

Thesis

**Development of Enantioselective Fluorination Reactions
Toward Medicinal Chemistry**

2009

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Contents:

Introduction

Fluorine properties	1
Examples of fluorinated biologically active molecules.....	2
Asymmetric fluorination examples.....	3
Catalytic asymmetric fluorination examples.....	9

Chapter 1. Desymmetrization-like Catalytic Enantioselective Fluorination of Malonates and Its Application to Pharmaceutically Attractive Molecules

1. 1. Introduction.....	23
1. 2. Synthesis of malonic esters.....	26
1. 3. Synthesis of racemic α -fluoro malonic esters.....	30
1. 4. Enantioselective fluorination screening for the condition.....	32
1. 5. Enantioselective fluorination of various substrates (Ni).....	33
1. 6. Enantioselective fluorination of various substrates (Zn).....	35
1. 7. Chemoselective reduction.....	36
1. 8. Chemoselective reduction.....	38
1. 9 Synthesis of α -Fluorinated β -Amino Acids.....	40
1.10 Synthesis of α -Fluorinated β -Lactam.....	41
1.11 Synthesis of α -Fluoro Alacepril.....	42
1.12 Synthesis of HIV-1 inhibitor.....	45
1.13 Efficient synthesis of fluoro-oxindole by fluorinated malonate.....	40
1.14 Determination of the absolute configuration.....	41
1.15 Conclusion.....	43

Chapter 2. DBFOX-Ph/metal complexes: Evaluation as catalysts for enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones

2. 1. Introduction.....	44
2. 2. Synthesis of α -aryl acetyl thiazolidinones.....	48
2. 3 Synthesis of racemic fluorination.....	49
2. 4 Optimization of reaction conditions	51
2. 5 Screening for bases.....	53
2. 6 Enantioselective fluorination of various substrates.....	54
2. 7 Optimization of reaction conditions with additives.....	56
2. 8 HFIP at -20 various substrates	59
2. 9 HFIP at -60 various substrates	60
2. 10 HFIP at -80 various substrates	61
2. 11 Optimization of reaction conditions of allylic substrates.....	65
2. 12 Enantioselective fluorination of various allylic substrates.....	66
2. 13 Preparation of Indoleacetyl thiazolidinone.....	67
2. 14 Enantioselective fluorination of Indoleacetyl thiazolidinone.....	68
2. 15 Enantioselective chlorination of arylacetyl thiazolidinones.....	70

2. 16 Enantioselective bromination of arylacetyl thiazolidinones.....	71
2. 17 Conclusion.....	72

Chapter 3. Dynamic Kinetic Asymmetric Transformation in the α -hydroxylation of racemic malonates and its Application to Biologically Active Molecules

3. 1. Introduction.....	73
3. 2. Synthesis of malonic esters	82
3. 3 Synthesis of racemic hydroxylation	86
3. 4 Optimization of reaction conditions.....	88
3. 5. Enantioselective hydroxylation of various substrates	90
3. 6. Synthesis of chlozolate.....	92
3. 7. Synthesis of bicalutamide.....	94
3. 8. Synthesis of amino acid derivative.....	95
3. 9. Determination of absolute stereochemistry.....	96
3. 10. Enantioselective chlorination of malonates.....	97
3. 11 Conclusion	98

Chapter 4. Summary.....	99
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Experimental section.....	100
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Publication list.....	161
------------------------------	------------

Oral and poster presentations.....	162
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Acknowledgement.....	163
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Abbreviations:

AcOH

Ac₂O

Ac

Bn

Bu

CBz

CDCl₃

CHCl₃

CBz

CCl₄

CH₃CN

CH₂Cl₂ (DCM)

DIPEA

DMAP

DMSO

DIBAL

DCC

DMF

EtOH

EtOAc

ee

EDCI

g

HRMS

h

IR

ⁱPr

HCl

HFIP

Acetic acid

Acetic anhydride

Acetyl

Benzyl

n-Butyl

Benzyloxycarbonyl

Deuterated chloroform

Chloroform

Benzyloxycarbonyl

Carbon tetrachloride

Acetonitrile

Dichloromethane

Diisopropylethylamine

Dimethylaminopyridine

Dimethylsulfoxide

Diisobutylaluminiumhydride

N,N'-Dicyclohexylcarbodiimide

Dimethyl formamide

Ethanol

Ethyl acetate

Enantiomeric excess

Ethyl-3-(3-dimethylaminopropyl)-
-carbodiimide

Gram

High-resolution mass spectrum

Hour(s)

Infra red

Isopropyl

Hydrochloric Acid

Hexafluoro isopropanol

HOAt	1-hydroxy-7-azabenzotriazole
HOBt	N-hydroxy benzotriazole
HPLC	High performance liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
LiAl(O^tBu)₃H	Lithium aluminium tri tertiary butoxy-hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	Methyl
<i>m</i>-CPBA	<i>meta</i>-chloroperbenzoic acid
M⁺	Molecular ion
M.S.	Molecular sieves (4Å)
M.W.	Molecular weight
MHz	Megahertz
min	Minute(s)
mL	Milliliter(s)
mmol	Millimole(s)
M.p.	Melting point
NMR	Nuclear magnetic resonance
<i>n</i>-BuLi	Normal butyllithium
Pd/C	Palladium on carbon
Ph	Phenyl
Py	Pyridine
NFSI	N-fluorobenzene sulfonamide
R_f	Retention factor (in chromatography)
RT	Room temperature
NaN₃	Sodium Azide
NaHCO₃	Sodium bicarbonate
NaH	Sodium hydride
NaOH	Sodium hydroxide
Na₂SO₄	Sodium sulphate
Na₂S₂O₃	Sodium thiosulphate

H₂SO₄

TLC

***p*-TsCl**

THF

Et₃N

TFA

***t*-BuOH**

CF₃CH₂OH

Zn(OAc)₂

Sulfuric Acid

Thin layer chromatography

***p*-toluenesulphonyl chloride**

Tetrahydrofuran

Triethyl amine

Trifluoroaceticacid

***tert*-butanol**

Trifluoroethanol


Zincacetate

Organofluorine Chemistry

Introduction:

Organic molecules containing fluorine atoms have attracted much attention because they often show different characters from the parent compounds, probably due to the unique properties of the fluorine atom and/or carbon-fluorine bond¹. The replacement of a hydrogen or a hydroxyl group with a fluorine atom is an extensively used strategy for enhancement of biological activity in the design of analogues of biologically important molecules². The analogues are often regarded as isosters of the parent molecules because of the following considerations³. First, fluorine most closely resembles hydrogen in size among atoms; therefore, the fluorine replacement is often regarded as an isosteric substitution. Second, both from the structural and electronegativity points of view, fluorine and oxygen, not fluorine and hydrogen, are very nearly isosteric. Recent evidence indicated that the advantages of the fluorine substitution include an increase in stability, changes in lipophilicity, introduction of a highly electronegative center, and altered patterns of reactivity of the C–F versus the C–H or C–OH bond

- 1). Steric size effect
- 2). Strong bond energy [C-F: 116 Kcal/mol; C-H: 99 Kcal/mol]
- 3). The largest electronegativity
- 4). Change of lipophilicity
- 5). Hydrogen bond acceptor



	H	F	O
Electronegativity	2.1	4.0	3.5
Van der Waals radius (Å)	1.20	1.35	1.40
C-X bond length(Å)	1.09	1.39	1.43

Figure 1. Properties of the fluorine atom and carbon–fluorine bond.

¹ (a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2004; (b) R.D. Chambers (Ed.), *Fluorine in organic chemistry*, Blackwell Publishing, Oxford, UK, 2004; (c) B.E. Smart, *J. Fluor. Chem.* 109 (2001) 3-11.

² (a) R. Filler, Y. Kobayashi (Eds.), *Biomedical Aspects of Fluorine Chemistry*, Elsevier Biomedical Press and Kodansha Ltd., New York, Tokyo, 1982; (b) *Biomedical Frontiers of Fluorine Chemistry*, I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), ACS Symposium Series No. 639, American Chemical Society, Washington, DC, 1996; (c) R. Filler (Ed.), *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, 1993; (d) Y. Kobayashi, I. Kumadaki, T. Taguchi (Eds.), *Fusso Yakugaku*, Hirokawa, Tokyo, 1992; (e) J.T. Welch, *Tetrahedron* 43 (1987) 3123-3197.

³ (a) R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum, New York, 1994, pp. 57-88 (chapter 3); (b) Special issue on "Fluorine in the Life Sciences", *chemBioChem* 5 (2004) 557-726.

Biologically Active Molecules Containing a Fluorine Atom at Chiral Center:

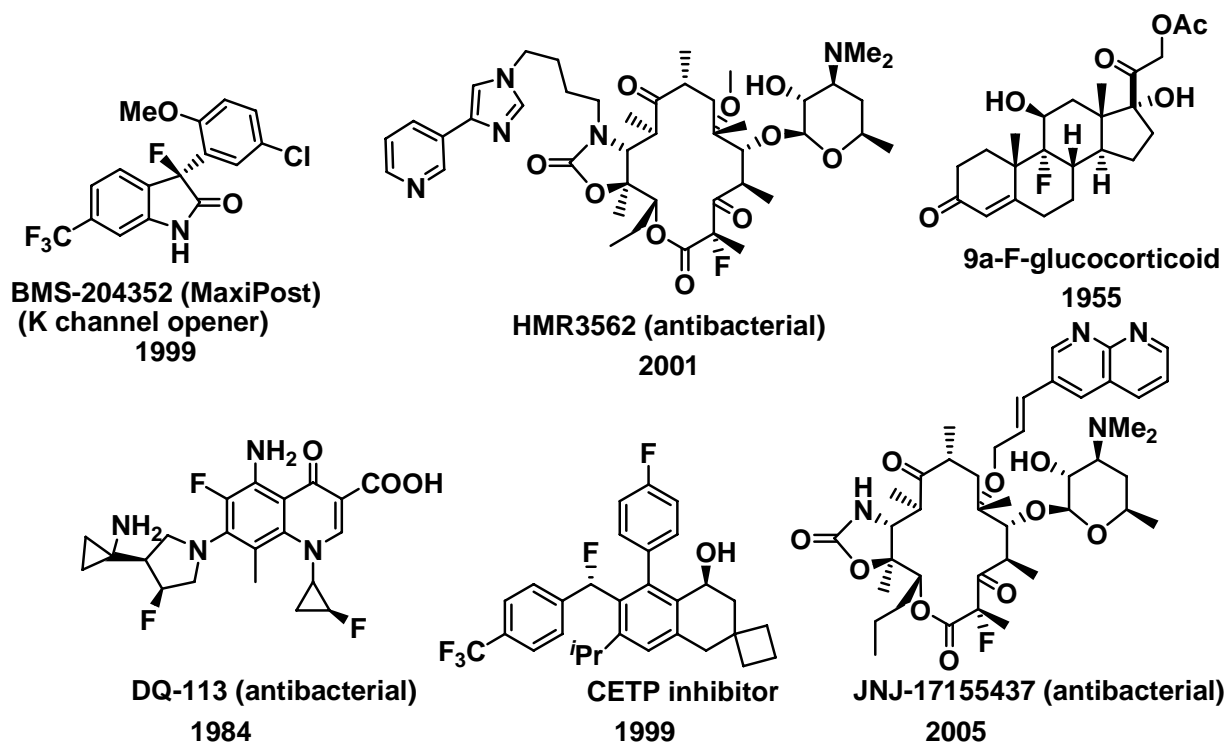
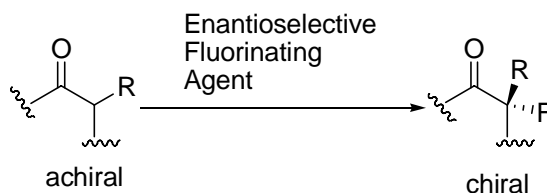


Fig 2

Chiral organofluorine compounds are interesting and important materials with uses in biological and medicinal chemistry⁴. These biologically active molecules have contained a fluorine atom at chiral carbon centers (Fig 2).

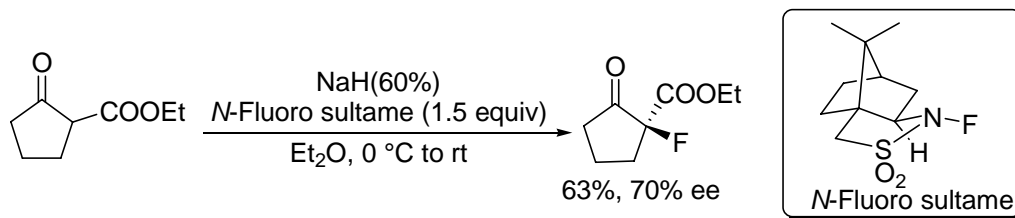
⁴ (a) F. Fried, E. F. Sabo. *J. Am. Chem. Soc.* **1954**, 76, 1455. (b) H. Paulsen, S. Antons, A. Brandes, M. Logers, S. N. Muller, P. Naab, C. Schmeck, S. Schneider, J. Stoltefub. *Angew. Chem. Int. Ed.* **1999**, 38, 3373. (c) P. Hewawasam, V. K. Gribkoff, Y. Pendri, I. S. Dworetzky, N. A. Meanwell, E. Martinez, G. C. Biossard, D. J. Post-Munson, J. T. Trojnacki, K. Yelswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone, J. E. Starrett. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1023. (d) H. Inagaki, S. Miyauchi, R. N. Miyauchi, H. C. Kawato, H. Ohki, N. Mastuhashi, K. Kawakami, H. Takahashi, M. Takemura. *J. Med. Chem.* **2003**, 46, 1005.

The development of effective methodologies for the preparation of selectively electrophilic fluorinated stereogenic carbon centers (Scheme 1).



Scheme 1

In 1989, Differding and Lang, who first introduced this idea, reported the chiral sulfonamide-type electrophilic fluorinating reagents. The reagent-controlled enantioselective fluorination is an efficient method, its have been developed for the electrophilic enantioselective fluorination of β -ketoester enolates, to give the anticipated α -fluoro carbonyl compounds in up to 70% ee by using optically active camphor-derived *N*-fluorocamphorsultam in 1988 (Scheme 2).⁵

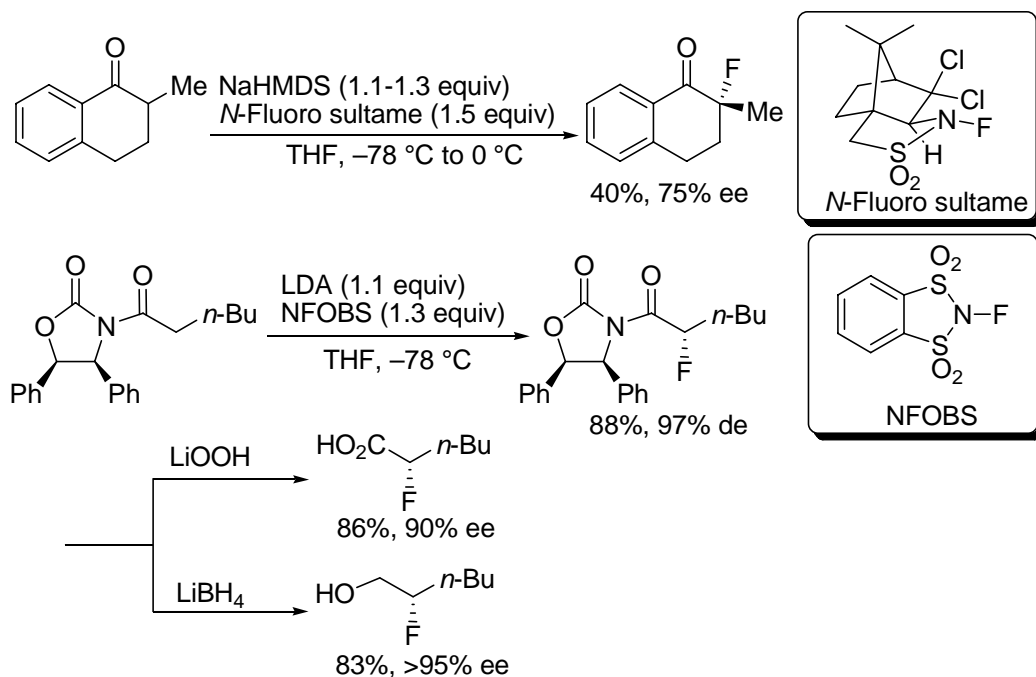


Scheme 2

The same strategy was adopted later by other researchers and efforts in particular from the group of Davis and co-workers were reported in 1993 and 1998 closely related structures of fluorinating reagents, *N*-fluoro-2,10-(3,3-dichlorocamphorsultam) affords α -fluoro carbonyl compounds in good yield and up to 75% ee. Diastereoselective fluorination of chiral imide enolates to α -fluoro carboximides in 86-95% de, using electrophilic fluorinating reagent *N*-fluoro-*o*-benzenedisulfonimide (NFOBS). The

⁵ (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, 29, 6087. (b) Differding, E.; Ruegg, G. M.; Lang, R. W. *Tetrahedron Lett.* **1991**, 32, 1779.

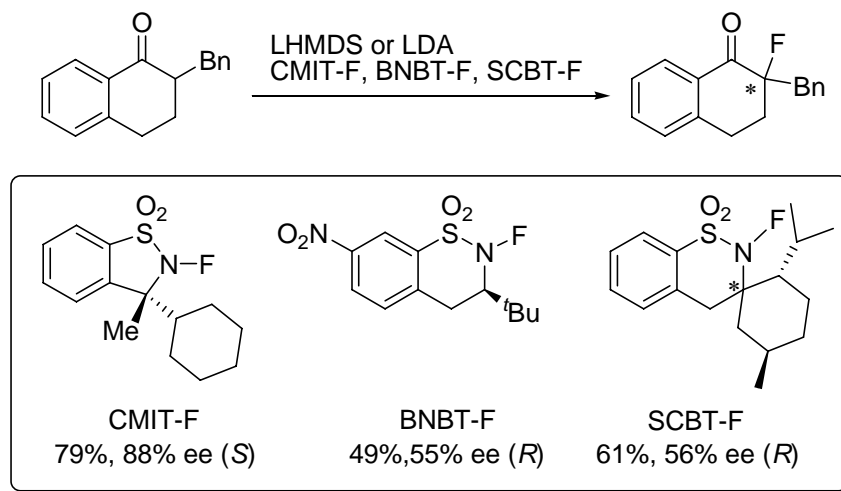
removal of the oxazolidinone auxiliary to furnish α -fluoro acids and β -fluoro alcohols with good ee's (Scheme 3).⁶



Scheme 3

⁶ (a) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, 32, 1631. (b) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, 33, 1153. (c) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, 34, 3971. (d) Davis, F. A.; Qi, H. *Tetrahedron Lett.* **1996**, 37, 4345. (e) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, 39, 6135. (f) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, 63, 2273.

After that Shibata and Takeuchi have designed and developed for the saccharin-type novel electrophilic fluorinating reagents, such as CMIT-F, BNBT-F, and SCBT-F were prepared and used in asymmetric electrophilic fluorination reaction (Scheme 4).⁷



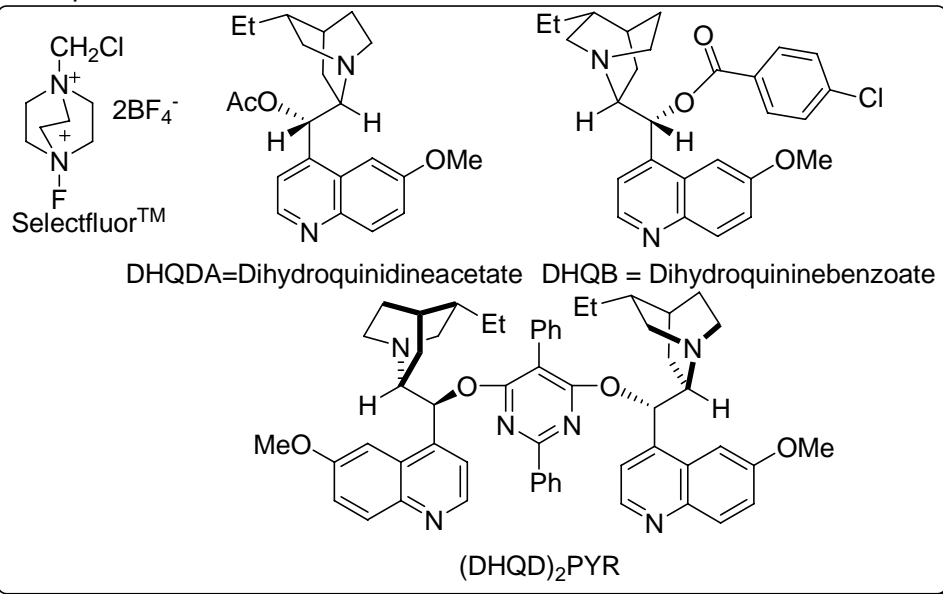
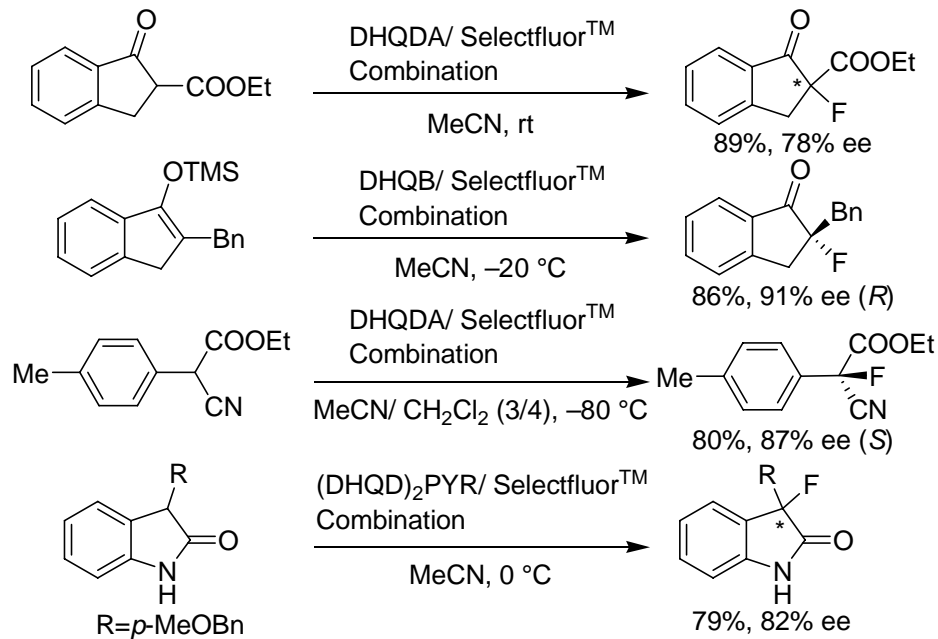
Scheme 4

In 2000, our group has developed a fundamentally new approach, mild and practical enantioselective fluorination reaction mediated by cinchona alkaloid derivatives, in combination with commercially available fluorinating reagent, Selectfluor® was disclosed. This procedure is based on in situ-generated *N*-fluoroammonium salts of cinchona alkaloids named cinchona alkaloid/Selectfluor® combinations.

Various substrates like, silyl enol ethers, metal enolates, α -cyano esters, β -keto esters, oxindoles, lactones, dipeptides and allylsilanes were treated with stoichiometric amount of cinchona alkaloid/ Selectfluor® combinations, fluorinated with high yields and high enantioselectivities up to 91% ee (Scheme 5).⁸

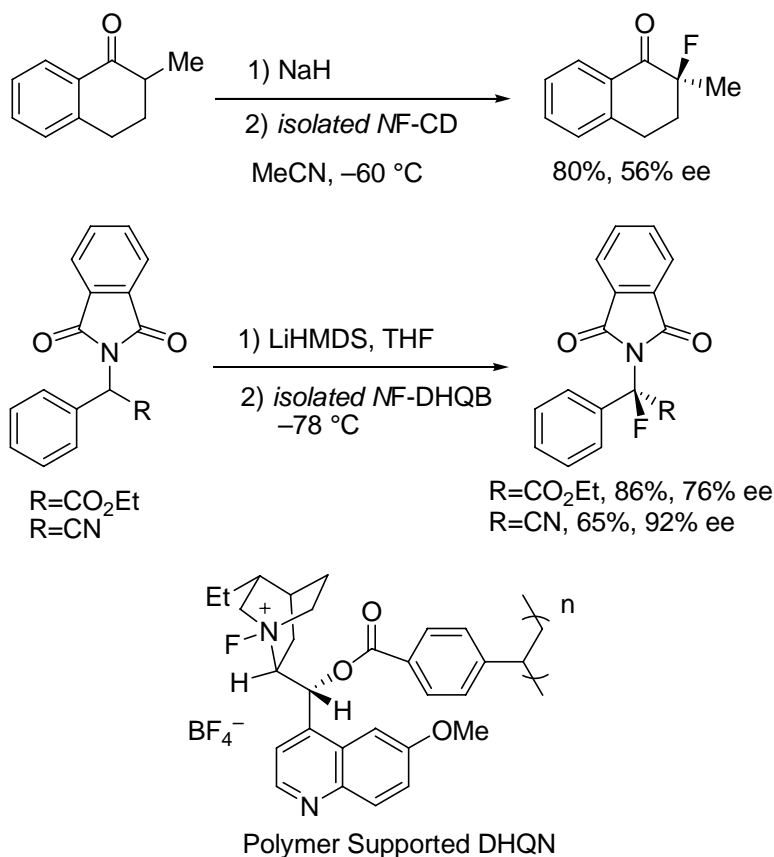
⁷ (a) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708. (b) Takeuchi, Y.; Liu, Z.; Suzuki, E.; Shibata, N.; Kirk, K. L. *J. Fluorine Chem.* **1999**, *97*, 65. (c) Shibata, N.; Liu, Z.; Takeuchi, Y. *Chem. Pharm. Bull.* **2000**, *65*, 1954. (d) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583.

⁸ (a) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (b) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.



Scheme 5

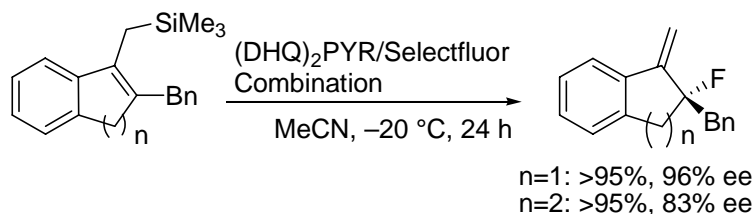
The enantioselective fluorination can also perform by the use of isolated *N*-fluoroammonium salts of cinchona alkaloids. In 2001, Cahard et.al independently developed the electrophilic fluorination of *N*-phthaloylphenylglycine derivatives using various cinchona alkaloids $[N-F]^+$ (isolated) (*N*-fluoroammonium salts) reagents in high yields and up to 94% ee (Scheme 6).⁹



Scheme 6

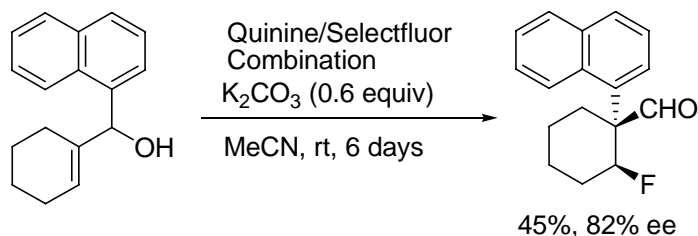
⁹ (a) Cahard, D.; Audouard, C.; Plaquevent, J-C.; Roques, N. *Org. Lett.* **2000**, 2, 3699. (b) Mohar, B.; Baudoux, J.; Plaquevent, J-C.; Cahard, D. *Angew. Chem. Int. Ed.* **2001**, 40, 4214. (c) Cahard, D.; Audouard, C.; Plaquevent, J-C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, 42, 1867. (d) Baudequin, C.; Plaquevent, J-C.; Audouard, C.; Cahard, D. *Green Chem.* **2002**, 4, 584. (e) Baudequin, C.; Loubassou, J-F.; Plaquevent, J-C.; Cahard, D. *J Fluorine Chem.* **2003**, 122, 189. (f) Thierry, B.; Plaquevent, J-C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, 14, 1671. (g) Ma, J-A. Cahard, D. *Chem. Rev.* **2004**, 104, 6119. (h) Mohar, B.; Sterk, D.; Ferronb, L.; Cahard, D. *Tetrahedron Lett.* **2005**, 46, 5029.

