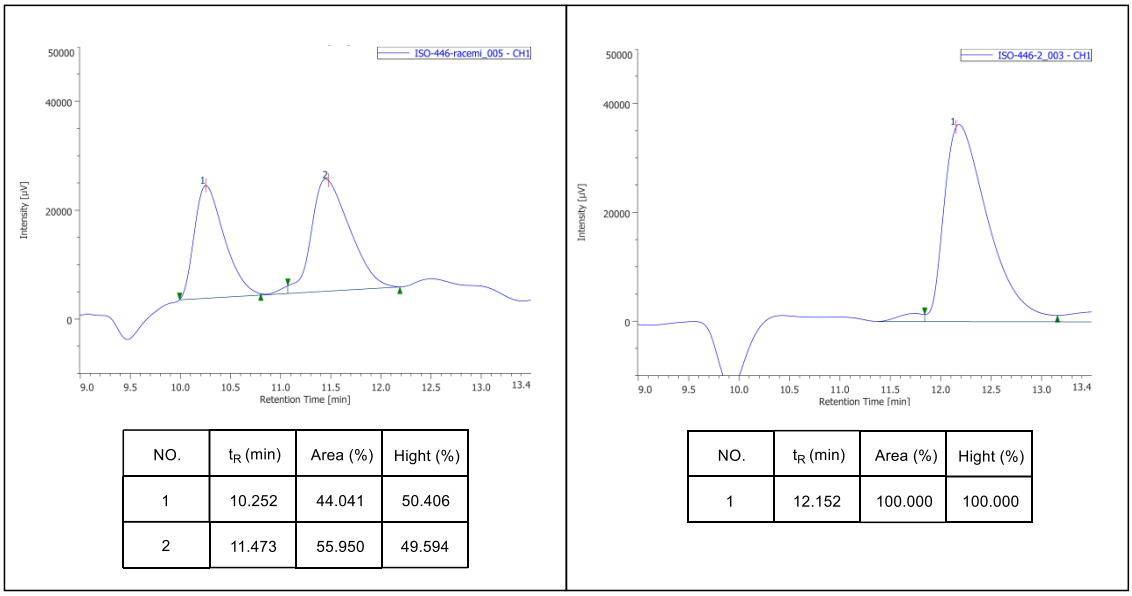
Following the general procedure D, the mixture was purified by column chromatography on silica gel (*n*-hexane/Ethyl acetate = 2/1) to give **22vj** (49.7 mg, 81% yield) as a white solid. When reaction completed, diluted it with ethyl acetate, Thereafter, $NaHCO_3$ sat. (1.0 mL) was added, and the aqueous layer was extracted with ethyl acetate (5.0 mL × 3). The combined organic layer was washed with 1N HCl and brine successively, dried over Na_2SO_4, concentrated under reduced pressure. The residue was recrystallized from *n*-hexane/Ethyl acetate to give **22vj** (44.5 mg, 72%) as a pale-yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.29 (m, 5H), 6.88 (s, 1H), 5.58 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H), 4.61-4.51 (m, 1H), 4.34-4.29 (m, 1H), 3.72 (s, 3H), 1.38 (d, *J* = 7.0 Hz, 6H) ppm.

MS (ESI): *m/z* 331 $[M+Na]^+$.

HPLC condition: Chiralcel OZ-3 column, *n*-hexane/i-PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm).

[223] Z. J. Kamiński, B. Kolesińska, J. Kolesińska, G. Sabatino, M. Chelli, P. Rovero, M. Błaszczyk, M. L. Główka, A. M. Papini, *N*-Triazinylammonium Tetrafluoroborates. A New Generation of Efficient Coupling Reagents Useful for Peptide Synthesis. *J. Am. Chem. Soc*. **2005**, *127*, 16912-16920.



NO.	t_R (min)	Area (%)	Hight (%)
1	10.252	44.041	50.406
2	11.473	55.950	49.594

NO.	t_R (min)	Area (%)	Hight (%)
1	12.152	100.000	100.000

Spectroscopic data was agreement with the literature.[224]

[224] H. Chen, X. Xu, L. Liu, G. Tang, Y. Zhao, Phosphorus oxychloride as an efficient coupling reagent for the synthesis of esters, amides and peptides under mild conditions. *RSC Adv.* **2013**, *3*, 16247-16250.