Gouverneur and co-workers were disclosed the extensions of the α -fluorination of carbonyl compounds strategy. Using the (DHQ)₂PYR/selectfluor® combination, allyl silanes were elegantly fluorinated in MeCN via the fluoro-desilylation pathway, leading to allylic fluorides with very high enantioselectivities (Scheme 7).¹⁰



Scheme 7

And also Tu and co-workers were reported asymmetric semipinacol rearrangement induced by cinchona alkaloid/ Selectfluor® combinations, up to 82% ee (Scheme 8).¹¹

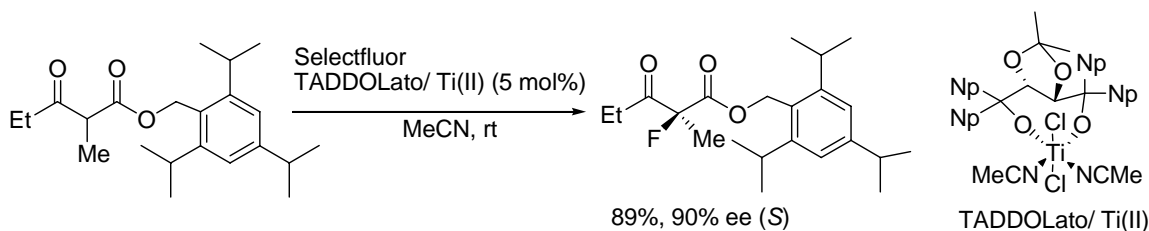


Scheme 8

¹⁰ (a) Greedy, B.; Paris, J-M.; Vidal, T.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2003**, 42, 3291. (b) Gouverneur, V.; Greedy, B. *Chem. Eur. J.* **2002**, 8, 766.

¹¹ Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C-A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. *Chem. Commun.* **2005**, 5580.

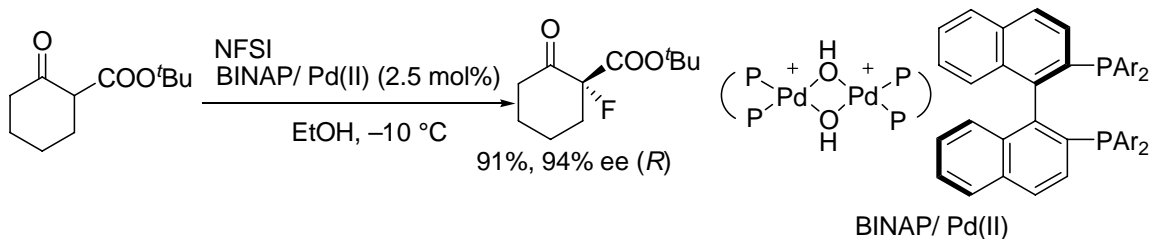
The first example of a catalytic enantioselective fluorination of β -keto ester was reported by Togni and co-workers in 2000. β -keto esters were enantioselectively fluorinated with Selectfluor® in the presence of catalytic amount of TADDOLato/Ti(II) (chiral titanium taddolate) to allow the β -keto esters to participate in the catalytic cycle via coordination at their two carbonyl oxygens that stabilizes the transition state, and hence effects enantioselective electrophilic fluorination by Selectfluor®. This observation eventually led to the successful development of a two point-binding protocol for the catalytic enantioselective fluorination (Scheme 9).¹²



Scheme 9

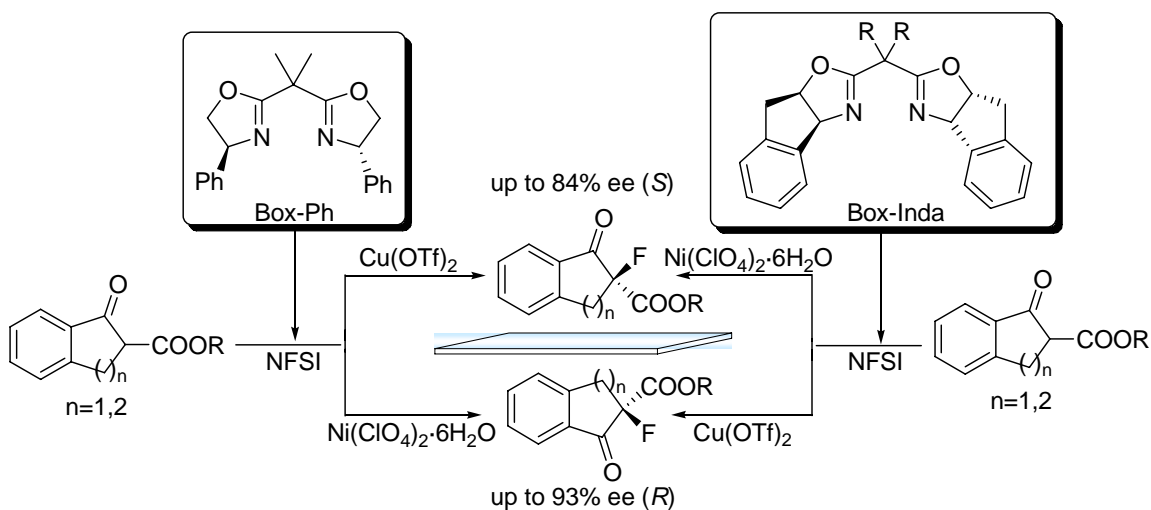
Since then, the earliest was a reported by Sodeoka et al. that the palladium BINAP complexes dicationic catalysis of the enantioselective fluorination of β -keto esters with very high enantioselectivities. An electrophilic fluorinating reagent, NFSI (N-fluorobenzenesulfonimide), was used instead of Selectfluor®. While the substrate generality had not been fully explored in the initial, the Sodeoka method utilizing palladium complexes allows access to a very broad range of fluorinated 1,3-dicarbonyl compounds including acyclic and cyclic β -keto esters with very high control of enantioselectivity in many instances (Scheme 10).¹³

- ¹² (a) Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, 39, 4359. (b) Hintermann, L.; Togni, A. *Helv. Chim. Acta.* **2000**, 83, 2425. (c) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem. Int. Ed.* **2002**, 41, 979. (d) Hintermann, L.; Broggini, D.; Togni, A. *Helv. Chim. Acta.* **2002**, 85, 1597. (e) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, 5, 1709. (f) Ibrahim, H.; Togni, A. *Chem. Comm.* **2004**, 1147. (g) Ibrahim, H.; Kleinbeck, F.; Togni, A. *Helv. Chim. Acta.* **2004**, 87, 605. (h) Toullec, P. Y.; Devillers, I.; Frantz, R.; Togni, A. *Helv. Chim. Acta.* **2004**, 87, 2706.
- ¹³ (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, 124, 11240. (b) Hamashima, Y.; Yagi, K.; Takano, H.; Tomas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, 124, 14530. (c) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, 5, 3225. (d) Hamashima, Y.; Sodeoka, M. *Pharmacia* **2004**, 40, 507. (e) Hamashima, Y.; Sodeoka, M. *The Chemical Record* **2004**, 4, 231.



Scheme 10

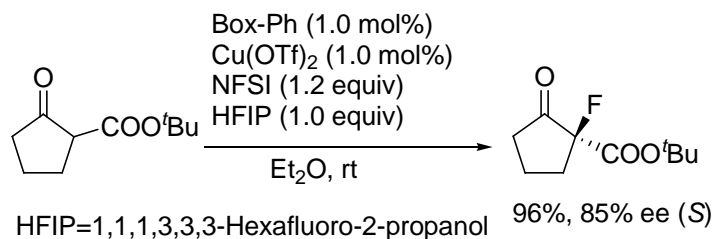
Inspired by the successes for the catalytic enantioselective fluorination by Togni and co-workers, and Soeoka and co-workers, our group was actively working to develop an enantioselective fluorination reaction that produces either product enantiomer selectively, depending on the reaction conditions, from only chiral ligand. Our group was demonstrated that when the fluorination of β -keto esters was carried out with NFSI in the presence of a catalytic amount of Box-Ph/Cu(II), the reaction predominately gave the fluorides with (*S*) configuration, when the fluorination was carried out using a catalytic amount of Box-Ph/Ni(II), afforded the opposite (*R*) isomer. Using the same chiral ligand, but switching the metal catalyst, gave a complete reversal enantioselectivity (Scheme 11).¹⁴



Scheme 11

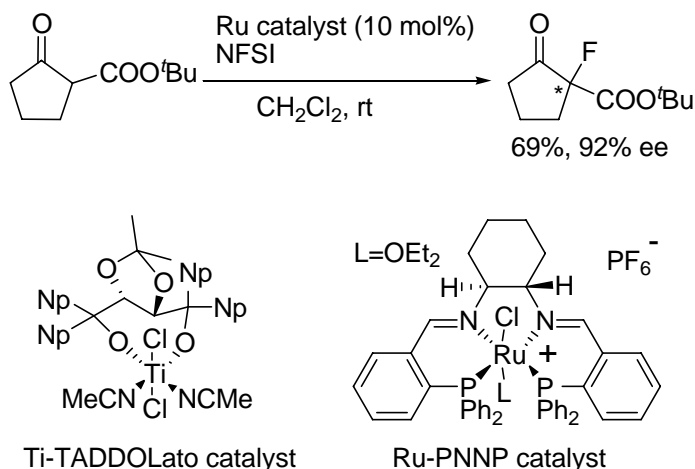
¹⁴ Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703.

Ma and Cahard was independently reported the enantioselective fluorination of both acyclic and cyclic β -keto esters by using electrophilic fluorinating agents such as NFSI and Box-Ph/Cu(II)-catalyzed, in the presence of HFIP(1,1,1,3,3,3-hexafluoro-2-propanol) in high yields with the corresponding optically active fluorinated products being obtained in moderate to good enantioselectivities (Scheme 12).¹⁵



Scheme 12

Ruthenium catalyzed enantioselective fluorination of β -keto esters were reported by Togni et al. with high enantioselectivities (Scheme 13).¹⁶

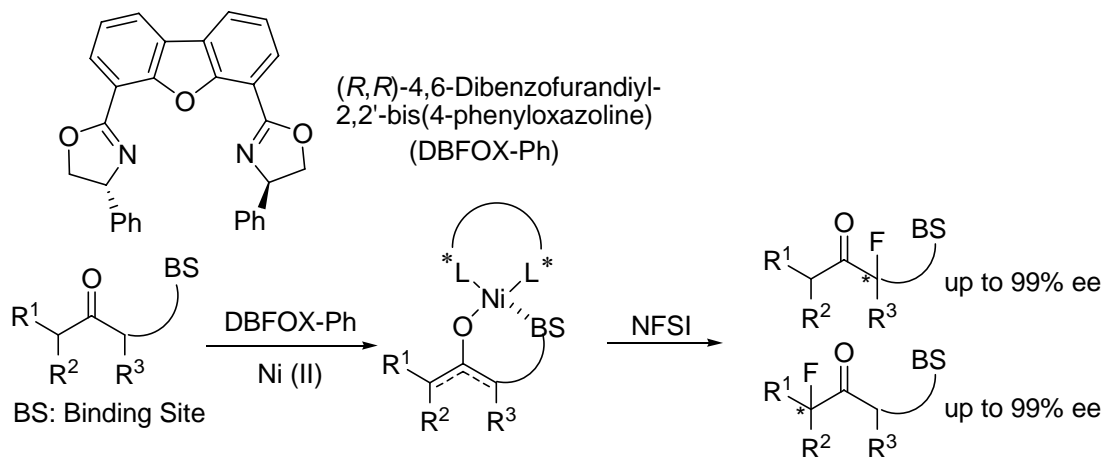


Scheme 13

¹⁵ (a) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119.

¹⁶ (a) Ibrahim, H.; Togni, A. *Chem. Comm.* **2004**, 1147. (b) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Nat. Acad. Sci.* **2004**, 5810. (c) Ramírez, E.; Huber, D. P.; Togni, A. *Synlett* **2007**, 1143. (d) Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Organometallics* **2007**, *26*, 5902.

An improved methodologies by others and our group have made greater contributions; however, the enantioselectivity were not enough. We found that the DBFOX ligand, (*R,R*)-4,6-Dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) (DBFOX-Ph), which is well-known as Kanemasa's catalyst for asymmetric Diels-Alder and Michael addition reactions. It was also highly effective in our fluorination process. Enantioselective fluorination of a wide range of substrates capable of two-point binding including both cyclic and acyclic β -keto esters using 10 mol% of DBFOX-Ph/Ni(II) in CH_2Cl_2 indicated the extraordinary reliable and high enantioselectivity up to 99% ee. The DBFOX-Ph/Ni(II) catalyst also demonstrates the enantioselective fluorination of oxindoles in high enantioselectivities, it is noted that Maxipost® can be derived from oxindole. We assumed that an octahedral complex coordinated with a water molecule for substrate/DBFOX/Ni(II) is a transition state structure. In the complex, one of the face is covered so efficiently that the NFSI was approaches from the *Si* face of the substrate (Scheme 14).¹⁷



Scheme 14

¹⁷ Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem. Int. Ed.* **2005**, 44, 4204.

Sodeoka and co-workers used Pd-BINAP complexes and Ni-BINAP complexes catalysts in various substrates fluorinated like β -keto esters, β -keto phosphates, oxindoles, cyanophosphates, lactones and lactams were fluorinated in high enantioselectivities (Fig. 3).¹⁸

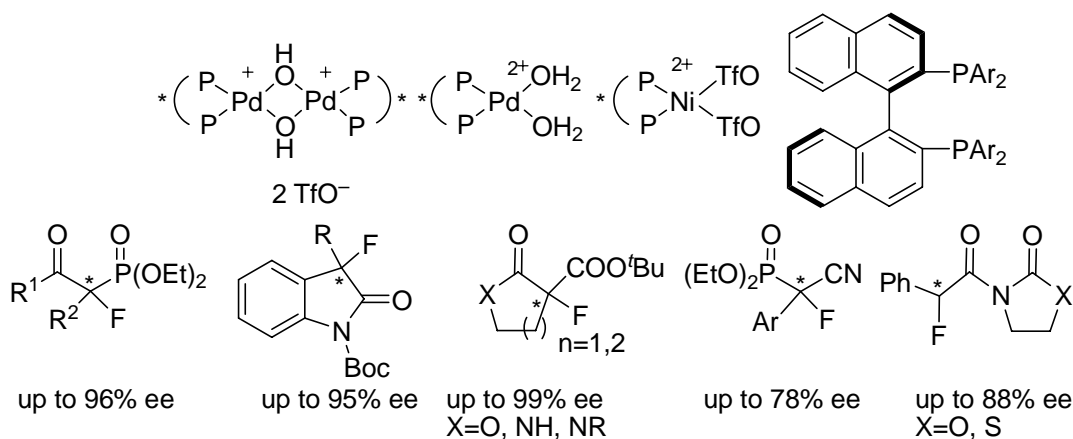


Fig. 3

Kim et al. also used the Pd-BINAP complexes for used enantioselective fluorination of β -keto-phosphates, α -cyano esters, and even oxindoles also fluorinated (Fig. 4).¹⁹

¹⁸ (a) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, 46, 1447. (b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, 127, 10164. (c) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.; Goto, T.; Sodeoka, M. *Tetrahedron* **2006**, 62, 7168. (d) Suzuki, T.; Goto, T.; Hamashima, Y.; Sodeoka, M. *J. Org. Chem.* **2006**, 72, 246. (e) Moriya, K.; Hamashima, Y.; Sodeoka, M. *Synlett* **2007**, 1139. (f) Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2007**, 46, 5435.

¹⁹ (a) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Chem.* **2005**, 7, 2309. (b) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, 46, 3115. (c) Kim, S. M.; Kang, Y. K.; Lee, K. S.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, 27, 423. (d) Kang, K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135.

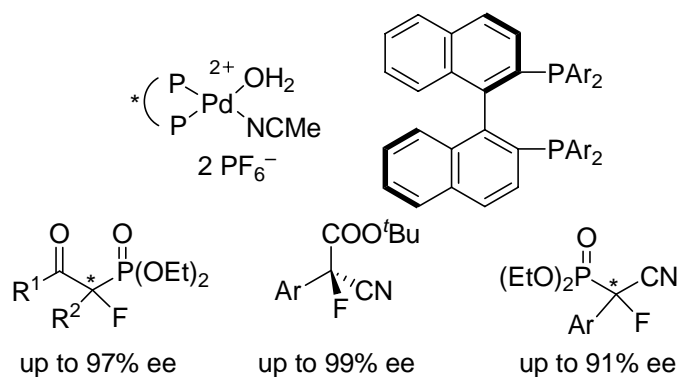
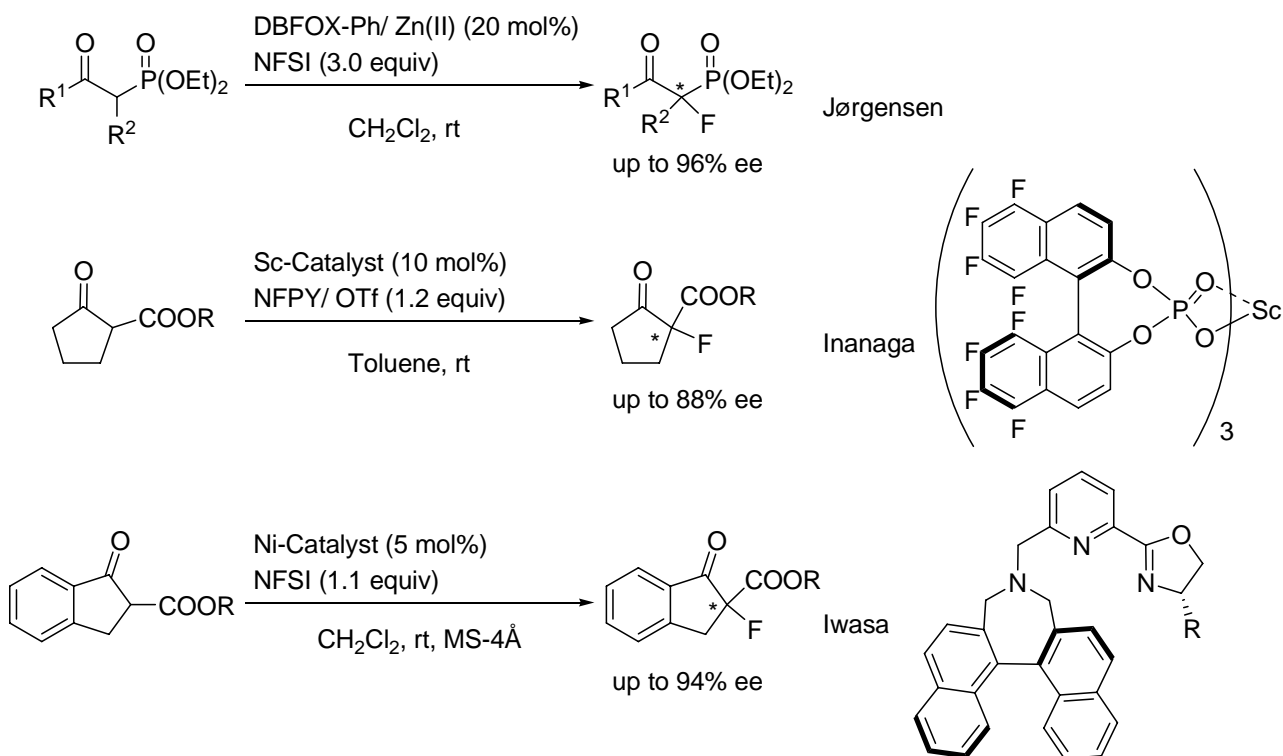


Fig. 4

Jørgensen et al. reported β -keto-phosphates fluorinated by using DBFOX-Ph/Zn(II) metal complexes in high yields with up to 96% ee.

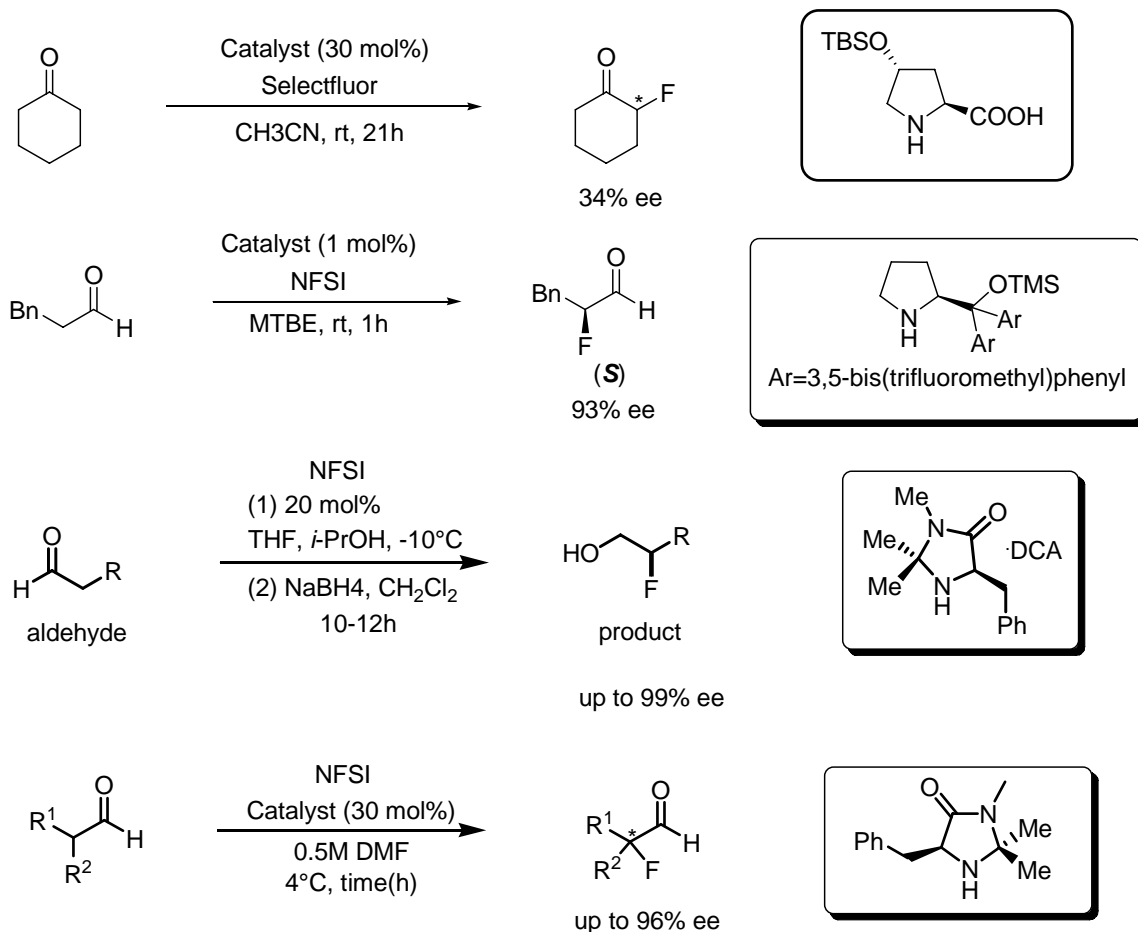
Inanaga and co-workers were reported Scandium/BINAP catalyzed for β -keto esters fluorinated with NFPY fluorinating agent up to 86% ee. Iwasa also reported β -keto esters fluorinated with using Ni catalyst and NFSI reagent with up to 94% ee (Scheme 15).²⁰



Scheme 15

²⁰ (a) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324. (b) Suzuki, S.; Furuno, H.; Yokoyama Y.; Inanaga, J. *Tetrahedron: Asymmetry* **2006**, 17, 504. (c) Shibatomi, K.; Tsuzuki, Y.; Nakata, S.; Sumikawa, Y.; Iwasa, S. *Synlett* **2007**, 551.

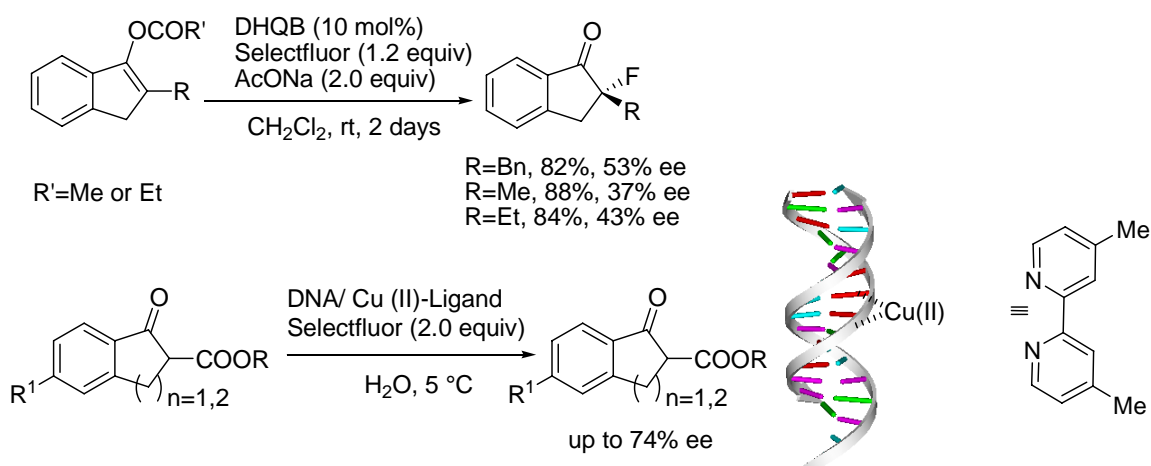
Very recently other direct organocatalytic enantioselective fluorinations of ketones and aldehydes were successfully realized. The first (*S*) proline and related compounds was reported by Enders and Huttel. However, the observed enantioselectivities were low. Recently, three research groups (Jorgensen, Barbas and MacMillan) have reported simultaneously their findings on the use of various cyclic secondary amines as catalysts for the direct organocatalytic enantioselective α -fluorination of aldehydes with excellent asymmetric induction (Scheme 16). This year (2008) Hisashi Yamamoto also reported for asymmetric fluorination reaction using organocatalysts.²¹



Scheme 16

²¹ (a) Enders, D.; Huttel, M. R. M. *synlett* **2005**, 991. (b) Steiner, D. D.; Mase, N.; Barbas, III. C. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706. (c) Marigo, M.; Fielenbach, D.; Branton, A.; Kjoersgaard, A.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (e) Shibatomi, K.; Yamamoto H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5796.

Recently, our group have used a novel catalytic approach to the enantioselective electrophilic fluorination of acyl enol ethers of ketones by using *N*-fluoroammonium salts of cinchona alkaloids with selectfluor[®] which produces non-racemic α -fluoroketones is described in moderate enantioselectivity. And also enantioselective electrophilic fluorination of β -ketoesters with selectfluor[®], catalyzed by DNA and nonchiral ligand Cu(II) complex is presented, this study provides the first DNA-mediated enantioselective C-F bond formation (Scheme 17).²²



Scheme 17

²² (a) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2006**, 127, 548.
 (b) Shibata, N.; Yasui, H.; Nakamura, S.; Toru, T. *Synlett* **2007**, 1153.

Chapter 1

Desymmetrization-like Catalytic Enantioselective Fluorination of Malonates and Its Application to Pharmaceutically Attractive Molecules

1.1 Introduction:

During the recent past years, tremendous efforts have been made to establish enantioselective electrophilic fluorination routes for the preparation of enantiomerically pure fluorine compounds. Optically active organofluorine compounds are attractive in the pharmaceutical, and food materials science, especially the simple chiral vicinal fluohydrins that are employed as important building blocks in the synthesis of polyfunctional bioactive molecules. Fluorinated malonates with a fluorine atom at a quarternary carbon center are a class of versatile and imported monofluorinated chiral synthons²³, utilized in the synthesis of liquid crystals,²⁴ antitumor agents,²⁵ enzyme inhibitors,²⁶ antiviral agents,²⁷ antibiotics,²⁸ and anti-Alzheimer agents (Scheme 18).²⁹

²³ (a) Haufe, G. *J. Fluorine Chem.* **2004**, 125, 875. (b) Haufe, G. *Science of Synthesis* **2006**, 34, 345. (c) Resnati, G. *Tetrahedron* **1993**, 42, 9385.

²⁴ (a) Yoshizawa, A.; Nishiyama, I.; Iria, T. *Jpn. Kokai Tokkyo Koho* **1991**, Jp 03112944. (b) Yoshino, K.; Ozaki, M.; Nakao, K.; Taniguchi, H.; Yamasaki, N.; Satoh, K. *Liq. Cryst.* **1989**, 5, 1203. (c) Taniguchi, H.; Ozaki, M.; Yoshino, K. *Jpn. J. App. Phys.* **1987**, 26, 101. (d) Yoshino, K.; Ozaki, M.; Taniguchi, H.; Ito, M.; Kazuo, Y.; Yamasaki, N.; Kitazume, N. *Chem. Exp.* **1987**, 2, 56.

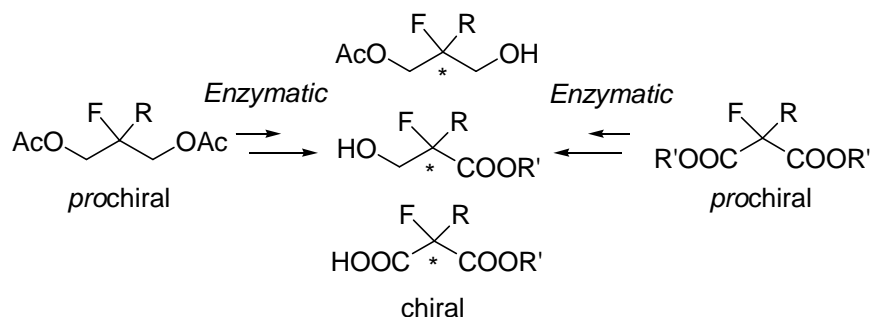
²⁵ (a) Haufe, G.; Burchardt, A. *Eur. J. Org. Chem.* **2001**, 23, 4501. (b) Burchardt, A.; Takahashi, T.; Takeuchi, Y.; Haufe, G. *J. Org. Chem.* **2001**, 66, 2078. (c) Ogawa, Y.; Iga, K.; Igari, Y. *Eur. Pat. Appl.* 331504, **1989**. (d) Okutani, T.; Ukawa, K.; Yamamoto, H.; Amano, T.; Nombra, H.; Ootsu, K.; Kozai, Y. *Chem. Pharm. Bull.* **1986**, 34, 713. (e) Miyashita, O.; Kasahara, T.; Wada, Y. *Chem. Pharm. Bull.* **1982**, 30, 3005. (f) Miyashita, O.; Kasahara, T.; Mastumura, K.; Shimadzu, H.; Takamoto, M.; Hashimoto, N. *Chem. Pharm. Bull.* **1982**, 30, 2333. (g) Marunaka, T.; Umeno, Y. *Chem. Pharm. Bull.* **1982**, 30, 1868.

²⁶ (a) Abouabdellah, A.; Boros, L.; Gyenes, F.; Welch, J. T. *J. Fluorine Chem.* **1995**, 72, 255. (b) Abouabdellah, A.; Welch, J. T. *Tetrahedron: Asymmetry* **1994**, 5, 1005. (c) Leeper, F.; Rock, M. *J. Fluorine Chem.* **1991**, 51, 381. (d) Barch, A.; Shanahan, W. *Eur. Pat. Appl.* 393575, **1990**. (e) Kitazume, T.; Yamamoto, T. *J. Fluorine Chem.* **1987**, 35, 467.

²⁷ Lee, K.; Choi, Y.; Hong, J.; Schinazi, R.; Chu, C. *Nucleosides Nucleotides* **1999**, 18, 537.

²⁸ Ihara, M.; Satoh, K.; Ishida, Y.; Taniguchi, N.; Tokunaga, Y.; Takemura, m.; Fukumoto, K. *Heterocycles* **1996**, 42, 437.

²⁹ Flohr, A.; Guido, G.; Jacob-Roetne, R.; Kitas, E. A.; Peters, J.-U.; Wostl, W. U.S. patent 2005054633, **2005**.



Scheme 18

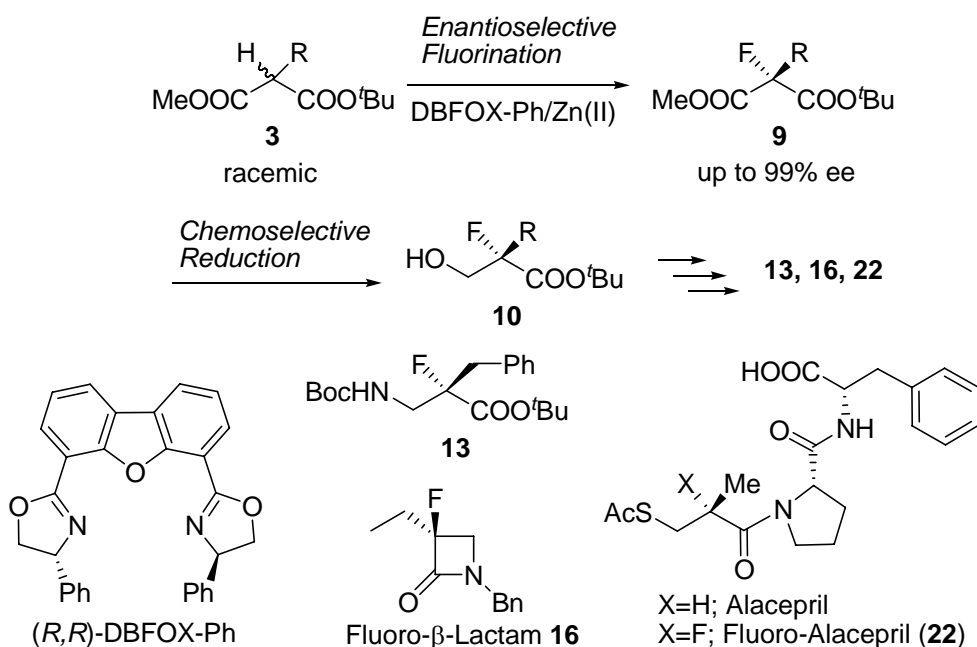
A variety of enantioselective synthesis of fluorinated compounds have been developed for the elaboration of optically active fluorinated malonates, as well their synthetic equivalents such as vicinal fluorohydrins and fluorinated half hydroxyl esters. These approaches include the enzymatic desymmetrization of substituted 2-fluoromalononic diesters, 2-fluoropropane-1,3-diols, and 2-fluoro-1,3-diacetoxyp propane derivatives, which lead in each case to similar 2-fluorinated synthons (Scheme 18).³⁰

Chemical approach for the diastereoselective fluorination of malonates has been reported by Fukumoto and co-workers. L-Menthylphenyl esters of malonates were fluorinated with fluoropyridinium triflate in high yield with moderate diastereoselectivities by using lithium hexamethyldisilazane (LHMDS). Kaneko and co-workers also reported that fluorination of chiral 5-substituted 1,3-oxazine-4,6-dione derivatives proceeded diastereoselectively to give the 5-fluorooxazinediones, which were readily transformed to optically pure fluoromalonic acids (Scheme 19).³¹

³⁰ (a) Narisano, E.; Riva, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1223. (b) Kitazume, T.; Kobayashi, T. *Synthesis* **1987**, 187. (c) Yamazaki, T.; Yamamoto, T.; Kitazume, T. *J. Org. Chem.* **1989**, *54*, 83. (d) Guanti, G.; Narisano, E.; Riva, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1859. (e) Kitazume, T.; Yamamoto, T. *J. Fluorine Chem.* **1986**, *31*, 357. (f) Kitazume, T.; Murata, K.; Ikeya, T. *J. Fluorine Chem.* **1986**, *32*, 233. (g) Kitazume, T.; Sato, T.; Kobayashi, T. *J. Org. Chem.* **1986**, *51*, 1003. (h) Kitazume, T.; Sato, T.; Ishikawa, N. *Chem. Lett.* **1984**, *13*, 1811. (i) Yamazaki, T.; Yamamoto, T.; Kitazume, T. *J. Org. Chem.* **1989**, *54*, 83. (j) Sattler, A.; Haufe, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2841. (k) Kitazume, T.; Murata, K.; Ikeya, T. *J. Fluorine Chem.* **1986**, *31*, 143.

³¹ (a) Coe, P.; Lohr, M.; Rochin, C. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2803. (b) Ihara, M.; Tanaka, Y.; Takahashi, N.; Okunaga, Y.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3043. (c) Ihara, M.; Kawabuchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1041. (d) Ihara, M.; Taniguchi, N.; Kai, T.; Satoh, K.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1992**, 221. (e) Sato, M.; Kitazawa, N.; Kaneko, C. *Heterocycles* **1992**, *33*, 105. (f) Dugave, C.; Dubois, J.; Bory, S.; Gaudry, M.; Marquel, A. *Bull. Soc. Chim. Fr.* **1991**, 381.

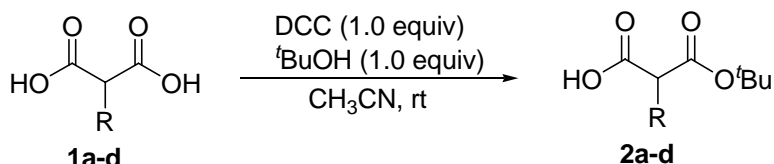
We have now extended our protocol from β -keto esters, to the desymmetrization-loke enantioselective fluorination of malonates and herein show that a DBFOX-Ph/ $\text{Zn}(\text{OAc})_2$ complex is an effective catalyst to give the optically active 2-fluorinated malonates with very high enantioselectivity. The 2-fluoromalonates can be selectively converted into 2-fluorinated hydroxy esters. The synthetic utility of the method was demonstrated by the synthesis of pharmaceutically attractive compounds, namely, chiral fluorinated α -benzyl- β -alanine, fluorinated β -lactam, and fluoro-alacepril. The synthesis of an HIV-1 protease inhibitor was also achieved through the chemoselective ester-amide exchange reaction of chiral fluorinated malonates (Scheme 21).



Scheme 21

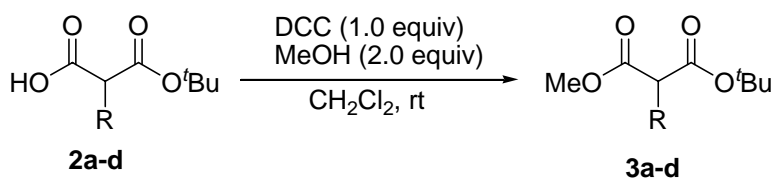
1. 2 Synthesis of Malonic esters:

Comercially available α -substituted malonic acids, which are benzyl, ethyl, methyl and *n*-butyl malonic acids were monoesterificated by using *tert*-butanol (1.0 equiv), *N,N'*-dicyclohexylcarbodiimide (DCC) (1.0 equiv) in acetonitrile solvent at room temperature, obtained the major amount of the product was formed mono *tert*-butyl ester corboxylic acids in high yields, which were used as crude compounds, without any purification for the next step (Scheme 22).



Scheme 22

The above crude product of monocarboxylic *tert*-butyl esters were diesterified by using methanol, DCC in dichloromethane at room temperature, after purified pure methyl *tert*butyl malonic diester compounds were obtained in moderate yields (Scheme 23, Table 1).

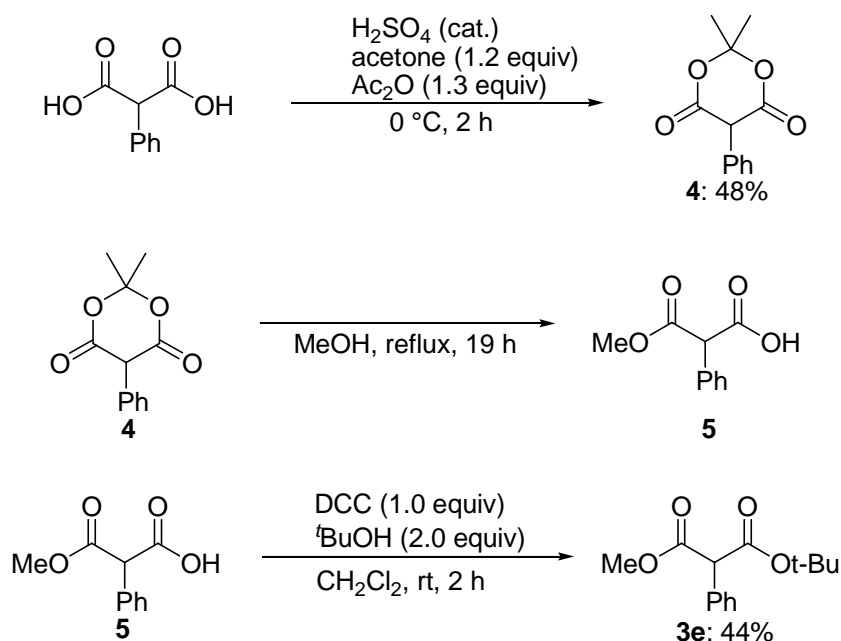


Scheme 23

Table 1

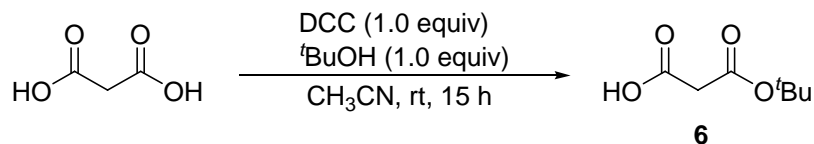
Entry	R	Substrate	Product	Time (h)	Yield (%)
1	Bn	1a	3a	3	40
2	Et	1b	3b	15	21
3	Me	1c	3c	15	39

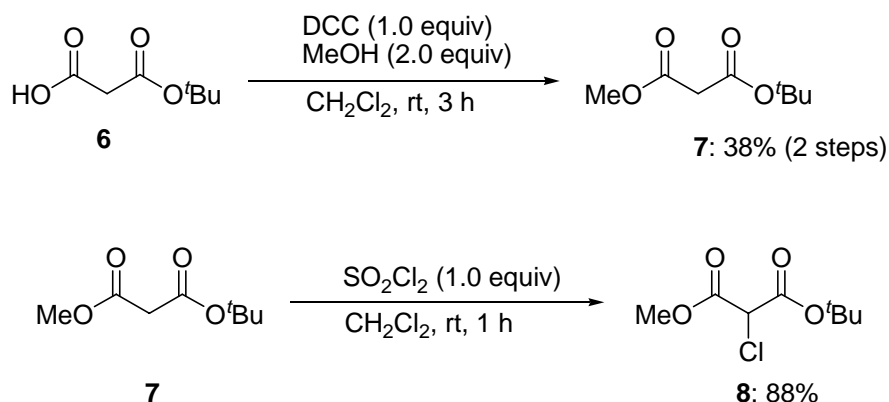
α -Phenyl malonic ester preparation was not successful by using above procedure, then we prepared other method, first step we prepared α -Phenyl maldrum acid by using acetone (1.2 equiv), acetic anhydride (1.3 equiv) and catalytic amount of sulfuric acid obtained in 48% yield. The next step which was refluxed in methanol for 19 hours, obtained the monoester carboxylic acid crude compound, which is proceeded to the next step for preparation of *tert*butyl, methyl ester compound, followed by the above step, in 44% yield (Scheme 24).



Scheme 24

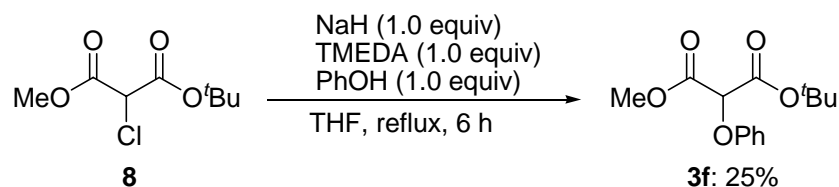
We also prepared α -phenoxy, thiophenyl, phthalimide and bromophthalimide substrates, these substrates malonic acids were not available in commercial. We prepared following this procedure, first we prepared simple malonic diester **7**, and which was subsequently α -chlorinated by using sulfuryl chloride (SO_2Cl_2) (1.0 equiv), in dichloromethane at room temperature for 1 h obtained **8** in 88% yield (Scheme 25).





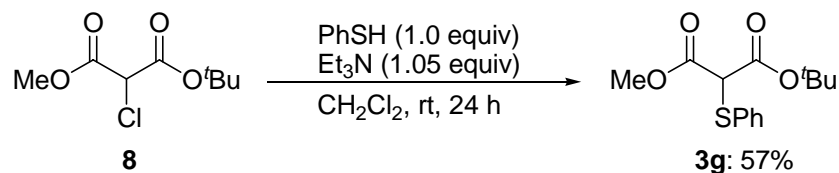
Scheme 25

Reaction of compound **8** with sodium phenoxide, prepared in situ from phenol (1.0 equiv), and sodium hydride (1.0 equiv), in refluxing tetrahydrofuran (THF) solution containing one equiv of hexamethylphosphoramide (HMPA) gave *t*-Butyl methyl 2-(phenoxy)malonate **3f** in 25% yield (Scheme 26).



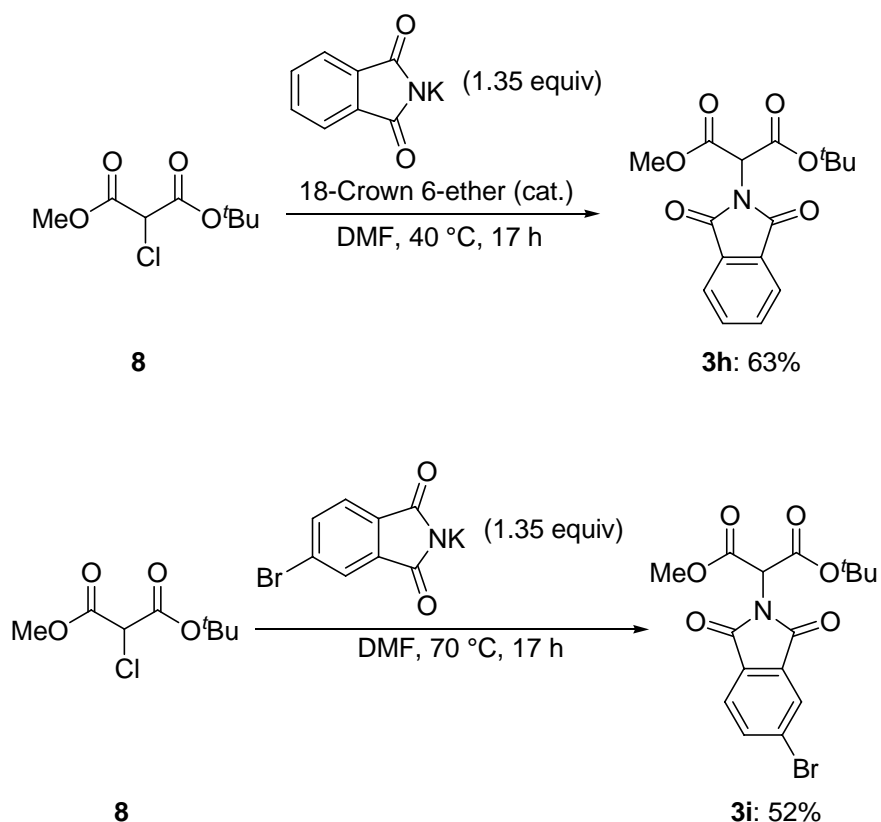
Scheme 26

α -Sulfenylated *tert*-Butyl methyl malonate ester was prepared in 57% yield by the reaction of commercially available thiophenol (1.0 eq), and equimolar triethylamine in dichloromethane at room temperature for 24 h obtained **3g** in 57% yield (Scheme 27).



Scheme 27

Furthermore, we prepared amide derivatives such as, compound **8** was reacted by using of potassium phthalimide in DMF for 17 hours obtained the product **3h** in 63% yield. Similar compound like 4-bromo phthalimide malonic ester **3i** was prepared same procedure in 52% yield (Scheme 28).



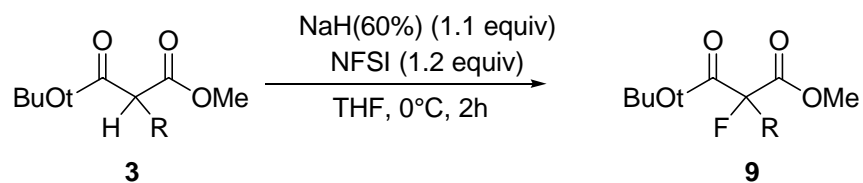
Scheme 28

1.3 Synthesis of Racemic α -Fluoro Malonic esters:

Firstly, we prepared racemic fluorination of various substrates malonic esters were fluorinated as shown in Table 2, all the substrates were fluorinated by using sodium hydride (1.1 equiv), and *N*-fluorobenzenesulfonimide (NFSI) (1.2 equiv) was in THF solvent at 0 °C for 2 hours, afforded the corresponding racemic α -substituted, α -fluoro malonic esters in high yields. Various α -alkyl substrates such as, methyl, ethyl and *n*-butyl (Table 2, entries 1-3) were obtained in good yields, and aromatic α - substrates, like phenyl and benzyl as well as hetero aromatic substrates (Table 2, entries 4-7) in good yields. Finally we also prepared amide substrates such as, phthalimide and 4-bromophthalimides (Table 2, entries 8-9) were in high yields, the results are collected in Table 2.

Fluorination of racemic malonates:

Table 2

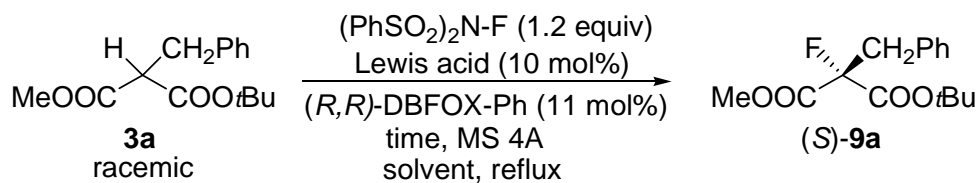


Entry	3	Substrate(R)	9	Yield(%)
1	3a	CH ₂ Ph	9a	62
2	3b	Et	9b	73
3	3c	Me	9c	81
4	3d	Bu	9d	90
5	3e	Ph	9e	91
6	3f	OPh	9f	55
7	3g	SPh	9g	60
8	3h	NPht	9h	83
9	3i	NPht(4-Br)	9i	79

1.4 Enantioselective Fluorination of Malonates (Screening for metal salts and solvents):

Since asymmetric electrophilic fluorination of β -keto esters and β -keto phosphates or other β -carbonyl compounds has been well developed to provide α -fluoro β -keto esters or their derivatives in high yields and with excellent selectivity. However there is no reports on enantioselective fluorination of malonates, initially we attempted the fluorination of racemic *tert*-butyl methyl 2-benzylmalonate (**3a**) was used for this reaction, and screening the various metal salts and solvents as shown in (Scheme 29 and Table 3). We first attempted our previous reported conditions for enantioselective fluorination of β -keto esters, namely, in the presence of metal salt (10 mol%), (*R,R*) DBFOX-Ph (11 mol%), and *N*-fluorobenzenesulfonimide in dichloromethane under the reflux for several hours. The (*S*)-2-fluoro-2-benzyl-*tert*-butyl methyl malonate (**9a**) was obtained in excellent yield and high enantioselectivity (Run 1; 97% yield and 89% ee). The conditions described for the enantioselective fluorination of oxindoles (Ni(OAc)₂·4H₂O in CH₂Cl₂) also gave good results (Run 2, 90% yield and 86% ee). These enantioselectivity are acceptable, but not excellent when compared to the enantioselective fluorination of β -keto esters and oxindoles.

Therefore, we turned our attention to increase the high enantioselectivity, so we optimized experiments for changing the Lewis acid metals such as Mg(ClO₄)₂, Mg(OTf)₂, Zn(SbF₆)₂, Zn(OTf)₂, Zn(OAc)₂ were performed. When we used Mg metal salts the enantioselectivity was very poor, in case of using Zn metal salts the enantioselectivity was improved up to 98% ee (Runs 3-7). Zn(OAc)₂ was found to be very effective for the desymmetrization like-enantioselective fluorination of malonates. Changing the solvents like Toluene (Run 8, 71% yield, 96% ee), diethyl ether (Run 9, 52% yield, 68% ee), and in case of using ethanol (Run 10, 49% yield, 86% ee) was obtained. Thus, the use of NFSI, DBFOX-Ph (11 mol%), and Zn(OAc)₂ (10 mol%) in CH₂Cl₂ at reflux became the standard conditions for our desymmetrization-like enantioselective fluorination reaction of malonates. Dichloromethane was determined to be a suitable solvent after screening the reaction with several different Lewis acid metal salts and solvents. Molecular sieves (4Å) was indispensable for achieving high enantiocontrol (Run 11, 47% yield, 59% ee), it can work as a dehydrating agent, and the exact role of the Molecular sieves is not clear.



Scheme 29

Table 3^a

Run	Lewis acid	Solvent	Time (h)	Yield ^b (%)	Ee (%) ^c
1	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	48	97	89
2	Ni(OAc) ₂ ·4H ₂ O	CH ₂ Cl ₂	48	90	86
3	Mg(ClO ₄) ₂	CH ₂ Cl ₂	48	62	7
4	Mg(OTf) ₂	CH ₂ Cl ₂	48	59	0
5	Zn(SbF ₆) ₂	CH ₂ Cl ₂	36	59	69
6	Zn(OTf) ₂	CH ₂ Cl ₂	36	94	87
7	Zn(OAc) ₂	CH ₂ Cl ₂	15	90	98
8	Zn(OAc) ₂	Toluene	24	71	96
9	Zn(OAc) ₂	Et ₂ O	62	52	68
10	Zn(OAc) ₂	EtOH	62	49	86
11 ^d	Zn(OAc) ₂	CH ₂ Cl ₂	90	47	59

a) The reaction of **3a** with NFSI was carried out in the presence of Lewis acid (10 mol%), (*R,R*)-DBFOX-Ph (11 mol%), MS 4A in solvent under reflux temperature. The absolute stereochemistry of **9a** was assigned to be *S* by derivatization.

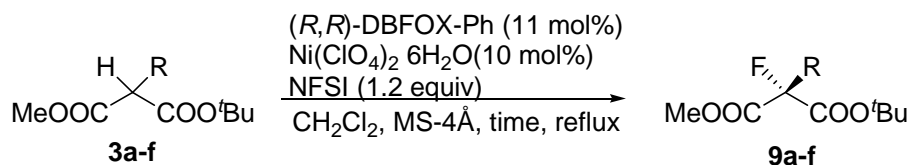
b) Isolated yield.

c) Determined by chiral HPLC analysis.

d) The reaction was carried out in the absence of MS 4Å.

1.5 Preparation of Optically Active Fluorinated Malonic Esters (various substrates using Ni(II)):

With the conditions now optimized, the scope of the desymmetrization fluorination reaction was investigated in terms of the range of substrates that could be tolerated (Table 4). Some optically active fluorinated malonic esters were prepared by asymmetric electrophilic fluorination according to our own method. The $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ /DBFOX-Ph combination was extremely general for the enantioselective fluorination of a broad range of malonates **9a-f** as shown in as (Table 4, Scheme 30). Various α -alkyl substrates such as, methyl, ethyl and *n*-butyl (Table 4, entries 2-4) were obtained chiral fluorinated malonates in good yields, with high enantioselectivities, and also aromatic substrates like phenyl, benzyl, and phenoxy malonates also fluorinated in good yields with high enantioselectivities were obtained.



Scheme 30

Table 4^a

Entry	3	R	9	Time (h)	Yield (%) ^b	Ee (%) ^c
1	3a	CH ₂ Ph	9a	48	97	89
2	3b	Et	9b	32	76	94
3	3c	Me	9c	36	81	95
4	3d	Bu	9d	62	69	94
5	3e	Ph	9e	48	96	99
6	3f	OPh	9f	48	52	91

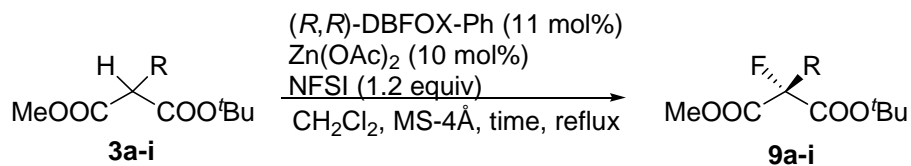
a) The reaction of **3** with NFSI was carried out in the presence of Lewis acid (10 mol%), (*R,R*)-DBFOX-Ph (11 mol%), MS 4A in solvent under reflux temperature. The absolute stereochemistry of **9** was assigned to be *S* by derivatization.

b) Isolated yield.

c) Determined by chiral HPLC or GC analysis.