Publication List

1. Enantioselective Benzylation and Allylation of α-Trifluoromethoxy Indanones under Phase-Transfer Catalysis. Yumeng Liang, Mayaka Maeno, **Zhengyu Zhao**, Norio Shibata, *Molecules* **2019**, *24*, 2774-2787.
2. Pd-catalyzed fluoro-carbonylation of aryl, vinyl and heteroaryl iodides using 2-(difluoromethoxy)-5-nitropyridine. Yumeng Liang, **Zhengyu Zhao**, Norio Shibata, *Commun. Chem*. **2020**, *3*, 59-67.
3. Deoxyfluorination of acyl fluorides to trifluoromethyl compounds by FLUOLEADR/Olah's reagent under solvent-free conditions. Yumeng Liang, Akihito Taya, **Zhengyu Zhao**, Norio Shibata, *Beilstein J. Org. Chem*. **2020**, *16*, 3052-3058.
4. Acyl fluorides from carboxylic acids, aldehydes, or alcohols under oxidative fluorination. Yumeng Liang, **Zhengyu Zhao**, Akihito Taya, and Norio Shibata. *Org. Lett*. **2021**, *23*, 847-852.
5. $AgBF_4$-Mediated Chlorine-Fluorine Exchange Fluorination for the Synthesis of Pentafluorosulfanyl (Hetero)arenes. Kazuhiro Tanagawa, **Zhengyu Zhao**, Norimichi Saito, Norio Shibata. *Bull. Chem. Soc. Jpn*. **2021**, *94*, 1682-1684.
6. Catalyst-free carbosilylation of alkenes using silyl boronates and organic fluorides via selective C-F bond activation. Jun Zhou, Bingyao Jiang, Yamato Fujihira, **Zhengyu Zhao**, Takanori Imai, Norio Shibata. *Nat. Commun.* **2021**, *12*, 3749-3757.
7. Silylboronate-mediated Defluorosilylation of Aryl Fluorides with or without Ni-catalyst. Jun Zhou, **Zhengyu Zhao**, Norio Shibata. *Front. Chem.* **2021**, *9*, 771473-771479. (chapter 2)
8. Etherification of Fluoroarenes with Alkoxyboronic Acid Pinacol Esters via C-F Bond Cleavage. Jun Zhou, Bingyao Jiang, **Zhengyu Zhao**, Norio Shibata. *Org. Lett.* **2022**, *24*, 5084-5089.
9. Synthesis of triarylmethanes by silyl radical-mediated cross-coupling of aryl fluorides and arylmethanes. Jun Zhou, **Zhengyu Zhao**, Bingyao Jiang, Katsuhiro Yamamoto, Yuji Sumii, Norio Shibata. *Chem. Sci.* **2023**, *14*, 4248-4256. (Chapter 3)
10. Transition-metal-free silylboronate-mediated cross-couplings of organic fluorides with amines. Jun Zhou, **Zhengyu Zhao**, Norio Shibata. *Nat. Commun.* **2023**, *14*, 1847-1855. (chapter 4)
11. An Innovative Approach to α-Arylation of acetonitrile. **Zhengyu Zhao**,[ǂ] Jun Zhou, [ǂ] Norio Shibata. (To be submitted). [ǂ]Authors contributed equally. (chapter 5)
12. Mechanochemical Deoxyfluorination of Carboxylic Acids to Acyl Fluorides and Successive Mechanochemical Amide Bond Formation. **Zhengyu Zhao**, Sota, Ikawa, Soichiro Mori, Yuji Sumii, Hiroaki Adachi, Takumi Kagawa, Norio Shibata. (Revision submitted to ACS Sustainable Chem. Eng.) (Chapter 6)
13. Cross-Coupling of Aryl Fluorides with Allenes: A Silyl-radical-relay Pathway for the Construction α-Alkynyl-Substituted All-Carbon Quaternary Centers. Jun Zhou, **Zhengyu Zhao**, Soichiro Mori, Norio Shibata. (Submitted to Chem. Sci.)
14. Copper-catalyzed Acylsilylation of Styrene using Acyl Fluorides. **Zhengyu Zhao**, Jun Zhou, Norio Shibata. (To be submitted)

Presentation List

1. ‘‘2-(Difluoromethoxy)-5-nitropyridine: A Novel Reagent for Pd-catalyzed Direct Fluoro-carbonylation of Aryl, Vinyl, and Heteroaryl Iodides’’ ○**Zhengyu Zhao**, Yumeng Liang, Norio Shibata. 日本病院薬剤師会東海ブロック・日本薬学会東海支部　合同学術大会 **2020**
2. カルボン酸、アルデヒド、およびアルコールからのフッ化アシル化合物への迅速合成 [28V05-pm17S] 日本薬学会第 141 年会　○**趙 正宇**，梁 雨蒙，田谷 彬人，柴田哲男
3. FLUOLEADR/ Olah 試薬を用いたフッ化アシルの脱酸素的フッ素化反応 [A-15S] 第 67 回日本薬学会東海支部総会・大会　○**趙正宇**、梁雨蒙、田谷彬人、斎藤紀庸、柴田哲男
4. Silyl Borane-mediated C-F Functionalization of Fluoroarenes [1-09] 第 21 回次世代を担う有機化学シンポジウム　○**Zhengyu Zhao**, Jun Zhou, Norio Shibata
5. Silyl borane-mediated cyanoalkylation via C-F bond cleavage of Fluoroarenes [O-02] 第 46 回 フッ素化学討論会　○**趙 正宇**、周 軍、柴田 哲男

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