1.6 Preparation of Optically Active Fluorinated Malonic Esters (various substrates using Zn(II)):

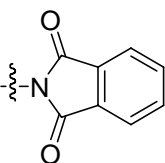
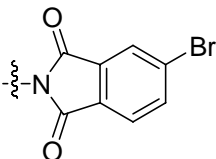
In the presence of Zn(OAc)₂ Lewis acid metal was found to be very effective for the desymmetrization like-enantioselective fluorination of malonates using the above developed procedure. We subsequently extended the scope of this reaction to other substrates like methyl, ethyl, *n*-butyl, **3b**, **3c**, **3d** were obtained high yields and extremely high enantioselectivities 95%, 94%, 94% in Table 5, entries 2-4). Aromatic substrates at α -position phenyl and benzyl (**3a**, **3e**) proceeded smoothly, affording the desired products in high yields and excellent enantioselectivity (98-99% ee). As in the case of using hetero atoms such as oxygen, sulfur substitutions were also underwent the fluorination reaction smoothly, giving the desired the product **3f**, **3g** in 85-81% yields, with 98-90% ees. In addition amino substitutions like phthalimide and 4-bromo phthalimide substrates were also subjected to the reaction in high enantioselectivities (entries 8-9). The desired products (*S*)-**9a-i** were obtained high yields, with excellent enantioselectivities of up to 99% ee (Table 5, entries 1-9). To our knowledge, this is the first example of the enantioselective fluorination of malonates **3** to provide chiral 2-fluorinated malonates **9** and this sequence surely serves as a potential non-enzymatic strategy for the desymmetrization of malonates. The reaction ee of the corresponding product was determined by chiral HPLC, the results are summarized in Table 5.



Scheme 31

Table 5^{a)}

Entry	3	R	9	Time (h)	Yield (%) ^{b)}	Ee (%) ^{c,d)}
1	3a	CH ₂ Ph	9a	15	90	98
2	3b	Et	9b	24	94	96
3	3c	Me	9c	24	90	99
4	3d	Bu	9d	36	93	99
5	3e	Ph	9e	24	95	99
6	3f	OPh	9f	15	85	98
7	3g	SPh	9g	24	81	90

8	3h		9h	18	91	93
9	3i		9i	24	93	97

a) The reaction of **3** with NFSI was carried out in the presence of Lewis acid (10 mol%), (*R,R*)-DBFOX-Ph (11 mol%), MS 4A in solvent under reflux temperature.

b) Isolated yield.

c) Determined by chiral HPLC or GC analysis.

d) The absolute configuration of **10c** was determined by comparing the optical rotation of the alcohol derivative of **27** with that of the known (*S*)-Ethyl 2-fluoro-3-hydroxy-2-methylpropanoate, and the stereochemistry of the other malonates **9** was tentatively assumed by analogy.

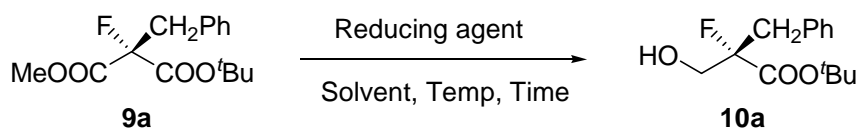
1.7 Optimization of Chemoselective Reduction of Chiral Fluorinated Malonate (**10a**)

In the described transformation, the observed chemical yields and enantioselectivities are excellent and the resulting chiral 2-fluorinated malonates **9** are potentially versatile starting materials for biologically important compounds. In this context, a synthetic application for biologically attractive molecules was attempted. The preparation of hydroxyl-ester derivatives **10** has typically, when first, we carried out the transformation Chemoselective reduction of (**9a**) (*S*)-1-*t*-Butyl 3-methyl 2-benzyl-2-fluoromalonate to **10a** was examined using DIBAL-H, LiAlH₄ or LiAl(*O**t*Bu)₃H. The selective reduction of malonates **9a** with hydride reagents like DIBAL-H (1.0 equiv) at -78°C in dichloromethane, provided trace amount of the product only (Table 6, Run 1). Even changing the equivalents as well as solvent also, there is no improvements to obtain yield (Table 6, Runs 2-4). Attempts with LiAlH₄ using same condition provided low yields, incase of 3.0 equiv (Table 6, Runs 5-6) was used over-reduction was occurred.

However, when **9a** was treated with 1.1 equivalents of LiAl(*O**t*Bu)₃H³³ at -78°C to room temperature in THF, even after 24 hours stirring, the reaction progress was slow and incomplete conversion (45% yield) to the desired hydroxyl-ester **10a** was observed (Table 6, Run 7). Increasing the amount of LiAl(*O**t*Bu)₃H same condition, yields also increased (Table 6, Runs 8-10). However, the reaction of **9a** with the amount of

³³ Ayers, T. A. *Tetrahedron Lett.* **1999**, 40, 5467.

LiAl(O^{*t*}Bu)₃H was used 5.0 equiv, the reaction was complete reduction to give an 89% yield of the desired fluorinated hydroxyl-ester derivative (*S*)-*t*-Butyl 2-fluoro-2-(hydroxymethyl)-3-phenylpropionate (**10a**). None of the diol product resulting in over-reduction was observed, it was hoped that the use of LiAl(O^{*t*}Bu)₃H would provide an intermediate aluminate species which would prevent further reduction due to the intrinsic steric nature of the aluminate species. The direct and chemoselective reduction of 2-fluoro malonate derivatives to the corresponding fluoro hydroxyl ester derivatives have been developed by the mild LiAl(O^{*t*}Bu)₃H system, which should have many applications for fluorinated biologically active molecules. To our delight, analysis of the corresponding hydroxyl ester (**10a**) by HPLC on chiral phase confirmed that no loss of optical purity had occurred (Scheme 32, Table 6).

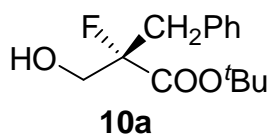


Scheme 32

Table 6

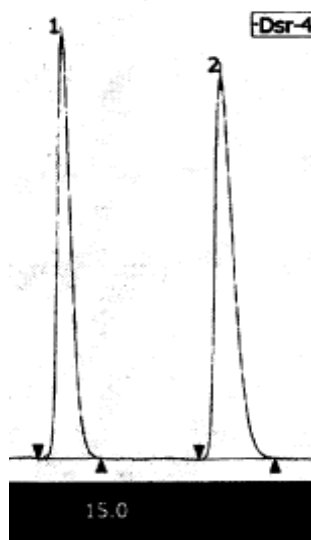
Run	Reducing agent	equiv	Solvent	Temp (°C)	Time (h)	Yield (%) ^a
1	DIBAL-H	1.0	CH ₂ Cl ₂	−78	0.5	trace
2	DIBAL-H	2.0	CH ₂ Cl ₂	−78	0.5	trace
3	DIBAL-H	3.0	CH ₂ Cl ₂	−78	0.5	trace
4	DIBAL-H	2.0	THF	−78	0.5	trace
5	LiAlH ₄	2.0	THF	−78	1.0	35
6	LiAlH ₄	3.0	THF	−78	2.0	30
7	LiAl(O ^{<i>t</i>} Bu) ₃ H	1.1	THF	−78 to rt	24	45
8	LiAl(O ^{<i>t</i>} Bu) ₃ H	3.0	THF	−78 to rt	2.0	76
9	LiAl(O ^{<i>t</i>} Bu) ₃ H	4.0	THF	−78 to rt	1.0	86
10	LiAl(O ^{<i>t</i>} Bu) ₃ H	5.0	THF	−78 to rt	1.0	89

a) Isolated yield



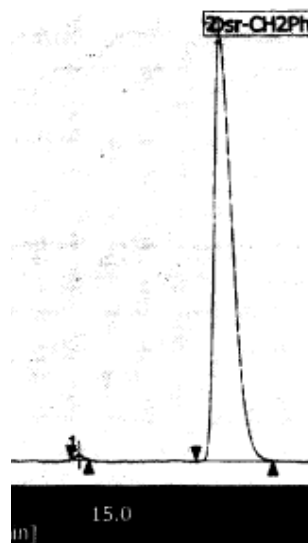
HPLC: (CHIRALCEL OJ-H hexane/*i*-PrOH = 90/10, 0.5 mL/min)

(99% ee)



Racemic compound of **10a**

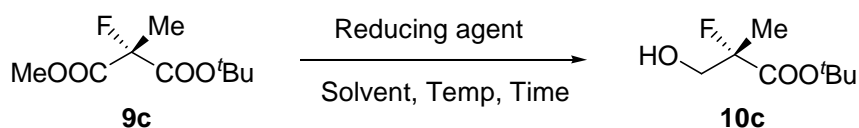
CH	PKNO	TIME	AREA%	HEIGHT%
9	1	14.26	50.16	57.36
9	2	17.52	49.83	42.63



CH	PKNO	TIME	AREA%	HEIGHT%
9	1	14.29	0.51	1.19
9	2	17.42	99.48	98.81

1.8 Optimization of Chemoselective Reduction of Chiral Fluorinated Malonate (**10c**)

Changing the substrate from benzyl **9a** to methyl **9c**, the selective reduction similar results was obtained, when compared to yields and optical purity.

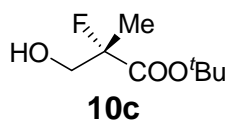
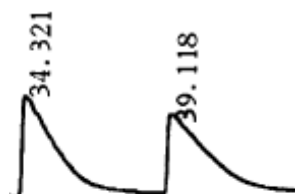


Scheme 33

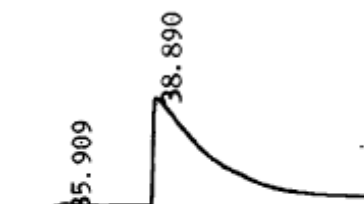
Table 7

run	Reducing reagent	equiv	solvent	temp (°C)	time (h)	yield (%) ^a
1	DIBAL-H	1.0	CH ₂ Cl ₂	-78	0.5	trace
2	DIBAL-H	2.0	CH ₂ Cl ₂	-78	0.5	trace
3	DIBAL-H	3.0	CH ₂ Cl ₂	-78	0.5	trace
4	DIBAL-H	2.0	THF	-78	0.5	trace
5	LiAlH ₄	2.0	THF	-78	1.0	31
6	LiAlH ₄	3.0	THF	-78	1.0	34
7	LiAl(O ^t Bu) ₃ H	1.0	THF	-78 to rt	24	37
8	LiAl(O ^t Bu) ₃ H	3.0	THF	-78 to rt	1.0	74
9	LiAl(O ^t Bu) ₃ H	4.0	THF	-78 to rt	1.0	79
10	LiAl(O ^t Bu) ₃ H	5.0	THF	-78 to rt	1.0	85

a) Isolated yield

GC (CP-CHIRASIL-DEX CB, 90 °C isothermal)
(99% ee)

- 35.0
- 37.5
- 40.0
- 42.5



- 35.0
- 37.5
- 40.0
- 42.5
- 45.0

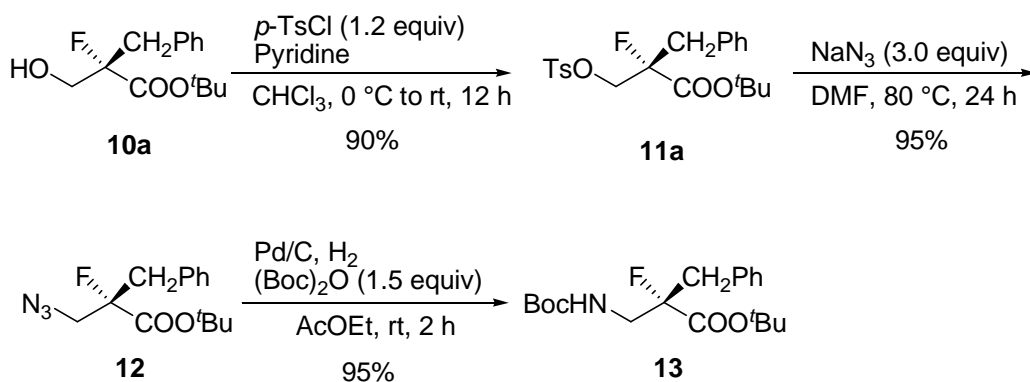
Racemic compound of **10c**

CH	PKNO	TIME	AREA%	HEIGHT%
1	1	34.32	51.13	1483
1	2	39.11	48.86	1183

CH	PKNO	TIME	AREA%	HEIGHT%
1	1	35.90	0.592	44
1	2	38.89	99.40	1602

1.9 Synthesis of α -Fluorinated β -Amino Acids (**13**):

A methodology for the synthesis of fluorinated α -benzyl- β -alanine (**13**) amino acid has been synthesized from compound (*S*)-*t*-Butyl 2-fluoro-2-(hydroxymethyl)-3-phenylpropionate (**10a**). The incorporation of fluorine at the 2-position of β -amino acids provided a significant synthetic challenge, and these compounds are known to influence its biological activity. First, the hydroxyl moiety (**10a**) was then protected using *p*-toluenesulfonyl chloride (*p*-TsCl) and pyridine in CHCl_3 at room temperature to give **11a** in 90% yield. Nucleophilic azidation of tosyl protected compound (**11a**) with NaN_3 (3.0 equiv) in DMF at 80°C for 24 hours, obtained (*S*)-*t*-Butyl 3-azido-2-benzyl-2-fluoropropionate (**12**) compound in 95% yield, and which was subsequent hydrogenolysis under H_2 in the presence of Pd/C and $(\text{Boc})_2\text{O}$ in AcOEt solvent afforded the α -Fluoro- α -benzyl- β -alanine target compound (**13**) in 95% yield (Scheme 34).



Scheme 34

1.10 Synthesis of α -Fluorinated β -Lactam (**16**):

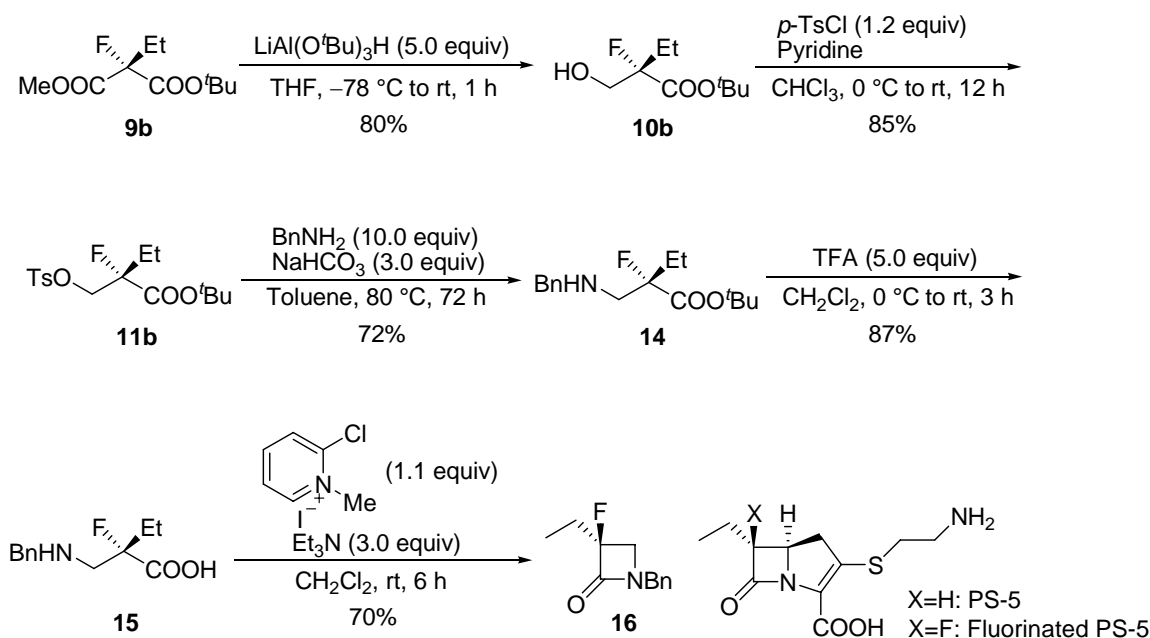
The utility of 2-fluorinated malonates was next demonstrated by synthesizing a 3-fluorinated β -lactam³⁴ (Scheme 35). β -lactam antibiotic compounds have long been attracting much interest as a synthetic target because of their biological activity and unique four-membered cyclic structure. Naturally-occurring carbapenem compounds such as PS-5 have marked β -lactamase-inhibitory activity, here we describes the fluorinated β -lactam from the fluoro malonte compounds, its key intermediate for the fluoro PS-5.

The (*S*)-*t*-Butyl 2-fluoro-2-(hydroxymethyl)butanoate (**10b**) was prepared from the chemoselective reduction of the (*S*)1-*t*-Butyl 3-methyl -2-fluoro-2-ethymalonate (**9b**) with the LiAl(O^{*t*}Bu)₃H (5.0 equiv) procedure mentioned above, to give the hydroxylated **10b** in (80% yield), which was protected by tosylate, by using *p*-Toluenesulfonyl chloride (*p*-TsCl) and pyridine in CHCl₃ at room temperature, which afforded the tosylate **11b** (85% yield). Nucleophilic amination of the resulting tosylate **11b** using benzylamine and sodiumbicarbonate in toluene solvent at 80°C for 72 h, provided the β -amino acid derivative **14** in 72% yield. Removal of *tert*-butyl ester from (*S*)-*t*-Butyl 2-((benzylamino)methyl)-2-fluorobutanoate with TFA (trifluoroacetic acid) excess amount was used, the obtained carboxylic compound (**15**) in 87% yield, which was followed by intramolecular cyclization by the Mukaiyama³⁵ procedure furnished the fluorinated β -lactam **16** in 70% yield, (*S*)-1-Benzyl-3-ethyl-3-fluoroazetidin-2-one (**16**) could be a useful synthon for the synthesis of fluorinated analogue of the antibiotic PS-5 (Scheme 35).³⁶

³⁴ (a) Abouabdellah, A.; Boros, L.; Gyenes, F.; Welch, J. T. *J. Fluorine Chem.* **1995**, 72, 255. (b) Abouabdellah, A.; Welch, J. T. *Tetrahedron: Asymmetry* **1994**, 5, 1005. (c) Sekiguchi, T.; Sato, K.; Ishihara, T.; Konno, T.; Yamanaka, H. *Chem. Lett.* **2004**, 33, 666. (d) Genet, J. P.; Durand, J. O.; Ronald, S.; Savignac, M.; Jung, F. *Tetrahedron Lett.* **1997**, 38, 69. (e) Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Sundee, D.; Vaccaro, W.; Sher, R.; Browne, M. E.; Margaret, E.; Zhao, H. *J. Med. Chem.* **1996**, 39, 3684. (f) Welch, J. T.; Araki, K.; Keweck, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, 58, 2454.

³⁵ (a) Iwasawa, N.; Hung, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 14, 1045. (b) Hung, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 13, 1465.

³⁶ (a) Sakamoto, M.; Yamamoto, K.; Isshiki, K.; Ishikura, T.; Fukagawa, Y.; Yoshioka, T. *J. Antibiotics* **1990**, 43, 1254. (b) Okamura, K.; Hirata, S.; Okumura, Y.; Fukagawa, Y.; Shimauchi, Y.; Kouno, K.; Ishikura, T. *J. Antibiotics* **1978**, 31, 480.



Scheme 35

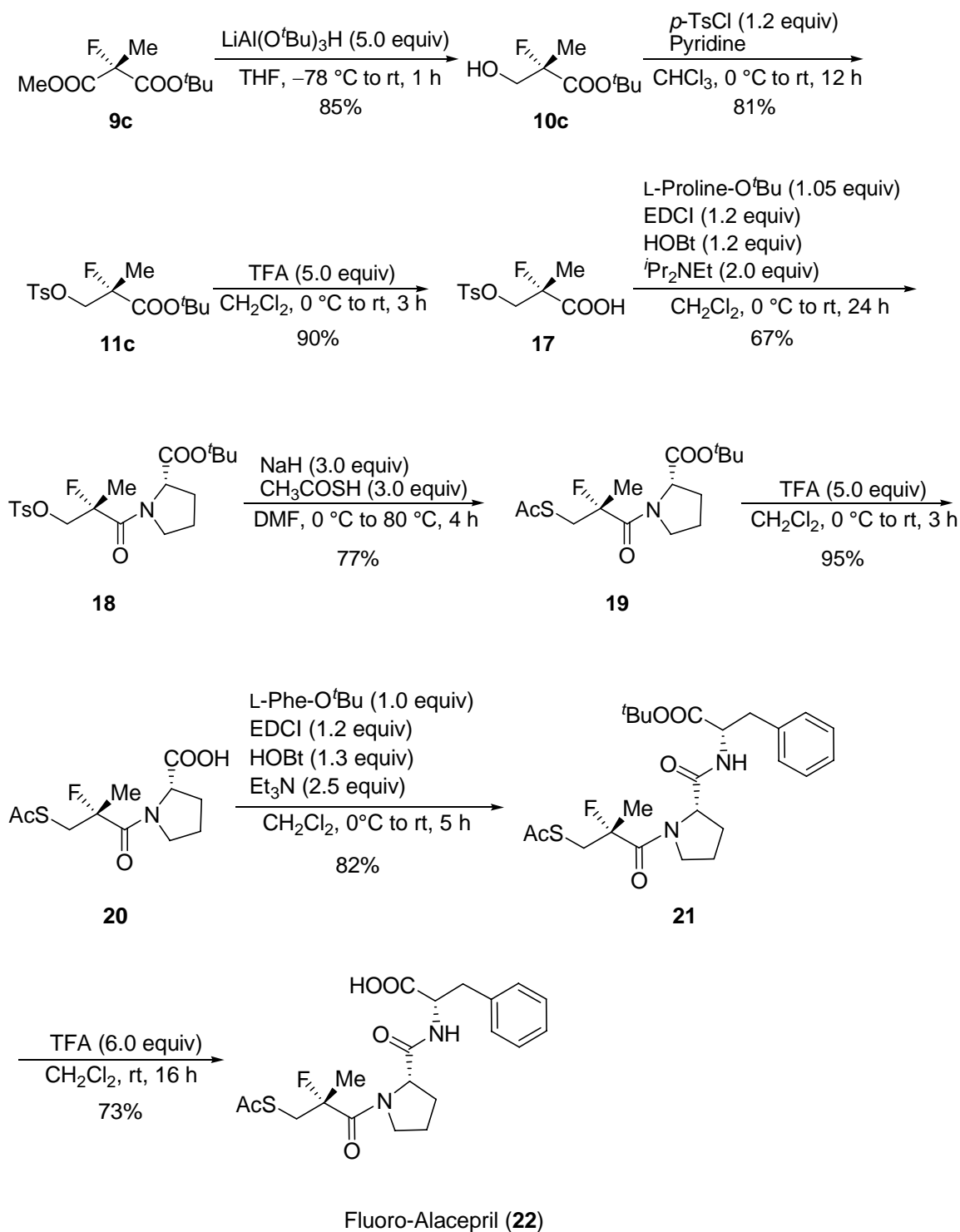
1.11 Synthesis of α -Fluoro Alacepril (22):

Furthermore, the synthesis of fluoro-Alacepril was examined. Alacepril is an orally active antihypertensive angiotensin-converting enzyme (ACE) inhibitor synthesized in 1978,³⁷ developed and launched in Japan in 1988, next to Captopril. Structurally, Alacepril is characterized by a tripeptide-like compound consisting of L-phenylalanine, L-proline and 3-mercapto-(2*S*)-methylpropionic acid. As in the case of Captopril, the presence of the 2-methyl unit with (*S*)-configuration in Alacepril is indispensable for its potential inhibitor activity against ACE. Fluoro Captopril was synthesized by Prof. Kitazume, as part of our continuous efforts to develop stereocontrolled synthesis in fluorine chemistry, we therefore are interested in the previously unknown fluoro-Alacepril as a non-epimerized isostere of Alacepril (Scheme 36).³⁸

³⁷ Ogihara, T.; Tachi, Y.; Uno, H. *Cardiovasc. Drug Reviews* **1992**, *10*, 88.

³⁸ (a) Chopra, M.; Beswick, H.; Claperton, M.; Dargie, H. J.; Smith, W. E.; McMurray, J. J. *Cardiovasc. Pharmacol.* **1992**, *19*, 330. (b) Shultz, P. J.; Raji, L. *Br. J. Clin. Pharmacol.* **1989**, *28*, 151. (c) Przykienk, K.; Kloner, R. A. *Am. Heart J.* **1991**, *121*, 1319. (d) Ribout, C.; Cardinal, R.; Gouin, L.; Moreau, P.; Godin, D.; Vermeulen, M.; Champlain, J.; Rochette, L.; Nadeau, R. *Cardiovas. Res.* **1994**, *28*, 221.

We present here some results of synthetic approaches to F-analogue of material used Angiotension converting enzyme inhibitor. Total synthesis of (*S*)-fluoro-Alacepril was accomplished in 8 steps starting from chiral malonate **9c**, based on this strategy. Optically active (*S*)-1-*t*-Butyl 3-methyl 2-methyl-2-fluoromalonate (**9c**) was treated with LiAl(O^{*t*}Bu)₃H in THF to give (*S*)-*t*-Butyl 2-fluoro-2-(hydroxymethyl)propionate (85% yield) (**10c**) followed by tosylation with *p*-TsCl and pyridine in CHCl₃ to give tosylate **11c** in 81% yield. After removal of *tert*-butyl ester with TFA dichloromethane at room temperature obtained carboxylic compound (**17**) in 90% yield. The proline-attached compound was then obtained from **17**, coupling to L-Pro-O^{*t*}Bu using standard peptide coupling conditions like in the presence of Diisopropylethylamine as a base, EDCI and HOBt, afforded peptide compound (**18**) in 67% yield. Nucleophilic substitution of tosyl protected compound (**18**) with MeCOSNa (3.0 equiv) in DMF at 80°C for 4 hours, to obtained thioacetyl (**19**) product in 77% yield, followed by TFA treatment of the resulting *tert*-butyl ester gave the carboxylic acid compound **20**. Subsequent coupling to L-phenylalanine *tert*-butyl ester with the condition of EDCI, HOBt and triethyl amine gave **21** in 82% yield. Finally by using TFA treatment afforded fluoro-Alacepril (**22**) in good overall yield 16% (Scheme 36).

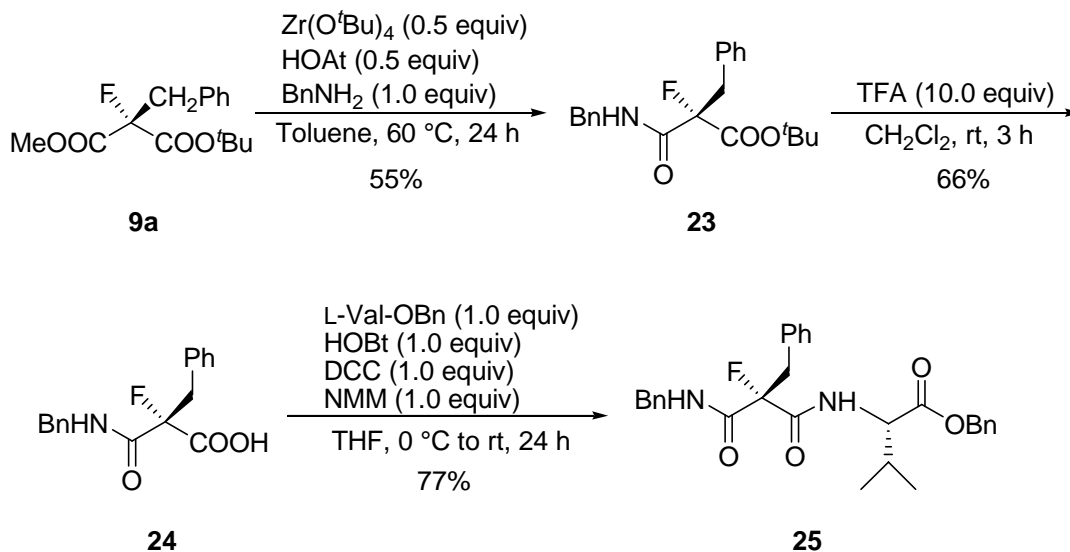


Scheme 36

1.12 Synthesis of HIV-1 inhibitor (25):

Finally, the synthesis of optically active fluorinated retroamide isostere 2-Fluoro-2-(bezyloxy-L-valylcarbonyl)-3-phenylpropanoic acid benzylamide (**25**) was carried out. Compound **25** is an HIV-1 protease inhibitor which was prepared by Welch et al. from enantiomerically pure 3-fluoro-2-azetidinones via ring opening reaction.³⁹ However, the synthesis requires multiple-step transformations including diastereoselective fluorination of 2-azetidinones and ring opening reaction. The fluorinated malonate (*S*)-**9a** thus synthesized can be easily transformed into fluorinated retroamide isostere **25** in only three steps via unsymmetrical ester-amide **23** as described in Scheme 37.

Chemoselective ester-amide exchange reaction⁴⁰ of (*S*)-1-*t*-Butyl 3-methyl 2-benzyl-2-fluoromalonate (**9a**) was successfully proceeded in the presence of group (IV) metal alkoxide $\text{Zr}(\text{O}^i\text{Bu})_4$ in conjunction with activator HOAt by using benzylamine (1.0 equiv) in toluene at 60°C, to give the unsymmetrical ester-amide **23** in good yield. The chemoselectivity observed apparently resulted from the larger bulkiness of *tert*-butyl group as compared to methyl ester moiety. Subsequent TFA treatment of **23** gave the carboxylic acid compound **24** and finally, coupling of **24** with L-Val-OBn proceeded smoothly when affected by DCC with HOBT and *N*-methyl morpholine as a base in THF providing the target HIV-1 protease inhibitor (*S*)-2-Fluoro-2-(bezyloxy-L-valylcarbonyl)-3-phenylpropanoic acid benzylamide (**25**) in 77% yield (Scheme 37).



Scheme 37

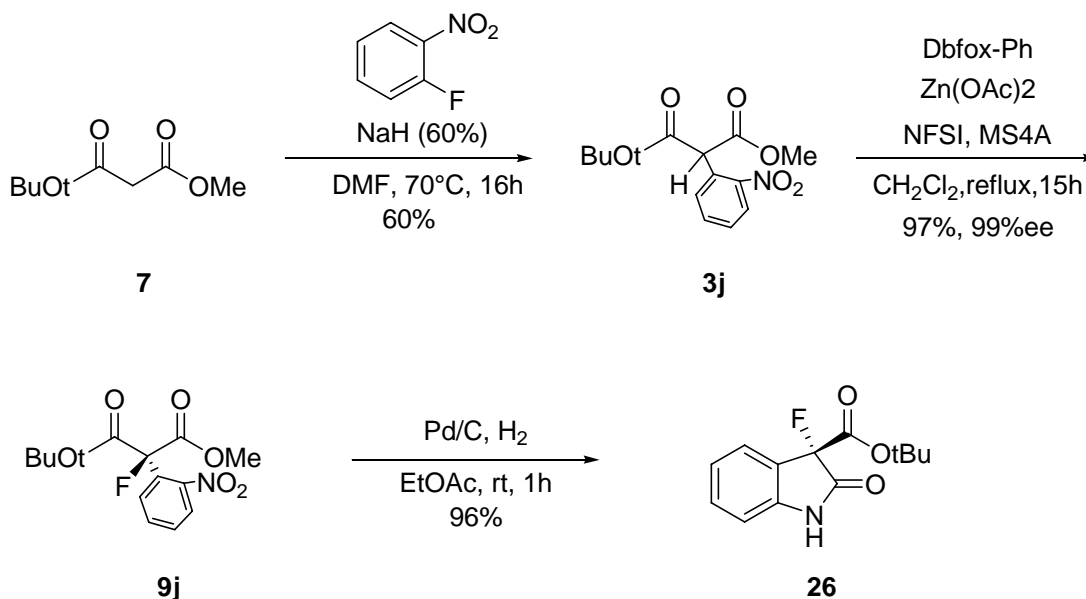
³⁹ (a) Abouabdellah, A.; Boros, L.; Gyenes, F.; Welch, J. T. *J. Fluorine Chem.* **1995**, 72, 255. (b) Abouabdellah, A.; Welch, J. T. *Tetrahedron: Asymmetry* **1994**, 5, 1005.

⁴⁰ Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, Jr., J. A. *J. Am. Chem. Soc.* **2005**, 127, 10039.

1.13 Efficient synthesis of fluoro-oxindole by fluorinated malonate (26):

A short and high yielding process has been developed for the synthesis of fluoro oxindole, first we attempted to prepare *ortho*-nitrophenyl⁴¹ substrate malonate (**3j**) was prepared from 4-fluoronitrobenzene by using sodium hydride as a base in DMF solvent, obtained the product in 60% yield. Further enantioselective fluorination reaction was performed in same our DBFOX-Ph/Zn(II) metal complex and NFSI fluorinating reagent, afforded (*S*)-1-*tert*-butyl 3-methyl 2-fluoro-2-(2-nitrophenyl)malonate (**9j**) in high yield (97%) with 99% optical purity.

The treatment of nitro adduct (**9j**) was hydrogenated and cyclization using palladium carbon in presence of hydrogen pressure in ethylacetate solvent at room temperature for 1 hour, the resulted *tert*-butyl 3-fluoro-2-oxindoline-3-carboxylate (**26**) in 96% yield (Scheme 38).

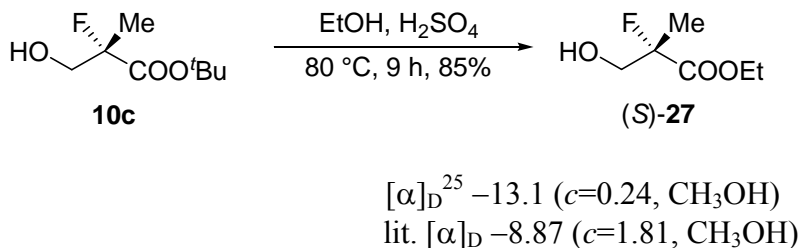


Scheme 38

⁴¹ (a) Selvakumar, N.; Yadi reddy, B.; Sunil kumar G.; Iqbql, J. *Tetrahedron Lett.* **2001**, 42, 8395.

1.14 Determination of the absolute configuration of (10c)

The absolute configuration of **9c** was determined to be *S* by comparing the optical rotation of **27** with the reported value by Kitazume⁴².



Scheme 39

The stereochemistry of the resulting fluoro-malonates **9** can be easily explained by the approach of fluorinating agent, NFSI, from the less hindered *Si* face of the substrates/*Zn*(II)/DBFOX-Ph complex, as explained in our previous work for the fluorination reaction of β -keto esters catalyzed by *Ni*(II)/DBFOX-Ph (Figure 5).

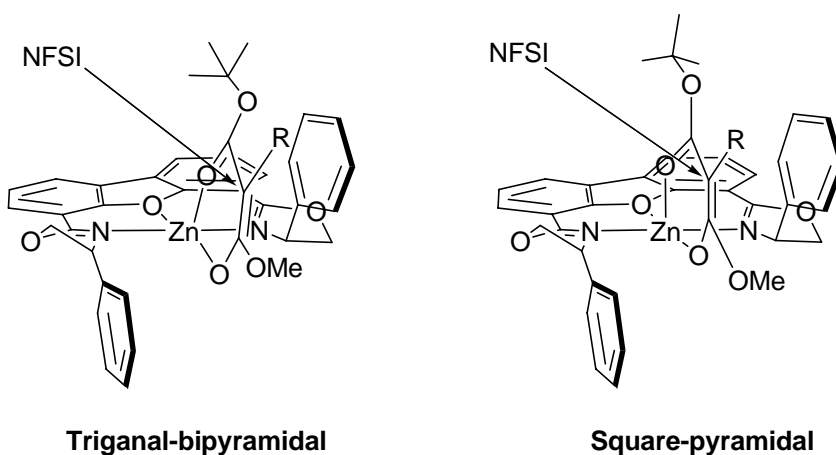


Fig. 5

⁴² Kitazume, T.; Yamamoto, T. *J. Fluorine Chem.* **1987**, 35, 467.

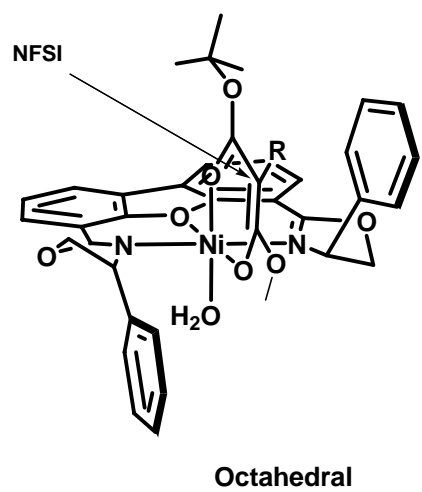


Fig 6

1.15 Conclusion:

In conclusion, we have described the first highly enantioselective fluorination of malonates catalyzed by DBFOX-Ph and $\text{Zn}(\text{OAc})_2$. This desymmetrization-like approach for chiral 2-fluoromalonates showed higher enantioselectivity and generality than the corresponding enzymatic approaches. The 2-fluoromalonates **9** can be easily converted to the corresponding chiral fluorinated hydroxyl esters **10** by chemoselective reduction with $\text{LiAl}(\text{O}t\text{Bu})_3\text{H}$. The 2-fluoromalonates **9** are also able to transform into the unsymmetrical ester-amides by chemoselective ester-amide exchange reaction. All the derivatives are valuable starting materials for the preparation of pharmaceutically attractive molecules and we have demonstrated the preparation of fluorinated β -amino acids and β -lactams. The total syntheses of ACE inhibitor, fluoro-Alacepril and HIV-1 protease inhibitor, fluorinated retroamide isoster were also accomplished. Our chemical desymmetrization procedure provides an efficient alternative to the usual microbial transformations for the preparation of fluorinated chiral building blocks.

Chapter 2

DBFOX-Ph/metal complexes: Evaluation as catalysts for enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones

2.1 Introduction:

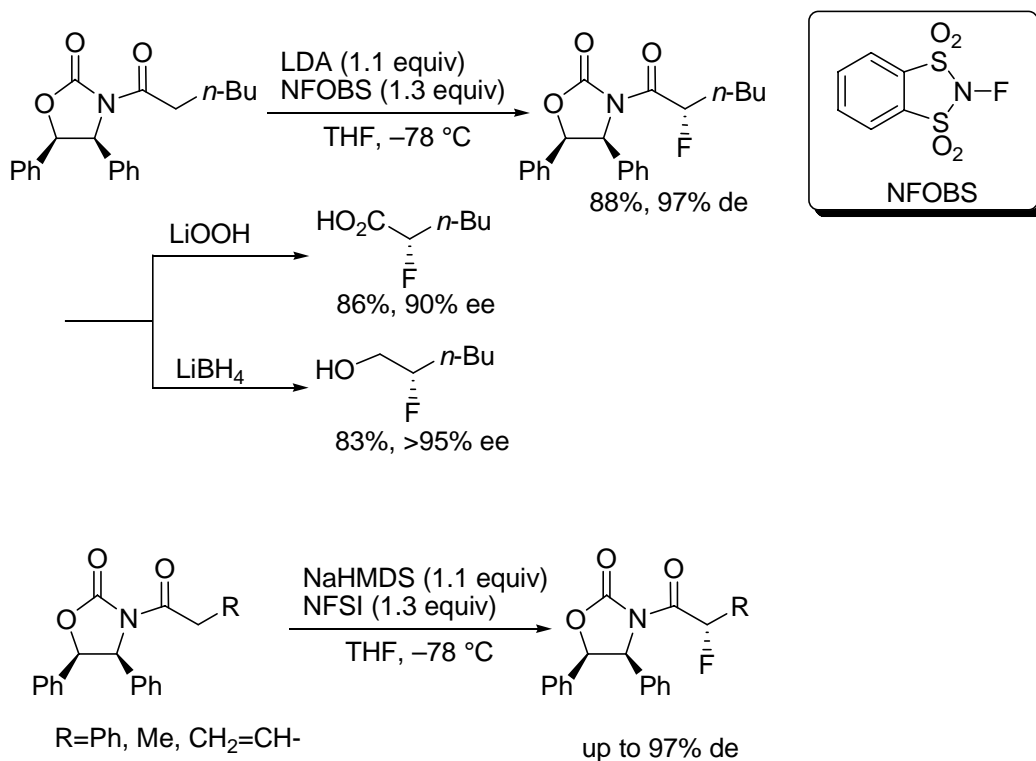
Because replacement of hydrogen atoms or hydroxyl groups in the parent compounds with fluorine atoms some time leads to improvement of their biological activity, development of efficient methods for the synthesis of optically active fluorinated compounds is extremely important. After pioneering work on enantioselective fluorination using chiral fluorinating reagents, catalytic asymmetric fluorination has witnessed great progress in the past few years. Several chiral metal complexes and phase transefer catalysts were developed for the fluorination of active methane compounds. In addition catalytic asymmetric fluorination of aldehydes recently became feasible using chiral secondary amines.

In contrast, the preparation of chiral α -fluorocarboxylic acids has not been explored as thoroughly, even though such compounds have great potential in medicinal chemistry. Only a few synthetically useful diastereoselective fluorination reactions of ester equivalents are known, and these compounds probably owing to the difficulty in the in situ generation of metal enolats (or enols) of ester equivalents under catalytic conditions. As the aryl acetic moiety is found in various important medicines, such as nonsteroidal anti-inflammatory drugs, the availability of chiral α -monofluorinated aryl acetic acids is expected to be useful for drug synthesis.

Recently catalytic method has been developed by Sodeoka group. They have also recently reported the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with their extended catalytic system, NiCl_2 -BINAP/ R_3SiOTf -lutidine with high enantioselectivities. This study is useful because, up until now, the fluorinated products obtained by Sodeoka's method have been prepared by diastereoselective methods.

Independently, our group has focused on the development of enantioselective fluorination and related reactions using bis(oxazoline) ligands, Box-Ph ((*S,S*)-bis(4-phenyloxazoline)) and DBFOX-Ph ((*R,R*)-4,6-dibenzofurandiyl-2-2'-bis(4-phenyloxazoline)). As an extension of this study, we herein evaluate our DBFOX-Ph/metal catalysis for the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with *N*-fluorobenzenesulfonimide (NFSI).

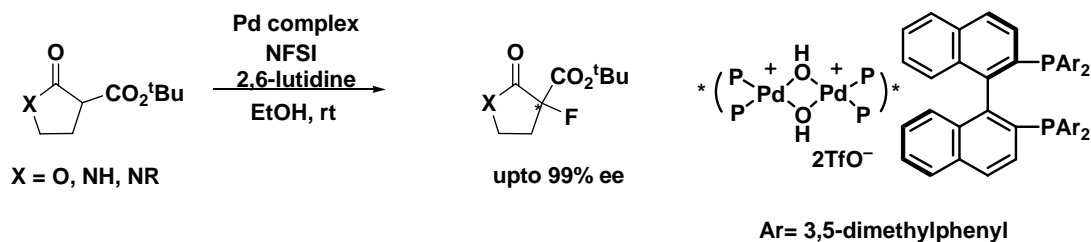
Davis and co-workers were reported in 1992 and 1998 closely related structures of fluorinating reagents, *N*-fluoro-2,10-(3,3-dichlorocamphorsultam) affords α -fluoro carbonyl compounds in good yield and up to 75% ee. Diastereoselective fluorination of chiral imide enolates to α -fluoro carboximides⁴³ in 86-95% de, using electrophilic fluorinating reagent *N*-fluoro-*o*-benzenedisulfonimide (NFOBS). The removal of the oxazolidinone auxiliary to furnish α -fluoro acids and β -fluoro alcohols with good ee's (Scheme 40).



Scheme 40

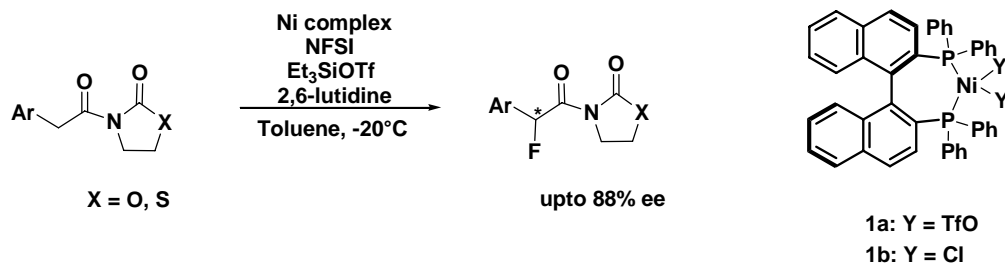
⁴³ (a) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, 33, 1153. (b) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, 39, 6135.

Prof. Sodeoka reported the enantioselective fluorination of *tert*-butoxy carbonyl lactones and lactams⁴⁴, which were less acedic substrates, asymmetric fluorinated catalyzed by the chiral palladium-binap complexes in an alcoholic solvent, and 2,6-lutidine as a cocatalyst was used, obtained in good yields with high enantioselectivity (Scheme 41).



Scheme 41

Recently prof. Sodeoka developed the first catalytic asymmetric fluorination reaction for ester equivalents of thia and oxazolidinone aryl acetyl⁴⁵ moieties. In the presence of NiCl₂-binap/R₃SiOTf/2,6-lutidine triad, the monofluorinated compounds were formed with high enantioselectivity (88% ee) and up to 99% yield (Scheme 42).

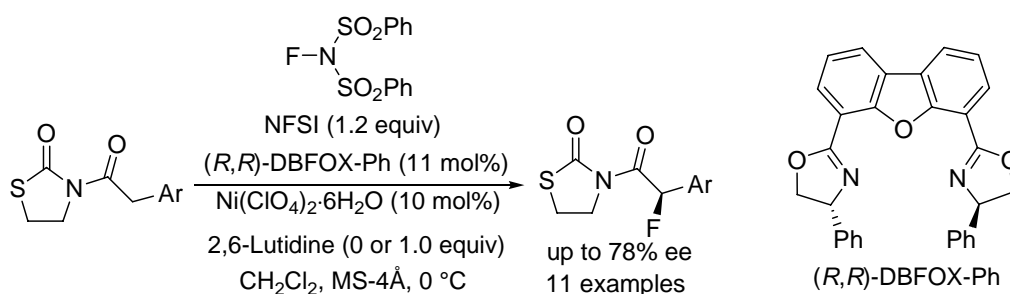


Scheme 42

⁴⁴ Suzuli, T, Goto, T, Hamashima, Y.; Sodeoka, M. *J. Org. Chem.* **2006**, 72, 246.

⁴⁵ Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2007**, 46, 5435.

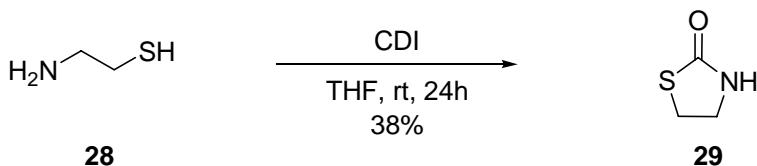
We examined the catalytic enantioselective fluorination of 3-(2- arylacetyl)-2-thiazolidinones **30** with *N*- fluorobenzenesulfonimide (NFSI) by DBFOX-Ph/metal complexes under a variety of conditions. After optimization of the metal salts, solvents and additives, we found that the fluoro-2-thiazolidinones **31** were obtained in good to high yields with moderate to good enantioselectivities (up to 78% ee) when the reaction was carried out in the presence of DBFOX-Ph (11 mol%), Ni(ClO₄)₂·6H₂O (10 mol%) and 2,6-lutidine (0 or 1.0 equiv) in CH₂Cl₂ (Scheme 43).



Scheme 43

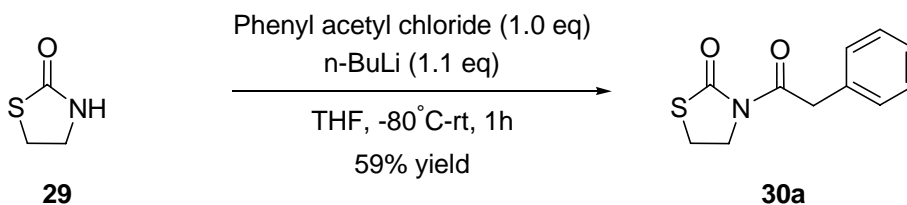
2.2 Synthesis of α -aryl acetyl thiazolidinones:

Thiazolidin-2-one was prepared by using commercially available 2-aminothiol in the presence of CDI (carbonyl diimidazole) in THF solvent at room temperature for 24 hours in 38% yield (Scheme 44).



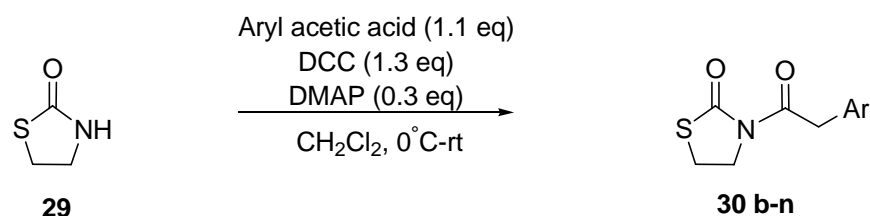
Scheme 44

Phenyl acetyl substrate thiazolidinone (**30a**) was prepared by treatment of thiazolidinone (**29**), *n*-butyl lithium and phenyl acetyl chloride in THF at -80°C to room temperature for 1 hour obtained the product in 59% yield (Scheme 45).



Scheme 45

All the starting materials were prepared by commercially available various aryl acetic acids, coupling with thiazolidinone (**29**) in the presence of DCC, DMAP condition in dichloromethane at room temperature for few hours, various substituted 3-(2-arylacetyl)-2-thiazolidinones products (**30 b-m**) were obtained in good yields (Scheme 46, Table 8).



Scheme 46

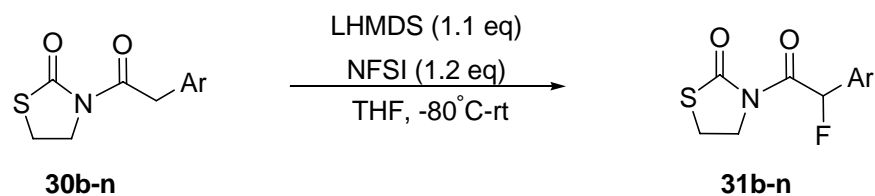
Table 8

Entry	Aryl	Time(h)	30	Yield (%)
1	C ₆ H ₄ - <i>o</i> -OMe	6	30b	66
2	C ₆ H ₄ - <i>m</i> -OMe	1	30c	96
3	C ₆ H ₄ - <i>p</i> -OMe	1	30d	99
4	C ₆ H ₄ - <i>o</i> -Me	5	30e	91
5	C ₆ H ₄ - <i>m</i> -Me	6	30f	93
6	C ₆ H ₄ - <i>p</i> -Me	4	30g	72
7	C ₆ H ₄ - <i>p</i> -F	4	30h	83
8	C ₆ H ₄ - <i>p</i> -Br	1	30i	58
9	1-Naphthyl	1	30j	96
10	2-Naphthyl	1	30k	97
11	C ₆ H ₄ - <i>p</i> -CF ₃	24	30l	46
12	C ₆ H ₄ - <i>o</i> -Cl	12	30m	46
13	C ₆ H ₄ - <i>p</i> -Cl	12	30n	96

2.3 Synthesis of racemic fluorination of α -aryl acetic acid derivatives:

Firstly, we prepared racemic fluorination of various substrates aryl acetates were fluorinated as shown in Table 9, all the substrates were fluorinated by using LiHMDS (1.1 eq), and *N*-fluorobenzenesulfonimide (NFSI) (1.2eq) was in THF solvent at -80°C

for 2 hours, afforded the corresponding racemic α -fluoro 3-(2-arylacetyl)-2-thiazolidinones (**31b-n**) products in good yields. The results are summarized in Table 2. The fluorination reaction was not very sensitive to substitution in the position of the phenyl group and the desired products with methoxy or methyl groups at the *o*-, *m*-, or *p*-position of the benzene ring were obtained in high yields (entries 1—6). The reactions of fluoro or bromo-substituted **31h,i** and bulky-substituted **31j,k** afforded the desired products **31b-n** in good yields (Scheme 47, Table 9).



Scheme 47

Table 9

Entry	30	Aryl	Time(h)	31	Yield (%)
1	30b	C ₆ H ₄ - <i>o</i> -OMe	3	31b	51
2	30c	C ₆ H ₄ - <i>m</i> -OMe	3	31c	63
3	30d	C ₆ H ₄ - <i>p</i> -OMe	2	31d	70
4	30e	C ₆ H ₄ - <i>o</i> -Me	3	31e	28
5	30f	C ₆ H ₄ - <i>m</i> -Me	4	31f	38
6	30g	C ₆ H ₄ - <i>p</i> -Me	3	31g	45
7	30h	C ₆ H ₄ - <i>p</i> -F	4	31h	32
8	30i	C ₆ H ₄ - <i>p</i> -Br	5	31i	50
9	30j	1-Naphthyl	3	31j	66
10	30k	2-Naphthyl	1	31k	57
11	30l	C ₆ H ₄ - <i>p</i> -CF ₃	1	31l	40
12	30m	C ₆ H ₄ - <i>o</i> -Cl	2	31m	17
13	30n	C ₆ H ₄ - <i>p</i> -Cl	6	31n	40

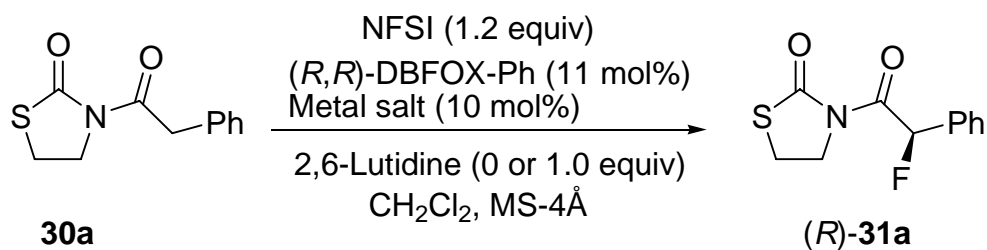
2.4 Optimisation of the Conditions for DBFOX-Ph/Ni(II)-Catalysed Enantioselective Fluorination of 3-(2-Phenylacetyl)-2-thiazolidinone (**31a**)

Our previous studies for the DBFOX-Ph/Ni(II)-catalyzed enantioselective fluorination of β -keto esters have shown that the optimal reaction conditions require NFSI as the fluorine source and a catalytic amount of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in CH_2Cl_2 at room temperature. Therefore, we first attempted the reaction of **30a** with the same conditions and found that the desired fluorinated product **31a** was obtained in 42% yield with 69% ee (Table 1, run 1). The reaction at higher temperature (40 °C) improved the yield to 62% with slightly lower enantioselectivity (63% ee, run 2). The reaction time in these experiments was shortened by the addition of 1 equiv of 2,6-lutidine and **31a** was obtained in 87% yield with 66% ee at room temperature (run 3). Both the yield and selectivity were improved to 90% and 74% ee when the reaction was performed at 0 °C (run 4). The highest ee value of **31a** was obtained at -20 °C, but resulted in a decrease in yield (24%, 79% ee, run 5). Changing the metal salts like $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ and $\text{Zn}(\text{OAc})_2$, were did not improve the results (runs 6 and 7).

The absolute stereochemistry of **31a** was determined by comparing the optical rotation and HPLC analysis with the literature values⁴⁶. Although the enantioselectivities are moderate to good in these examples (63—79% ees), the results are quite impressive because the fluorination proceeds even in the absence of base (runs 1 and 2). That is, both $\text{Ni}(\text{ClO}_4)_2$ -DBFOX-Ph (unary system, runs 1 and 2) and $\text{Ni}(\text{ClO}_4)_2$ -DBFOX-Ph/lutidine (binary system, runs 3—6) are moderately effective in the enantioselective fluorination of **31a**.

According to the report by Sodeoka using their NiCl_2 -BINAP/ R_3SiOTf -lutidine (ternary system, up to 88% ee obtained), the reaction requires both R_3SiOTf and lutidine. They mentioned in the paper that a binary system consisting of $\text{Ni}(\text{OTf})_2$ -BINAP complex and 2,6-lutidine failed to promote the asymmetric fluorination. We also briefly attempted the fluorination of **30a** using the (*S,S*)-Box-Ph ligand instead of DBFOX-Ph. While the Box-Ph/ $\text{Cu}(\text{OTf})_2$ catalyst was not effective (run 8), the Box-Ph/ $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ catalyst gave the desired product **31a** in 33 % yield with low enantioselectivity (15% ee, run 9) (Scheme 48, Table 10).

⁴⁶ Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 5435.



Scheme 49

Table 10

Run	Metal salt	2,6-Lutidine (equiv)	Temp (°C)	Time	Yield (%)	Ee (%) ^a
1	Ni(ClO ₄) ₂ ·6H ₂ O	none	rt	6 d	42	69
2	Ni(ClO ₄) ₂ ·6H ₂ O	none	40	4 d	62	63
3	Ni(ClO ₄) ₂ ·6H ₂ O	1.0	rt	17 h	87	66
4	Ni(ClO ₄) ₂ ·6H ₂ O	1.0	0	20 h	90	74
5	Ni(ClO ₄) ₂ ·6H ₂ O	1.0	−20	4 d	24	79
6	Ni(OAc) ₂ ·4H ₂ O	1.0	rt	4 d	55	72
7	Zn(OAc) ₂	1.0	rt	3 d	NR	—
8 ^{b,c}	Cu(OTf) ₂	1.0	0	2 d	NR	—
9 ^b	Ni(ClO ₄) ₂ ·6H ₂ O	1.0	0	2 d	33	15 ^d

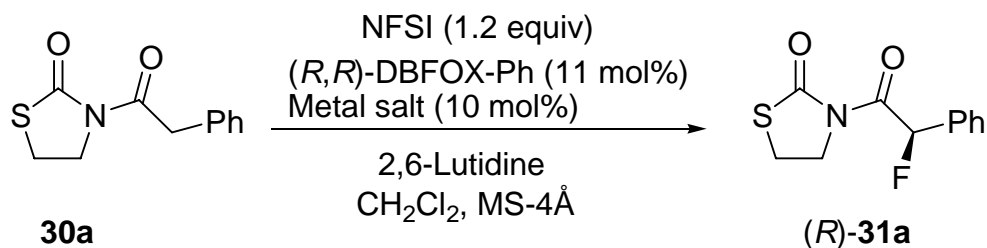
a) Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of **31a** was determined by comparison with the optical rotation and HPLC analysis in the literature⁴.

b) (*S,S*)-Box-Ph (11 mol%) was used instead of (*R,R*)-DBFOX-Ph.

c) Ether was used as solvent.

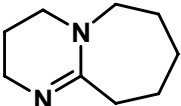
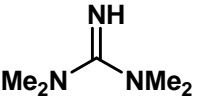
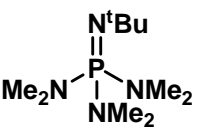
d) (*S*)-**31a** was obtained (opposite enantiomer).

2.5 Optimisation of the Base for DBFOX-Ph/Ni(II)-Catalysed Enantioselective Fluorination of 3-(2-Phenylacetyl)-2-thiazolidinone (31a)



Scheme 49

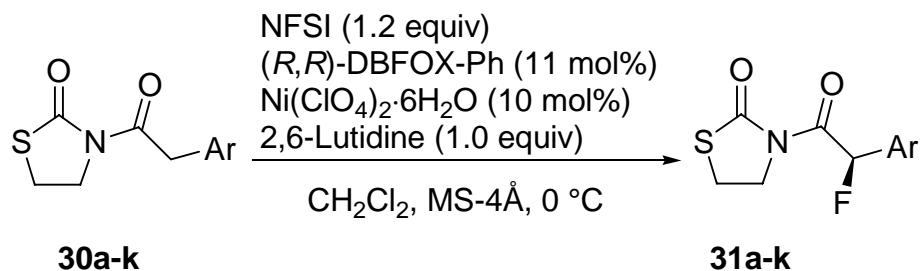
Table 11

Run	Base	Time (h)	Yield (%)	Ee (%)
1	2,6-Lutidine	20	90	74
2	2,6-Lutidine (0.5 equiv)	57	44	74
3		14	trace	-
4		14	trace	-
5		14	16	2

Changing the other bases like, DBU, Phosphagene, and guanidines are not effective for this enantiofluorination reaction (scheme 49, Table 11, run 3 to 6). When we reduced the equivalents of lutidine, there is no difference in the optical purity, only yield is low (44% yield, 74% ee, run 2).

2.6 Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II).

The DBFOX-Ph/Ni(ClO₄)₂·6H₂O catalysis for fluorination showed high generality for various 3-(2-arylacetyl)-2-thiazolidinones **31a—k** in good to high yields with moderate to good enantioselectivities. The results are summarized in Table 11. The fluorination reaction was not very sensitive to substitution in the position of the phenyl group and the desired products with methoxy or methyl groups at the *o*-, *m*-, or *p*-position of the benzene ring were obtained in 65—78% ees (entries 2—7). The reactions of *para*-fluoro or *para*-bromo-substituted **30h, i** and bulky-substituted like 1-naphthyl and 2-naphthyl **30j, k** afforded the desired products **31h—k** in good yields with slightly lower enantioselectivities (56–62% ees, entries 8—11), (Scheme 50, Table 12).



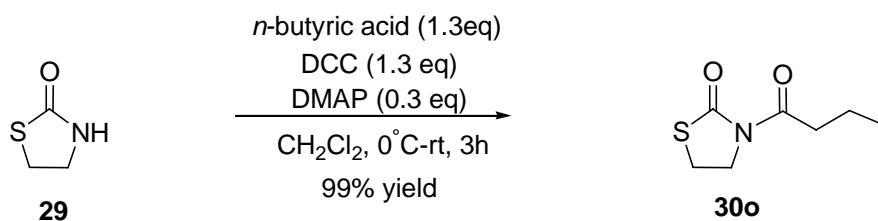
Scheme 50

Table 12

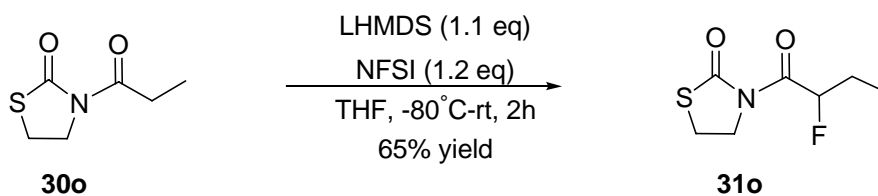
Entry	30	Ar	31	Time (h)	Yield (%)	Ee (%) ^a
1	30a	Ph	31a	20	90	74
2	30b	C ₆ H ₄ - <i>o</i> -OMe	31b	48	96	78
3	30c	C ₆ H ₄ - <i>m</i> -OMe	31c	24	94	66
4	30d	C ₆ H ₄ - <i>p</i> -OMe	31d	24	90	65
5	30e	C ₆ H ₄ - <i>o</i> -Me	31e	48	69	76
6	30f	C ₆ H ₄ - <i>m</i> -Me	31f	48	75	73
7	30g	C ₆ H ₄ - <i>p</i> -Me	31g	48	75	77
8	30h	C ₆ H ₄ - <i>p</i> -F	31h	48	60	62
9	30i	C ₆ H ₄ - <i>p</i> -Br	31i	48	77	56
10	30j	1-Naphthyl	31j	48	85	59
11	30k	2-Naphthyl	31k	48	90	60

a) Enantioselectivity was determined by chiral HPLC analysis.

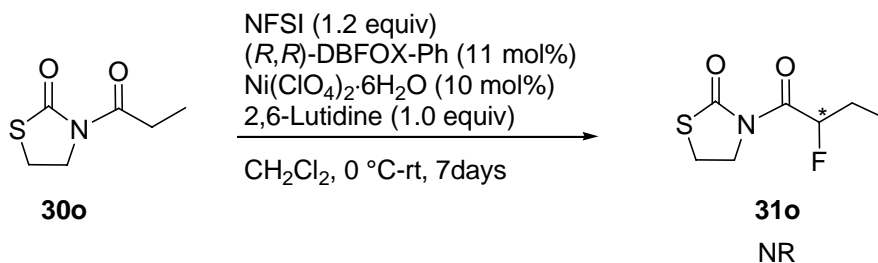
We prepared also aliphatic substrate like *n*-butyl acetyl, by the using above same condition *n*-butyric acid (1.3 eq) and DCC, DMAP condition, 3-butylthiazolidin-2-one (**30o**) in 99% yield was obtained (Scheme 51), and which was racemic fluorinated the using of LHMDs (1.1 eq) and NFSI (1.2 eq) fluorinating reagent, 3-(2-fluorobutanoyl) thiazolidin-2-one in 65% yield (Scheme 52). In case of enantioselective reaction no reaction was observed even after 7 days also (Scheme 53).



Scheme 51



Scheme 52



Scheme 53

2.7 Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II), Screening for Additives:

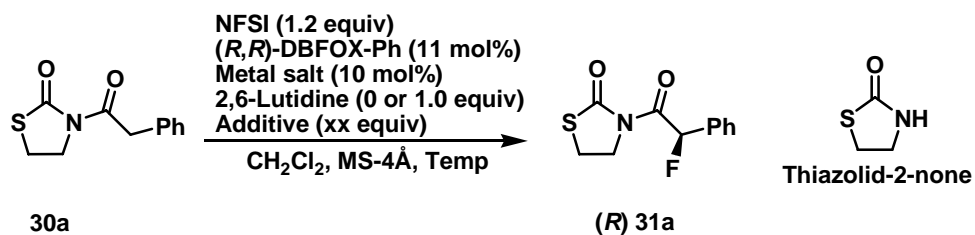
The enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones **31a—k** in high yields with moderate to good enantioselectivities, in Scheme 50, table 12, these enantioselectivities are acceptable, but not excellent. Our research has focused on the development of high enantioselective for these substrates, accordingly the use of external activating agent is necessary. A recent report⁴⁷ by Evans and Thomson as well as Sodeoka supported the validity of this idea. Here we tested several additives in Scheme 54, Table 13, first we used thiazolidinone as a additive in catalytic amount, but unfortunately the enantioselectivity was decreased, even changing the metals also (Table 13, entries 2-4). When we used trifluoroacetic acid and benzoic acids were used in catalytic, no reaction was observed (Table 13, entry 5 and 6), and according to the Sodeoka reported for these substrates by using silyltriflates, namely Me₃SiOTf, and Et₃SiOTf were used, but our DBFOX-Ph ligand combination with these triflates was not successful for achieving high enantioselectivity and high yields (Table 13, entry 7 and 8). While the use of 1 equiv of BF₃.OEt₂ at -20°C, there is no reaction was occurred (entry 9). Unfortunately when we used trifluoroethanol 20 mol% as a additive in catalytic amount, the enantioselectivity was increased up to 80% ee (entry 10).

Cahard⁴⁸ reported HFIP was used as a additive for enantioselective fluorination of β -keto esters. We used HFIP (Scheme 55, Table 14) as a catalytic amount 0.1 equiv, under the reflux in 63% ee, in case of 0°C 83% ee was obtained, when we followed to the reported 1.0 equiv of HFIP, no improvement in enantioselectivity, that means catalytic amount is suitable for this reaction (Table 14, entries 1-4). In case of at -20°C changing the various equivalents of HFIP, and changing the temperature, the ee was increased 0.1 equiv of HFIP was used. Changing the fluorinating reagent like FP-T300, no reaction was occurred (Table 14, entry 6).

Increasing the equivalent of 2,6-lutidine and catalytic amount of HFIP at low temperature, excellent enantioselectivity was obtained. The best results was obtained at -60°C by using 2 equiv of lutidine and HFIP 30 mol% (Table 14, entry 12).

⁴⁷ (a) D. A. Evans, C. W. Downey, J. L. hubbs. *J. Am. Chem. Soc.* **2003**, 125, 8706. (b) D. A. Evans, R. J. Thomson. *J. Am. Chem. Soc.* **2005**, 127, 10506.

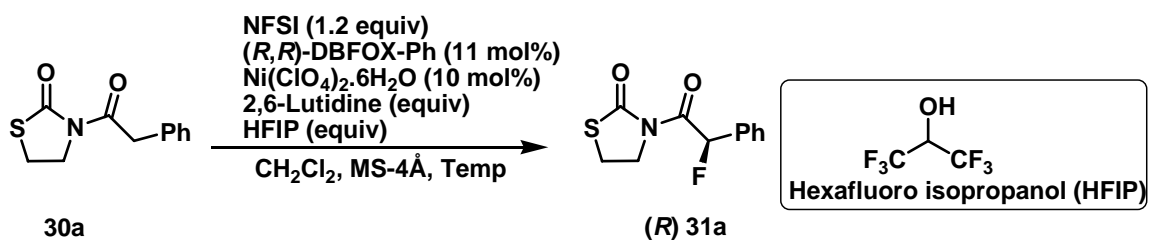
⁴⁸ Ma, J-A. Cahard, D. *Tetrahedron: Asymmetry* **2004**, 15, 1007.



Scheme 54

Table 13

Run	Metal salt	Additive (equiv)	Temp (°C)	Time (h)	Yield (%)	Ee (%)
1	Ni(ClO ₄) ₂ ·6H ₂ O	-	0	20	90	74
2	Zn(ClO ₄) ₂ ·6H ₂ O	thiazolidin-2-one (0.1)	0	48	38	40
3	Mg(ClO ₄) ₂	thiazolidin-2-one (0.1)	0	36	71	40
4	Ni(ClO ₄) ₂ ·6H ₂ O	thiazolidin-2-one (0.1)	0	36	83	72
5	Ni(ClO ₄) ₂ ·6H ₂ O	CF ₃ COOH (0.2)	rt-reflux	24	NR	-
6	Ni(ClO ₄) ₂ ·6H ₂ O	Benzoic acid (0.2)	-20	48	NR	-
7	Ni(ClO ₄) ₂ ·6H ₂ O	Me ₃ SiOTf(1.0)	-20	62	41	82
8	Ni(ClO ₄) ₂ ·6H ₂ O	Et ₃ SiOTf(0.75)	-20	62	57	83
9	Ni(ClO ₄) ₂ ·6H ₂ O	BF ₃ OEt ₂ (1.0)	-20	48	NR	-
10	Ni(ClO ₄) ₂ ·6H ₂ O	CF ₃ CH ₂ OH (0.2)	-20	20	88	80



Scheme 55

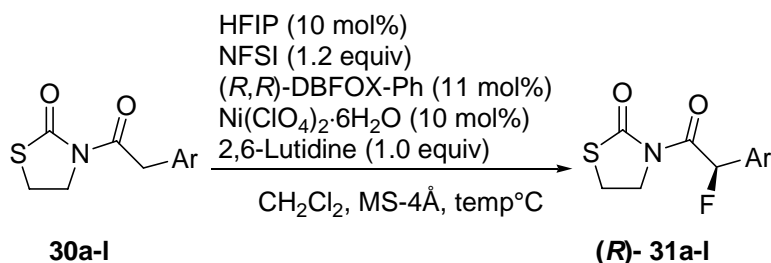
Table 14

Run	2,6-Lutidine (equiv)	HFIP (equiv)	Temp (°C)	Time (h)	Yield (%)	Ee (%)
1	1.0	0.1	reflux	3	93	63
2	1.0	1.0	0	14	83	70
3	1.0	0.1	0	30	86	83
4	1.0	0.2	0	14	93	86
5	1.0	0.1	-20	12	96	86
6 ^a	1.0	0.1	-20	48	NR	-
7	1.0	0.2	-20	24	95	86
8	1.0	0.5	-20	30	92	82
9	1.0	0.1	-50	14	90	90
10	1.0	0.1	-80	80	78	94
11	1.0	0.2	-80	80	74	92
12	2.0	0.3	-60	48	91	98
13	2.0	0.6	-80	48	85	87
14	2.0	0.3	0	8	94	88

^a= FP-T300 was used instead of NFSI

2.8 Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II), (HFIP at -20°C

We attempted various substrates on aromatic phenyl acetyl and naphthyl acetyl thiazolidinones were fluorinated at -20°C temperature, the obtained fluorinated enantioselectivity was up to 86% ee (Scheme 56, Table 15).

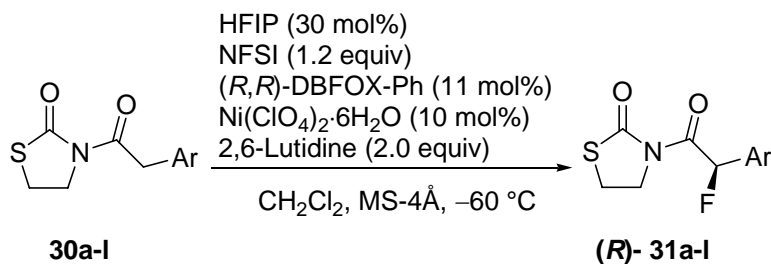


Scheme 56

Table 15

Entry	30	Ar	31	Temp	Time (d)	Yield (%)	Ee (%)
1	30a	Ph	31a	-20	0.5	96	86
2	30b	C ₆ H ₄ - <i>o</i> -OMe	31b	-20	5	81	83
3	30c	C ₆ H ₄ - <i>m</i> -OMe	31c	-20	2	94	73
4	30d	C ₆ H ₄ - <i>p</i> -OMe	31d	-20	4	93	90
5	30e	C ₆ H ₄ - <i>o</i> -Me	31e	-20	5	85	84
6	30f	C ₆ H ₄ - <i>m</i> -Me	31f	-20	2	92	87
7	30g	C ₆ H ₄ - <i>p</i> -Me	31g	-20	2	97	78
8	30h	C ₆ H ₄ - <i>p</i> -F	31h	0	5	66	48
9	30i	C ₆ H ₄ - <i>p</i> -Br	31i	0	5	71	48
10	30k	2-Naphthyl	31k	-20	7	69	75
11	30l	C ₆ H ₄ - <i>p</i> -CF ₃	31l	0	5	71	40

2.9 Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II), (HFIP at -60°C



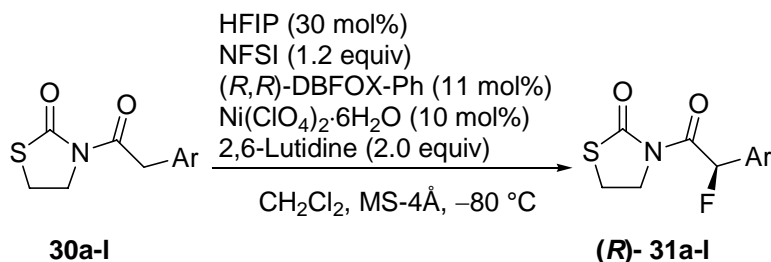
Scheme 57

Table 16

Entry	30	Ar	31	Time (d)	Yield (%)	Ee (%)
1	30a	Ph	31a	2	91	98
2	30c	C ₆ H ₄ - <i>m</i> -OMe	31c	3	93	96
3	30d	C ₆ H ₄ - <i>p</i> -OMe	31d	2	93	96
4	30f	C ₆ H ₄ - <i>m</i> -Me	31f	4	93	98
5	30g	C ₆ H ₄ - <i>p</i> -Me	31g	3	90	96
6	30h	C ₆ H ₄ - <i>p</i> -F	31h	3	90	94
7	30i	C ₆ H ₄ - <i>p</i> -Br	31i	3	93	96
8	30j	1-Naphthyl	31j	7	87	92
9	30k	2-Naphthyl	31k	3	94	95
10	30l	C ₆ H ₄ - <i>p</i> -CF ₃	31l	4	94	94

The best condition at -60°C, with 2.0 equiv of base and HFIP 0.3 equiv and DBFOX-Ph/Ni(II) was used for the enantioselective fluorination of various aryl acetyl substrates, afforded the fluorination products in extremely high yields with excellent enantioselectivities up to 98% ee, all the substrates were obtained more than 92% ee (Scheme 57, Table 16).

2.10 Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II), (HFIP at -80°C



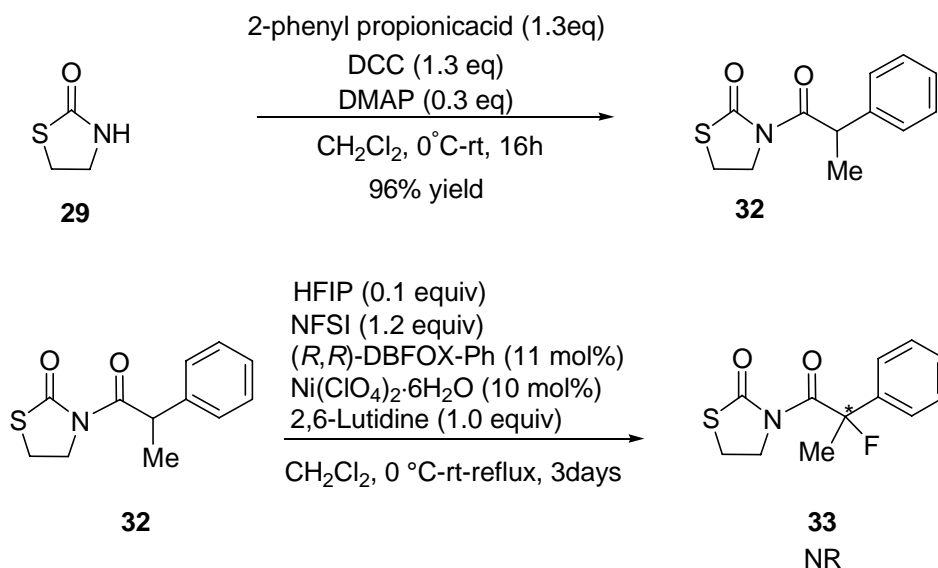
Scheme 58

Table 17

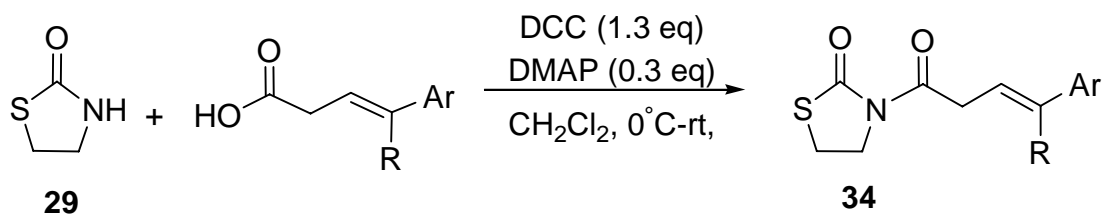
Entry	30	Ar	31	Time (d)	Yield (%)	Ee (%)
1	30a	Ph	31a	7	50	98
2	30c	C ₆ H ₄ - <i>m</i> -OMe	31c	7	12	98
3	30d	C ₆ H ₄ - <i>p</i> -OMe	31d	7	17	99
4	30f	C ₆ H ₄ - <i>m</i> -Me	31f	7	80	99
5	30g	C ₆ H ₄ - <i>p</i> -Me	31g	7	83	98
6	30h	C ₆ H ₄ - <i>p</i> -F	31h	7	58	98
7	30i	C ₆ H ₄ - <i>p</i> -Br	31i	7	87	99
8	30j	1-Naphthyl	31j	9	09	99
9	30k	2-Naphthyl	31k	7	70	99
10	30l	C ₆ H ₄ - <i>p</i> -CF ₃	31l	6	33	99

When we attempted reaction condition at -80°C, with 2.0 equiv of base and HFIP 0.3 equiv and DBFOX-Ph/Ni(II) was used for the enantioselective fluorination of various aryl acetyl substrates, afforded the all fluorination products in excellent enantioselectivities 98-99% ee, but the yields are moderates, even after 1 week also (Scheme 58, Table 17).

If any substrates at α -position, for example, we attempted methyl substrate at α -position phenyl acetyl substrate, there is no fluorination reaction was occurred even reflux condition also (Scheme 59).



Scheme 59

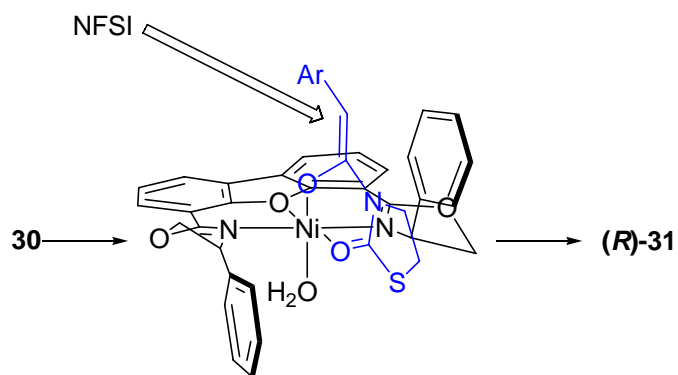


Scheme 61

All various (*E*)-allyl aryl thiazolidinones were prepared under the DCC, DMAP coupling condition method, these (*E*)-allyl carboxylic compounds were prepared by Knoevenegal condensation, according to the reported procedures.⁴⁹

⁴⁹ a) J. M. Garnier, S. Robin, G. Rousseau, *Eur. J. Org. Chem.* **2007**, 20, 3281 b) R. A. Bunce, H. D. Reeves, *J. Chem. Educ.* **1990**, 67, 69 c) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, 128, 13074

The *R*-enantioselection of **31** can be explained by assuming an octahedral complex coordinated with a water molecule for DBFOX-Ph/Ni(II)/**30** as shown in Scheme 57. In the complex, the *Si* face is shielded by one of the phenyl groups of DBFOX-Ph so that NFSI approaches from the *Re* face of the substrates (Scheme 60). Since a major difference in ee values of **31** was not observed for the fluorination reaction of **30** with NFSI in the presence or absence of 2,6-lutidine (runs 1—3, Table 10), 2,6-lutidine presumably just accelerates the tautomerization of **30** to its enol form.

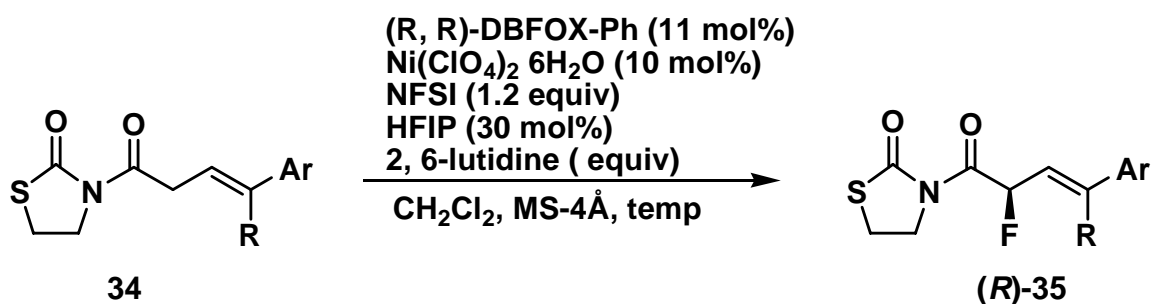


Scheme 60. Transition-State Structure for the DBFOX-Ph/Ni(II) Catalyzed Enantioselective Fluorination of **30** to **31**.

2.11 Enantioselective Fluorination Reaction of (*E*)-Allyl Aryl thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II) (Screening):

We were next concentrated our fluorination work, allylic substrates thiazolidinones substrates, these substrates fluorination was so far there is no any reports, we prepared all these (*E*)-allylic aryl thiazolidinones substrates were as per the reported methods. We optimized the reaction Scheme 62, Table 17. when we attempted enantioselective fluorination reaction with our known method, this reaction we performed without using HFIP additive, we got the moderate yield 59% (entry 1, Table 17). With HFIP at -40°C and changing the substrate, the enantioselectivity and yields were increased up to 53% ee (entries 2 and 3). When we reduced base and HFIP equivalents, but the enantioselectivity was not excellent (entry 4 and 5). The high enantioselectivity and as well as chemical yield was excellent when we attempted 30 mol% of HFIP and 2.0 equiv lutidine at -60°C or -70°C (entry 7 and 8), and also we attempted the reaction at -80°C, the yield is moderate (entry 9). We also performed all reagents were added as double, the reaction time is faster, but the enantioselectivity not much different 83% ee (entry 10, Table 17).

The DBFOX-Ph/Ni(ClO₄)₂·6H₂O catalysis and 2,6-lutidine with HFIP additive for fluorination showed high generality for various (*E*)-allyl arylacetyl-2-thiazolidinones **35a—g** in high yields with excellent enantioselectivities. The results are summarized in Table 18, Scheme 63. The fluorination reaction was not very sensitive to substitution in the phenyl group and the desired products with methyl, chloro, bromo groups at the *p*-position of the benzene ring were obtained in up to 85% ees (entries 3—7). The reactions bulky-substituted like 2-naphthyl **35g** afforded the desired products **35g** in excellent yield with high enantioselectivities (86% ee, entry 7), (Scheme 63, Table 18). In the case of same condition at -70°C, there is only slight difference in the enantioselectivities (entry 8 and 9, Table 18). We obtained for the first time (*E*)-allyl arylacetyl thiazolidinones were fluorinated in excellent yields with extremely high enantioselectivities.



Scheme 62

Table 17

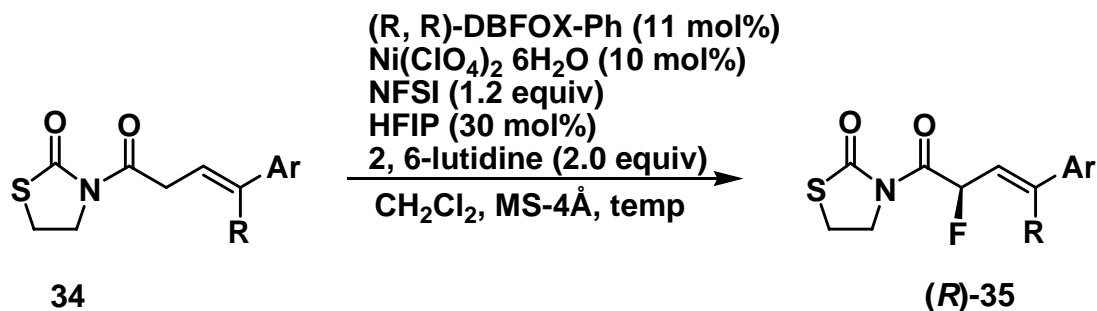
Run	Ar	R	2,6-lutidine (equiv)	Time (h)	Temp (°C)	Yield (%)	Ee (%)
1 ^a	Ph	H	1.0	24	rt	59	1.3
2	Ph	H	2.0	24	-40	59	37
3	Ph	Ph	2.0	20	-40	68	53
4	Ph	Me	1.0	20	-40	67	64
5 ^b	Ph	Me	2.0	20	-40	65	75
6	Ph	Me	2.0	19	-40	75	78
7	Ph	Me	2.0	24	-60	99	85
8	Ph	Me	2.0	26	-70	99	87
9	Ph	Me	2.0	4 days	-80	50	91
10 ^c	Ph	Me	4.0	3	-40	93	83

a=HFIP was not added

b=HFIP 20 mol% was added

c=all reagents was added double

2.12 Enantioselective Fluorination Reaction of (*E*)-Allyl Aryl thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II) complexes:

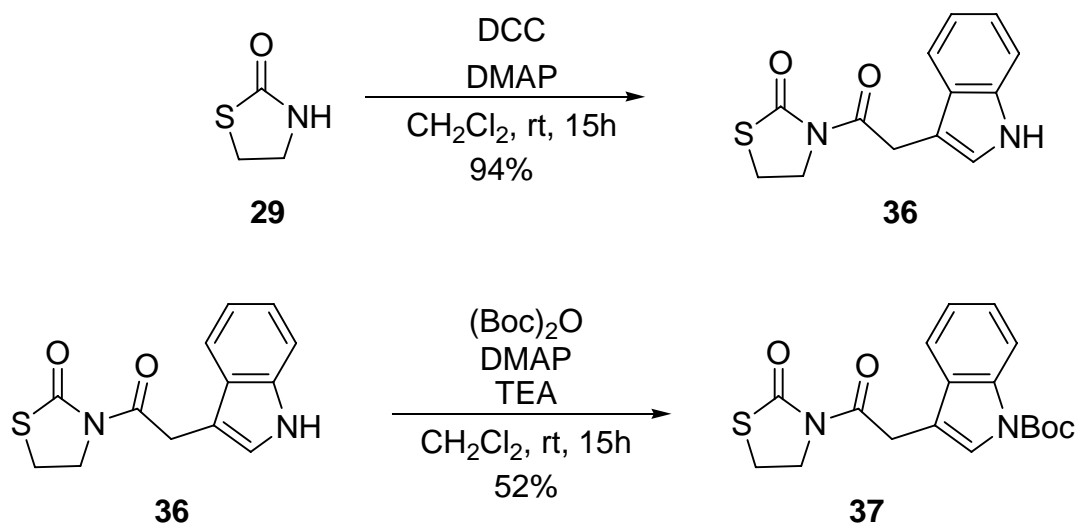


Scheme 63

Table 18

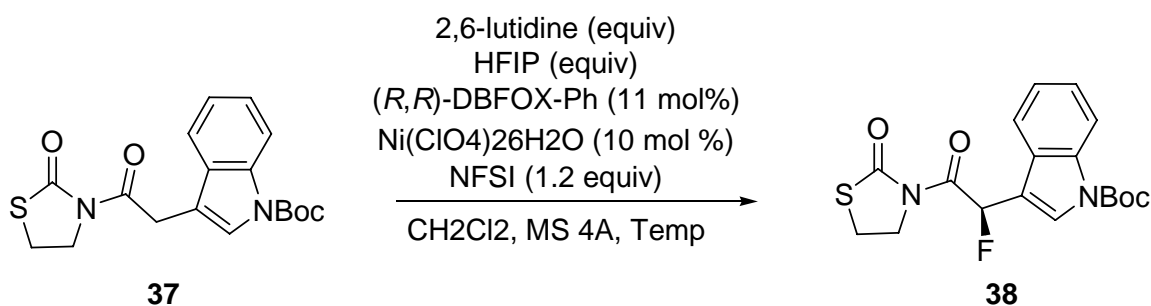
Run	34	Ar	R	35	Time (h)	Temp (°C)	Yield (%)	Ee (%)
1	34a	Ph	H	35a	24	-60	96	78
2	34b	Ph	Ph	35b	8	-60	99	86
3	34c	Ph	Me	35c	24	-60	99	85
4	34d	C ₆ H ₄ - <i>p</i> -Me	Me	35d	21	-60	99	85
5	34e	C ₆ H ₄ - <i>p</i> -Cl	Me	35e	21	-60	99	84
6	34f	C ₆ H ₄ - <i>p</i> -Br	Me	35f	21	-60	99	80
7	34g	2-Naphthyl	Me	35g	24	-60	97	86
8	34c	Ph	Me	35c	26	-70	99	87
9	34e	C ₆ H ₄ - <i>p</i> -Cl	Me	35e	21	-70	99	86

2.13 Preparation of 3-(2-Indole acetyl)-2-thiazolidinone:



Scheme 64

2.14 Enantioselective Fluorination of 3-(2-Indole acetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/ Ni(II), complexes:



Scheme 65

Table 19

Entry	2,6-lutidine (equiv)	HFIP (equiv)	Temp (°C)	Time (days)	Yield (%)	Ee (%)
1	2.0	0.3	0	3	51.5	76.1
2	1.0	0.1	0	3	38.7	83.1
3	2.0	0.3	-40	3	26.7	94.5
4	2.0	0.3	-60	7	47.6	96.8
5 ^a	2.0	0.3	-60	3	29.2	95.4
6 ^b	4.0	0.6	-60	3	32.4	94.6
7	6.0	0.3	-60	3	36.8	88.1
8 ^c	6.0	0.3	-60	3	54.6	74.2
9	2.0	1.0	-60	3	16.2	96.6
10 ^d	2.0	-	-60	3	10.2	48.3
11	2.0	1.0	-70	7	44.5	95.6
12 ^a	2.0	1.0	-70	3	38.1	96.8

a) catalysts were added double

b) all reagents were added double

c) base was added 3 times, every 1 hour

d) Me₃SiOTf was added instead of HFIP

The Stereochemistry '*R*' was confirmed by X-ray crystal structure, of the chiral fluorinated allyl aryl thiazolidinone **35** was shown in Fig 6.

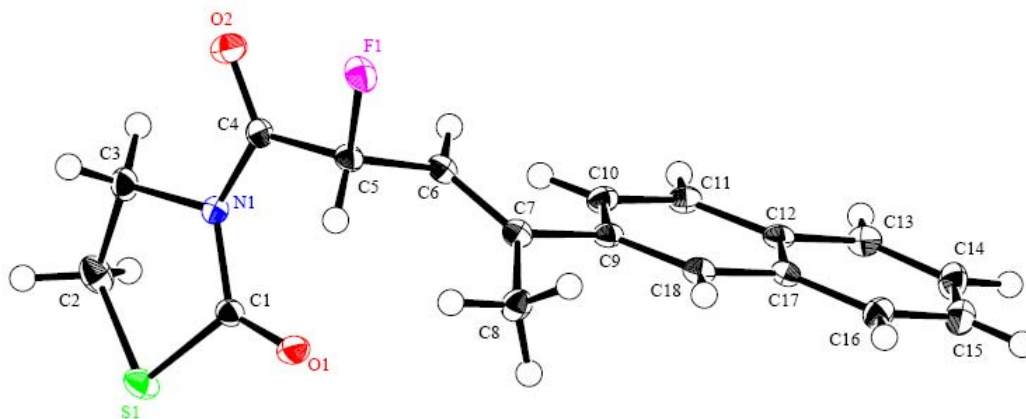
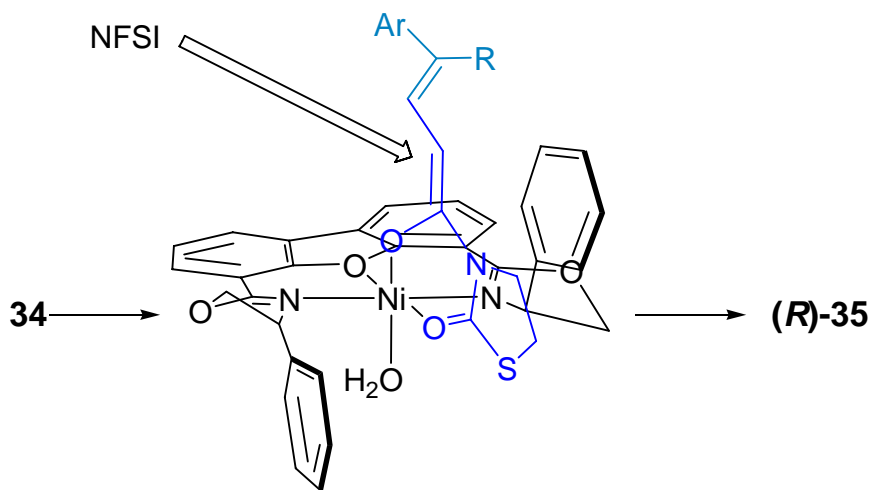


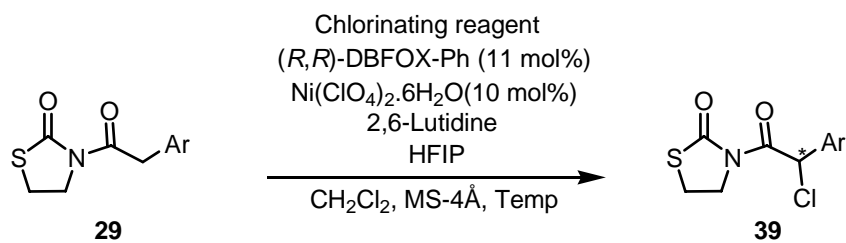
Fig: 6

The *R*-enantioselection of **35** can be explained by assuming an octahedral complex coordinated with a water molecule for DBFOX-Ph/Ni(II)/**34** as shown in Scheme 65. In the complex, the *Si* face is shielded by one of the Aryl groups of DBFOX-Ph so that NFSI approaches from the *Re* face of the substrates (Scheme 65).



Scheme 66. Transition-State Structure for the DBFOX-Ph/Ni(II) Catalyzed Enantioselective Fluorination of **34** to **35**.

2.15 Enantioselective Chlorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones Catalyzed by DBFOX-Ph/ Ni(II)

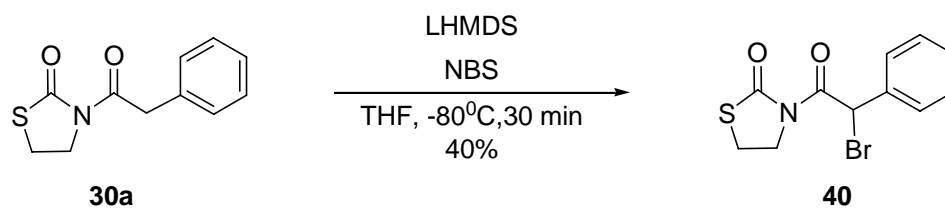


Scheme 67

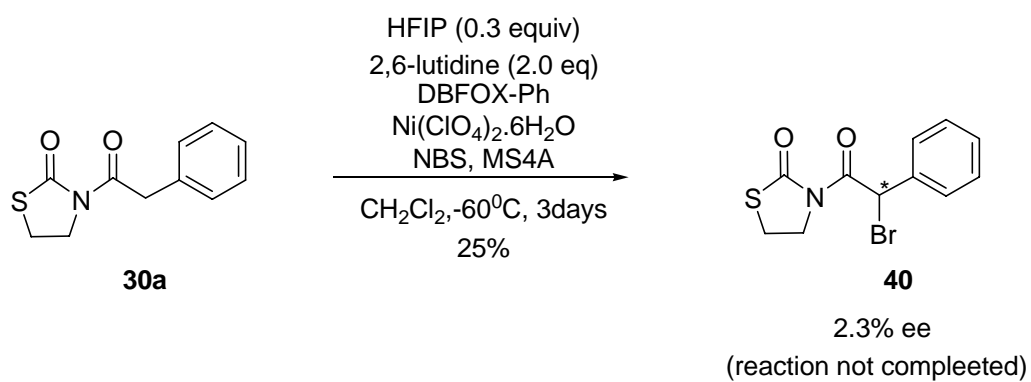
Table 20

Run	Ar	Cl-reagent	2,6-Lutidine	HFIP (equiv)	Temp (°C)	Time (h)	Yield (%)	Ee (%)
1	Ph	NCS	1.0 eq	0.2	0	12	95	85
2	Ph	CF ₃ SO ₂ Cl	1.0 eq	0.2	0	12	95	89
3	Ph	CF ₃ SO ₂ Cl	2.0 eq	0.3	-60	48	97	93
4	C ₆ H ₄ - <i>p</i> -Br	„	2.0 eq	0.3	-60	48	94	76
5	C ₆ H ₄ - <i>p</i> -Me	„	2.0 eq	0.3	-60	72	97	70

2.16 Enantioselective Bromination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones Catalyzed by DBFOX-Ph/ Ni(II)



Scheme 68



Scheme 69

2.17 Conclusion

We demonstrated that DBFOX-Ph/Ni(II) catalysis can be used for the catalytic enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with or without 2,6-lutidine to afford chiral 2-fluoro-2-arylacetyl derivatives in good to high yields with moderate to good enantioselectivities of up to 78% ee.

After these results we succeeded to obtain highly enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones by using same procedure with added additive (HFIP) as a catalytic amount and lutidine was used 2.0 equivalents at lower temperature, obtained high yield with excellent enantioselectivity. We also succeeded enantioselective fluorination of (*E*)-allyl arylacetyl thiazolidinones in high chemical yields with excellent enantioselectivities.

Chapter 3

Dynamic Kinetic Asymmetric Transformation in the α -Hydroxylation of Racemic Malonates and its Application to Biologically Active Molecules

3.1 Introduction:

The α -hydroxy- β -carbonyl moiety is a common structural motif in a variety of natural products and bioactive compounds, such as antibiotic kjellmanianone⁵⁰, SM-130686⁵¹ is a potent growth hormone secretagogue, convolutamide E⁵², and anti androgen bicalutamide⁵³, which is used for the treatment of prostate cancer. Moreover, this functional unit appears in key intermediates in many multi-step reaction sequences. 1,3-dicarbonyl compounds, which are the most convenient synthetic route to the direct oxidation of α -hydroxylated compounds (Fig. 6).

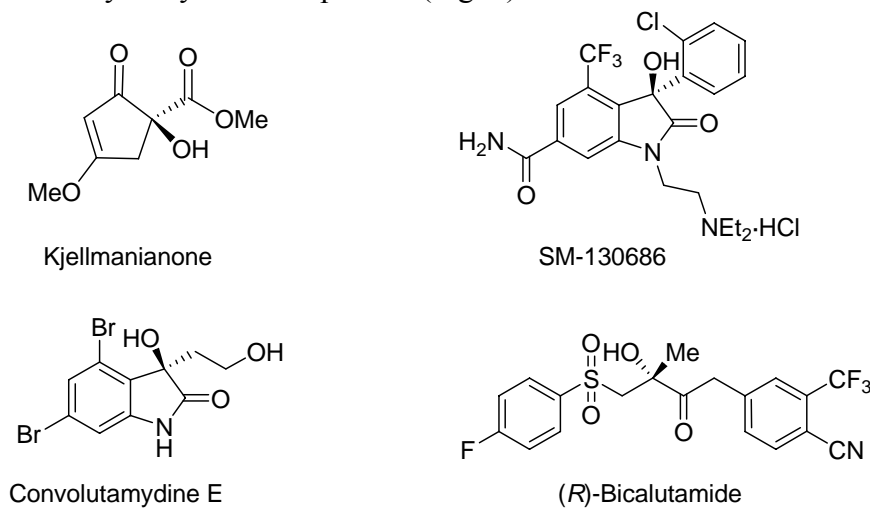
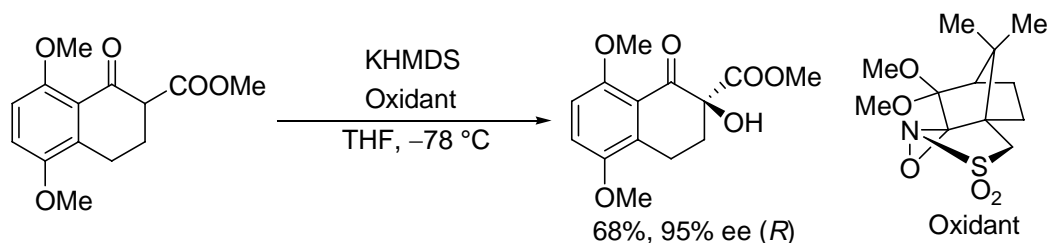


Fig 7

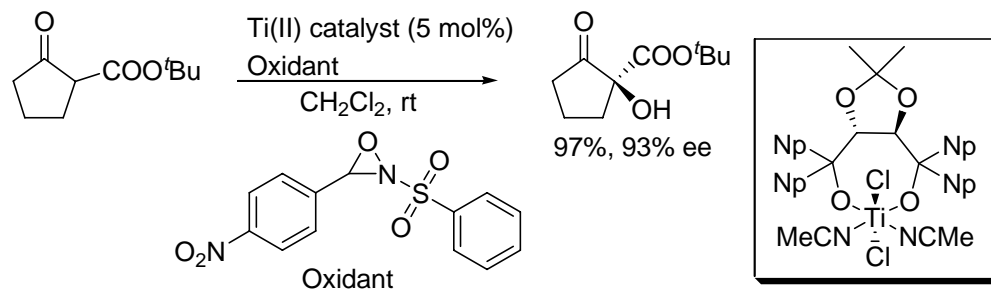
- ⁵⁰ (a) Nakamura, M.; Fukuoka, Y.; Nozaki, H.; Matsuo, A.; Hayashi, S. *Chem. Lett.* **1980**, 1243. (b) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, 346, 143. (c) Boschelli, D.; Smith, III, A. B.; Stringer, O. B.; Jenkins, R. H.; Davis, F. A. *Tetrahedron Lett.* **1981**, 22, 4385.
- ⁵¹ Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, 44, 4641.
- ⁵² (a) Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, 55, 4901. (b) Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **2000**, 53, 105. (c) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *Eur. J. Org. Chem.* **2001**, 261. (d) Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2004**, 60, 2489. (e) Hewawasam, P.; Meanwell, N. A.; Gribkoff, V. K.; Dworetzky, S. I.; Biossard, C. G. *Bioorg. Med. Chem. Lett.* **1997**, 7, 1255. (f) Hewawasam, P.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Gribkoff, V. K.; Meanwell, N. A. *J. Med. Chem.* **2002**, 45, 1487. (g) Di Malta, A.; Garcia, G.; Roux, R.; Schoentjes, B.; Serrandil-leGal, C.; Tonnerre, B.; Wagnon, J. PCT Int. Appl. No. WO2003008407, **2003**.
- ⁵³ (a) A. Fujino, M. Asano, H. Yamaguchi, N. Shirasaka, A. Sakoda, M. Ikunaka, R. Obata, S. Nishiyama, T. Sugai, *Tetrahedron Lett.* **2007**, 48, 979-983; (b) K. D. James, N. N. Ekwuribe. *Tetrahedron* **2002**, 58, 5905-5908;

In 1991 Davis and co-workers⁵⁴ demonstrated asymmetric oxidation of β -ketoesters potassium enolate by using an enantiomerically pure camphorsulfonyl oxaziridine as an oxidant, afforded chiral hydroxylated compound in good yields with up to 95% ee (Scheme 70).



Scheme 70

The direct enantioselective α -hydroxylation of β -ketoesters were reported by catalytic amount of chiral transition-metal lewis acid Ti TADDOLato complexes, and using 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine as the oxidizing agent, affords the hydroxylated products in high yields and enantioselectivity up to 93% enantiomeric excess (scheme 71).⁵⁵

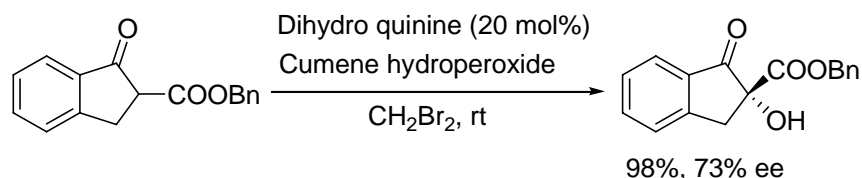


Scheme 71

⁵⁴ (a) Chen, B.-C.; Weismiller, M. C.; Davis, F. A.; Boschelli, D.; Empfield, J. R.; Smith, III, A. B. *Tetrahedron* **1991**, *47*, 173. (b) Davis, F. A.; Kumar, A.; Chen, B.-C. *Tetrahedron Lett.* **1991**, *32*, 867. (c) Davis, F. A.; Clark, C.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1994**, *59*, 1184. (d) Ma, L.; Dolphin, D. *Tetrahedron: Asymmetry* **1995**, *6*, 313. (e) Ma, L.; Dolphin, D. *J. Org. Chem.* **1996**, *61*, 2501. (f) Davis, F. A.; Liu, H.; Chen, B.-C.; Zhou, P. *Tetrahedron* **1998**, *54*, 10481.

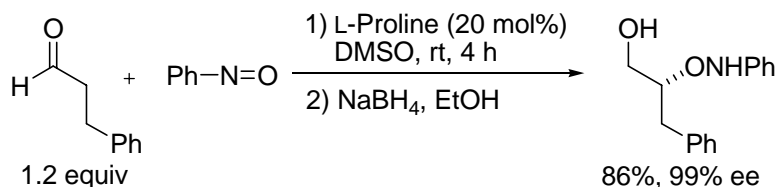
⁵⁵ Tollec, P. Y.; Bonnacorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5810.

Jorgensen was reported the organocatalytic α -hydroxylation of β -ketoesters using cinchona-alkaloid derivatives (dihydroquinine) as the catalyst and (cumene hydroperoxide) peroxides as the terminal oxidant to proceed optically active α -hydroxy of β -ketoesters in high yields and with good enantioselectivity (Scheme 72).⁵⁶



Scheme 72

In 2003, Zhong was reported direct catalytic enantioselective α -aminoxylation of aldehydes by using enantiopure proline as the catalyst and nitrobenzene as the oxygen source, followed by in situ reduction with NaBH_4 -affords 1,2-diols with excellent enantioselectivity (Scheme 73).⁵⁷



Scheme 73

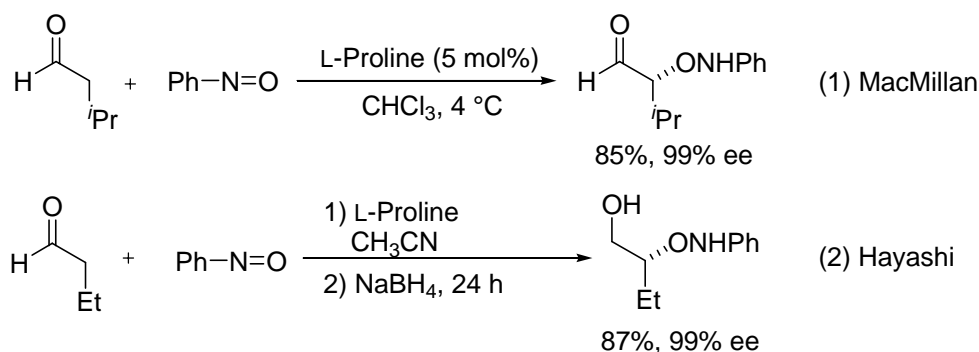
Similarly, MacMillan⁵⁸ as well as Hayashi⁵⁹ also reported the direct enantioselective α -oxidation of aldehydes by using L-proline as a organocatalyst, provides 1,2-amono alcohols in high yields with high enantioselectivity (Scheme 74).

⁵⁶ Acocella, M. R.; Mancheño, O. G.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2004**, 69, 8165.

⁵⁷ Zhong, G. *Angew. Chem. Int. Ed.* **2003**, 42, 4247.

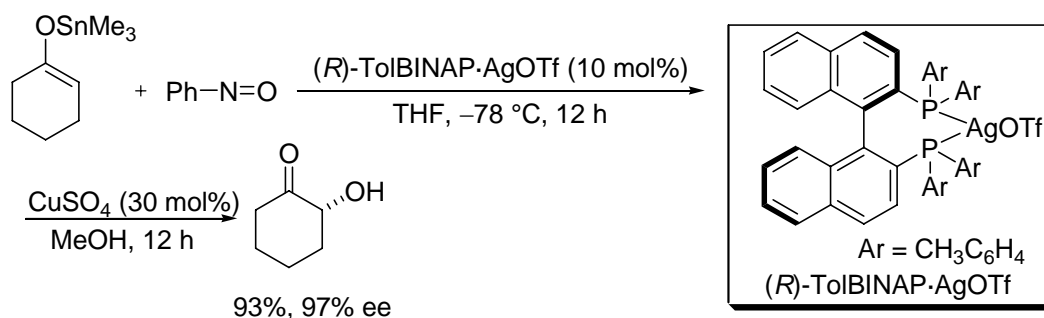
⁵⁸ Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, 125, 10808.

⁵⁹ Yamaguchi, J.; Hibino, K.; Shoji, M.; Hayashi, Y. *Tetrahedron Lett.* **2003**, 44, 8293.



Scheme 74

Yamamoto⁶⁰ and co-workers reported the BINAP-Ag complex catalyzed enantioselective synthesis of α -aminoxy and α -hydroxy ketone by the reaction of nitrosobenzene and silyl enolate, which provided chiral α -aminoxy and α -hydroxy ketone with highly enantioselectivity and high yields (Scheme 75). After that naphthyl glycolic acid catalyzed aciral enamine for enantioselective nitro aldol synthesis also reported.⁶¹



Scheme 75

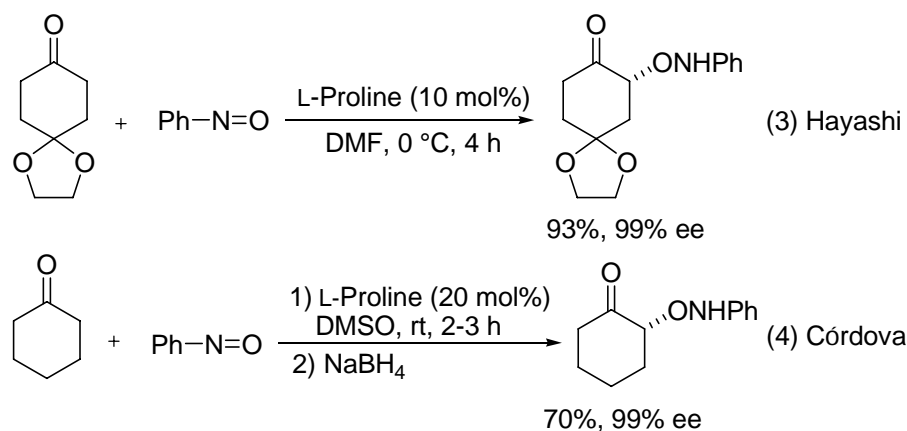
In 2004, Hayashi⁶² (eq 3), Cordova⁶³ (eq 4) were reported the catalytic enantioselective α -aminoxylation of ketone by using organocatalyst praline, using nitrosobenzene as the oxygen source, affording the products with high enantioselectivities (Scheme 76).

⁶⁰ Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.

⁶¹ Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080.

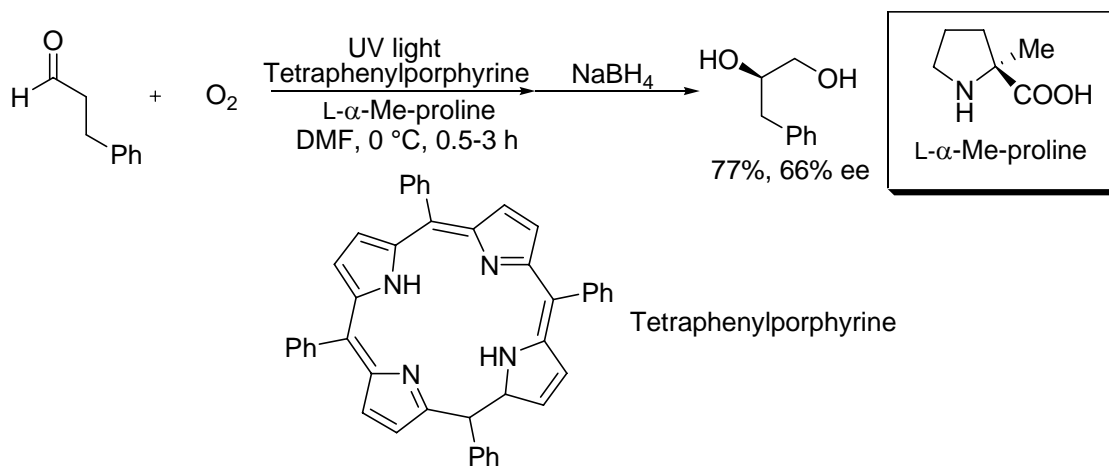
⁶² Yamaguchi, J.; Hibino, K.; Shoji, M.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.

⁶³ Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1109.



Scheme 76

And also Córdoba was reported the proline as a catalyst for the direct asymmetric α -oxidation reaction with molecular oxygen in the presence of UV light and tetraphenyl porphyrine afforded terminal diols in 66% ee (Scheme 77).⁶⁴

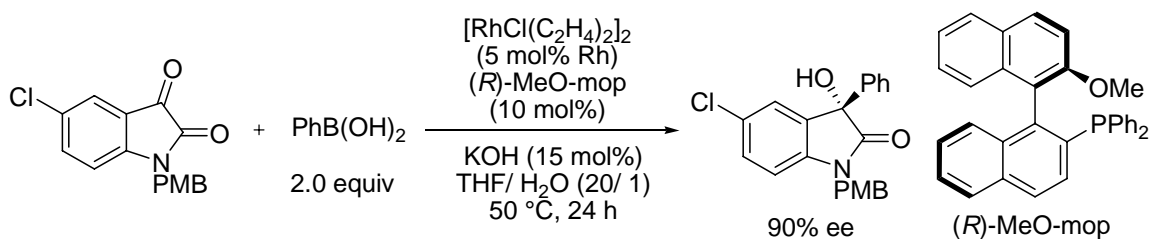


Scheme 77

⁶⁴ Sundén, H.; Engqvist, M.; Ibrahim, I.; Casas, J.; Córdoba, A. *J. Am. Chem. Soc.* **2004**, *126*, 8914.

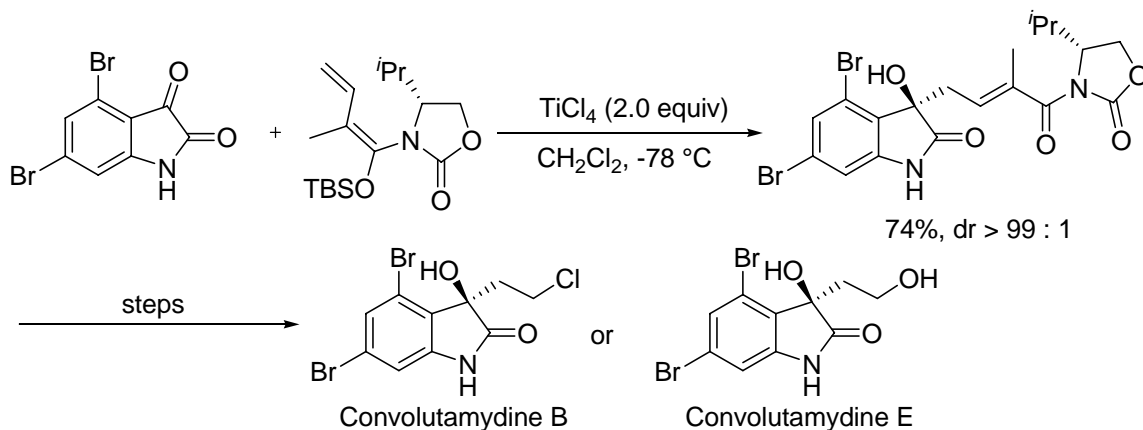
Up to here aldehydes and β -keto esters was hydroxylated by Togni and Jorgensen was reported, here some examples of hydroxylated oxindole were presented by the using of Isatin substrates.

Hayashi and co-workers⁶⁵ reported the Rh/(R)-MeO-mop complex catalyzed the asymmetric addition of arylboronic acids to Isatins to produce 3-aryl-3-hydroxy-2-oxindoles in high yields with high enantioselectivity (Scheme 78).



Scheme 78

In 2006, Kobayashi⁶⁶ and co-workers reported the diastereoselective addition to a Isatin derivative for the aldol reaction by using TiCl_4 , to further synthesized Convolutamyne B and E (Scheme 79).

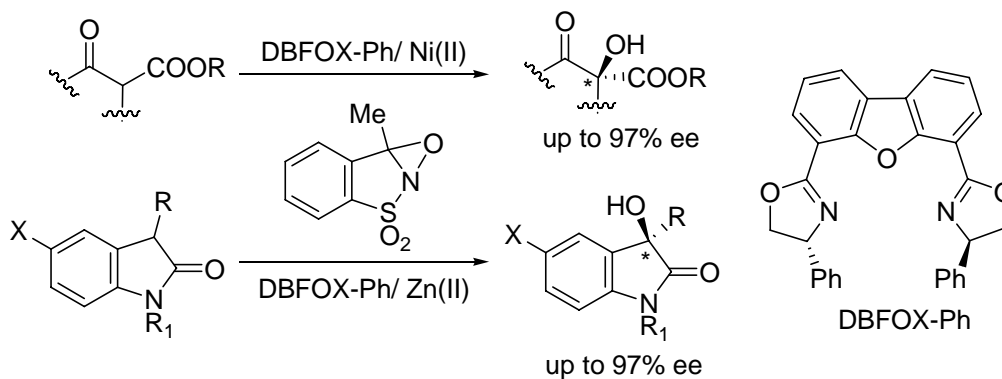


Scheme 79

⁶⁵Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2006**, 45, 3353.

⁶⁶Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, 8, 677.

Recently our group also developed highly enantioselective hydroxylation of oxindoles and β -keto esters by using DBFOX-Ph/lewis acid metal complexes with oxaziridine as an oxidizing agent in high yields with high enantioselectivities (Scheme 90).⁶⁷



Scheme 80

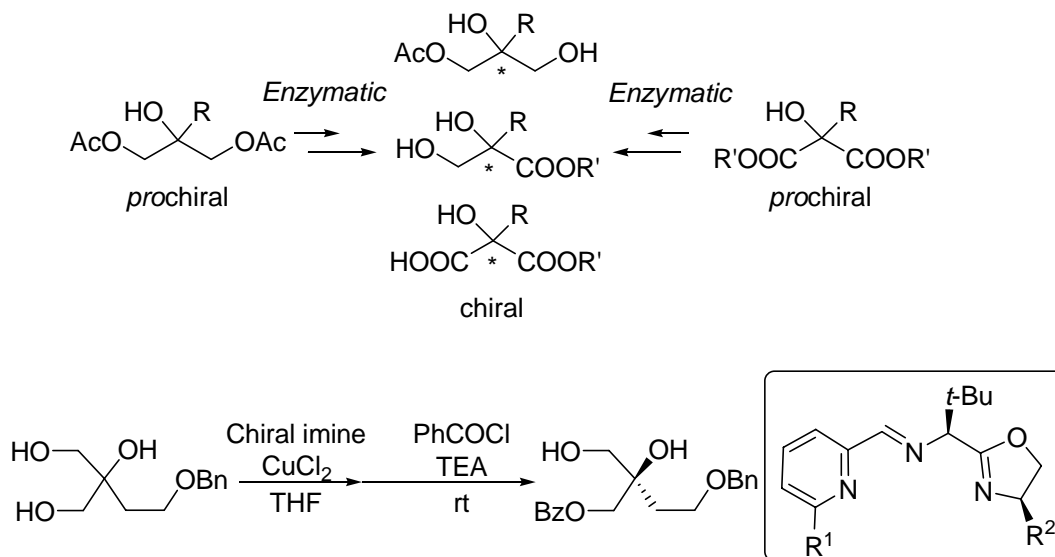
During the recent past, years, tremendous efforts have been made to establish enantioselective routes for the preparation of enantiomerically pure compounds by the enzymatic and chemical methods. Enantioselective enzymatic⁶⁸ desymmetrization of prochiral substrates are achieved by means of the employment of different enzymes. Catalytic enantioselective desymmetrization of meso-2-substituted glycerols has been developed to secure a novel synthetic route to chiral tertiary alcohols. Enantiomerically enriched tertiary alcohols have been readily prepared by chemical⁶⁹ desymmetrization,

⁶⁷ T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanamasa, *J. Am. Chem. Soc.* **2006**, *128*, 16488.

⁶⁸ (a) G. Guanti, L. Banfi, K. Powels, M. Rasparini, C. Scolastico, N. Fossati, *Tetrahedron: Asymmetry* **2001**, *12*, 271. (b) M. Breznik, D. Kikelji, *Tetrahedron: Asymmetry* **1997**, *8*, 425. (c) P. Mohar, N. W. Sarcewic, C. Tamm, K. Gawronska, J. K. Gawronski, *Helvetica Chimica Acta*, **1983**, *66*, 2501. (d) M. Breznik, S. G. Grdadolnik, G. Giester, I. Leban, D. Kikelj, *J. Org. Chem.* **2001**, *66*, 7044. (e) M. Breznik, V. Hrast, A. Mrcina, D. Kikelj, *Tetrahedron: Asymmetry*, **1999**, *10*, 153 (f) M. Breznik, V. Hrast, A. Mrcina, D. Kikelj, *Tetrahedron: Asymmetry*, **1998**, *9*, 1115 (g) M. Breznik, D. Kikelj, *Tetrahedron: Asymmetry*, **1997**, *8*, 425. (h) P. D. de Maria, C. A. Garcia-Burgos, G. Bargeman, R. W. van Gemert, *Synthesis*, **2007**, 1439

⁶⁹ (a) E. Garcia, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313. (b) K. Drauz, H. Waldmann in *Enzymatic Catalysis in Organic Synthesis: A Comprehensive Handbook*, Wiley-VCH, Weinheim, **2002**. (c) B. Jung, S. H. Kang, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 1471. (d) B. Jung, M. S. Hong, S. H. Kang, *Angew. Chem. Int. Ed.* **2007**, *46*, 2616. (e) C. A. Lewis, B. R. Sculimbrene, Y. Xu, S. J. Miller, *Org. Lett.* **2005**, *7*, 3021. (f) Y. Yashonara, N. Kizaki, K. Miyamoto, J. Hasegawa, T. Ohashi, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 2044. (g) J. Ichikawa, M. Asami, T. Mukaiyama, *Chem. Lett.* **1984**, *13*, 949. (h) S. Akai, T. Naka, T. Fujita, Y. Takabe, T. Tsujino, Y. Kita, *J. Org. Chem.* **2002**, *67*, 411.

which is the transformation has been realized by monobenylation using benzoyl chloride and triethylamine in the presence of imine ligand –CuCl₂ complex in THF. Chiral α-hydroxyl malonates and their equivalents has been achieved by enzymatic desymmetrization of prochiral malonates or enzymatic and chemical desymmetrization of prochiral glycerols (Scheme 81).



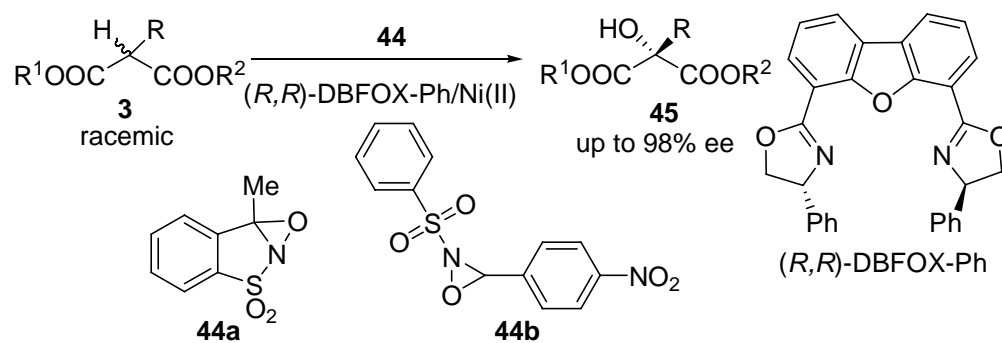
Scheme 81

Chiral α-hydroxy malonates and their equivalents are a valuable class of compounds utilized in the synthesis of drug candidates such as chlozolate and bicalutamide.⁷⁰ Recently we reported the desymmetrization-like enantioselective fluorination of malonates in the presence of DBFOX-Ph/Zn(II) complex⁷¹ and chiral α-fluorinated malonates were obtained in high yields with high enantioselectivities. We present here the first desymmetrization-like direct enantioselective hydroxylation of racemic malonate **3** using DBFOX-Ph/Ni(II) complex with oxaziridine **44a** to provide the

⁷⁰ a) G. Guanti, L. Banfi, K. Powels, M. Rasparini, C. Scolastico, N. Fossati, *Tetrahedron: Asymmetry* **2001**, 12, 271. b) A. Fujino, M. Asano, H. Yamaguchi, N. Shirasaka, A. Sakoda, M. Ikunaka, R. Obata, S. Nishiyama, T. Sugai, *Tetrahedron Lett.* **2007**, 48, 979. c) K. D. James, N. N. Ekwuribe, *Tetrahedron* **2002**, 58, 5905. d) M. Breznik, D. Kikelji, *Tetrahedron: Asymmetry* **1997**, 8, 425. e) D. Kikelj, L. Povsic, A. Stalc, P. Pristovsek, J. Kidric, *Med. Chem. Res.* **1996**, 6, 118. f) T. Harada, H. Nakajima, T. Ohnishi, M. Takeuchi, A. Oku, *J. Org. Chem.* **1992**, 57, 720. g) P. Blundell, A. K. Ganguly, V. M. S.-P. Girijavallabhan, *Synlett*, **1994**, 263. h) Y. Yasohara, K. Miyamoto, N. Kizaki, J. Hasegawa, T. Ohashi, *Tetrahedron Lett.* **2001**, 42, 3333.

⁷¹ a) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanamasa, *Angew. Chem. Int. Ed.* **2008**, 47, 164. b) N. Shibata, H. Yasui, S. Nakamura, T. Toru, *Synlett* **2007**, 1153. c) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanamasa, *Angew. Chem. Int. Ed.* **2005**, 44, 4204. d) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703.

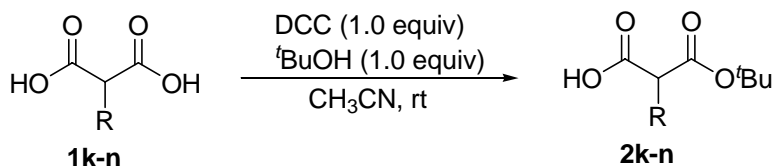
chiral α -hydroxy malonate **45** with a quaternary stereocenter in high yield with high enantioselectivity up to 98% ee. Application of this reaction to the syntheses of biologically attractive molecules illustrates the efficiency of this strategy (Scheme 82).



Scheme 82

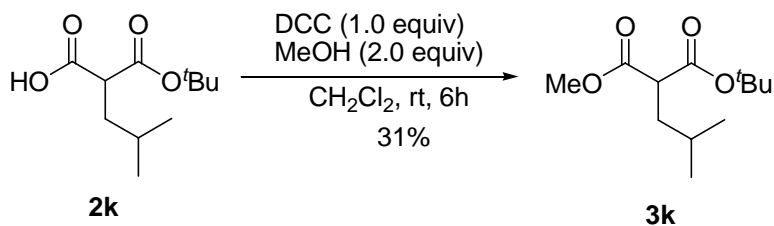
3.2 Synthesis of Malonic esters:

Comercially available α -substituted malonic acids, which are benzyl, ethyl, methyl, and isobutyl malonic acids were monoesterification by using *tert*-butanol (1.0 eq), *N,N'*-dicyclohexylcarbodiimide (DCC) (1.0 eq) in acetonitrile solvent at room temperature, obtained the major amount of the product was formed mono *tert*-butyl ester corboxylic acids in high yields, which were used as crude compounds, without any purification for the next step (Scheme 83).

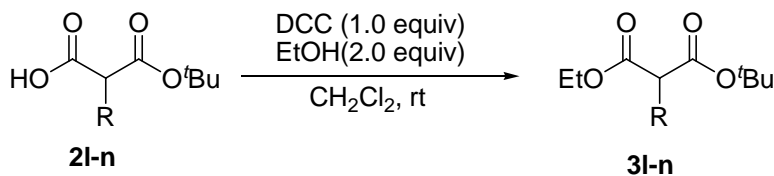


Scheme 83

The above crude product of monocarboxylic *tert*-butyl esters were diesterified by using methanol or ethanol DCC in dichloromethane at room temperature, after purified pure diester malonic compounds were obtained in moderate yields (Scheme 84 and Scheme 85, Table 21).



Scheme 84

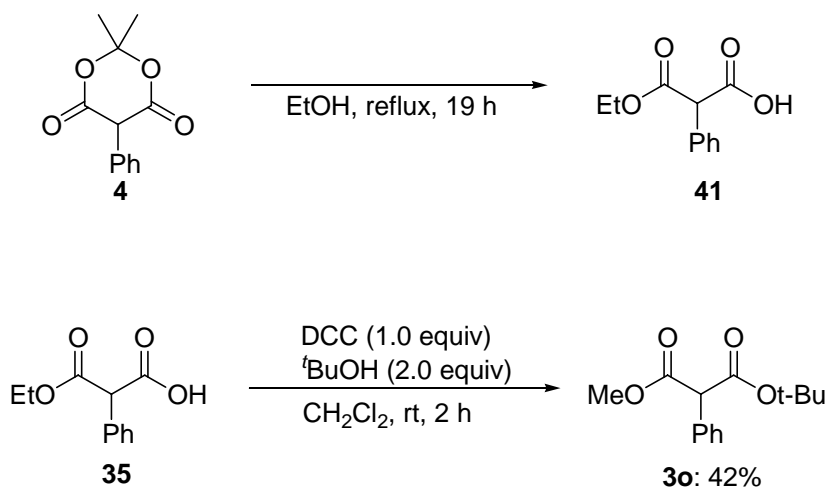


Scheme 84

Table 21

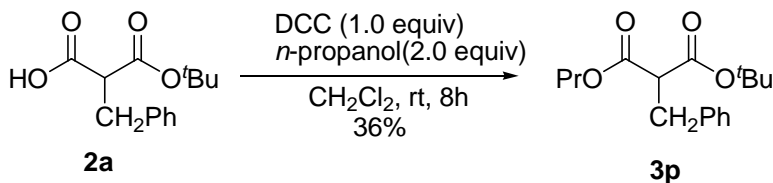
Entry	R	Substrate	Product	Time (h)	Yield (%)
1	Bn	1l	3l	6	44
2	Me	1m	3m	9	26
3	Et	1n	3n	9	40

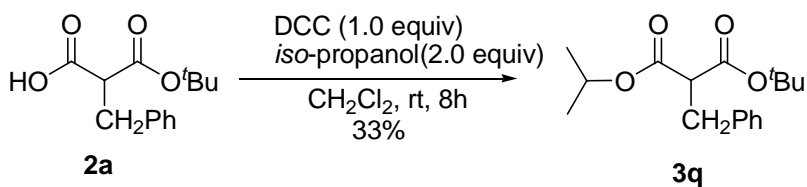
The compound **4** was refluxed in ethanol for 19 hours, obtained the monoester carboxylic acid crude compound **41**, which was proceeded to the next step for the preparation of *tert*butyl, ethyl ester compound, followed by the above step, compound **3o** in 42 yield (Scheme 86).



Scheme 86

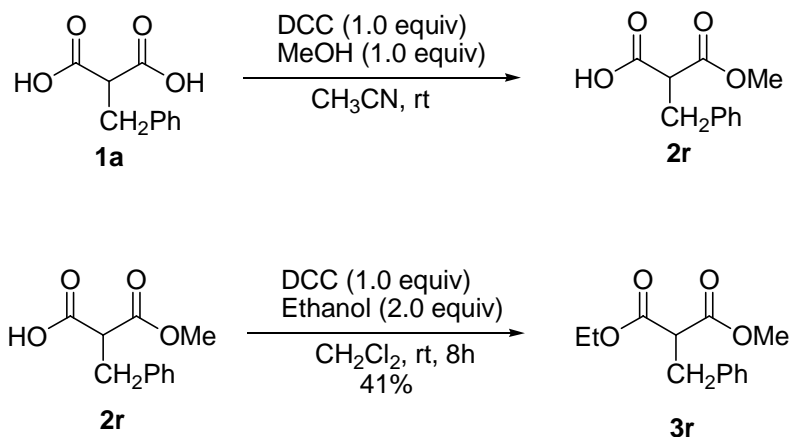
The crude product of benzyl substrate monocarboxylic *tert*-butyl ester **2a** was diesterified by using propanol or isopropanol with DCC in dichloromethane at room temperature, after purified pure diester malonic compounds **3p** and **3q** were obtained in moderate yields (Scheme 87).





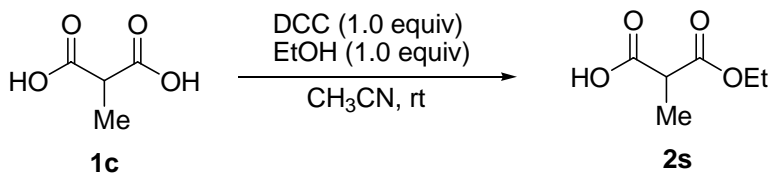
Scheme 87

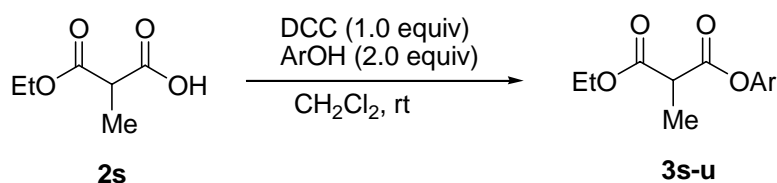
Benzyl substrate methyl ethyl ester malonic ester **3r** was prepared by using similar above procedure (Scheme 88).



Scheme 88

We next prepared methyl substrate various aryl ethyl malonaic esters such as aryl group like, phenyl, para fluorophenyl and 1-naphthyls were also prepared according to the same procedure in moderate to good yields (Scheme 89, Table 22).



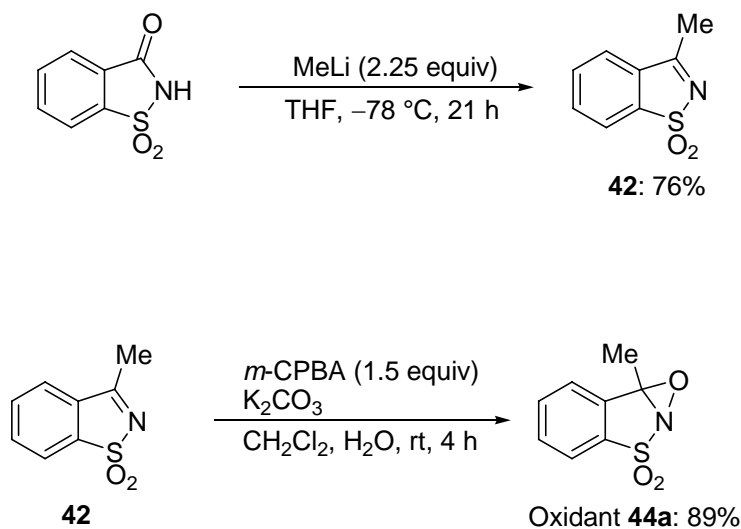


Scheme 89

Table 22

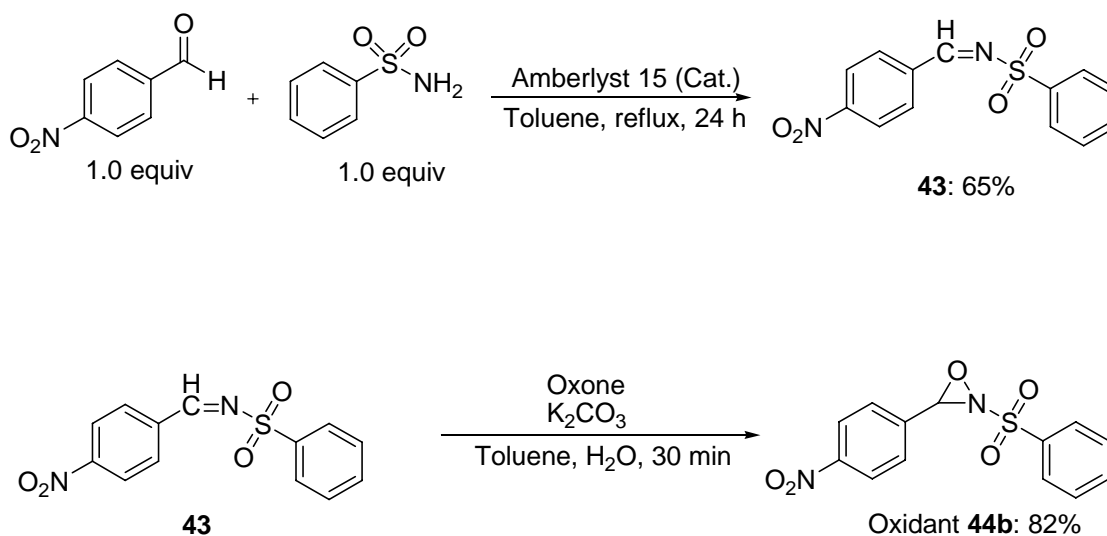
Entry	Ar	Substrate	Product	Time (h)	Yield (%)
1	Ph	1c	3s	6	36
2	4-F-Ph	1c	3t	12	39
3	1-Naphthyl	1c	3u	12	41

Oxidizing agents racemic oxaziridines were prepared according to the reported procedure to synthesized oxidant **44a**⁷² and oxidant **45b**⁷³ (Scheme 90).



⁷² (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinini, G. *Tetrahedron Lett.* **1990**, 31, 4117. (b) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P. Jr.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, 55, 1254.

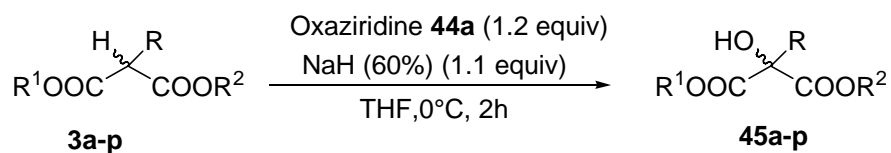
⁷³ (a) Davis, F. A.; Lal, S. G. *J. Org. Chem.* **1988**, 53, 5004. (b) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, 53, 2087.



Scheme 90

3.3 Synthesis of Racemic α -Hydroxy Malonic esters:

Firstly, we prepared racemic hydroxylation of various substrates malonic esters were hydroxylated as shown scheme 91, in Table 23, all the substrates were hydroxylated by using sodium hydride (1.1 eq), and Oxaziridine **44a** (1.2eq) was in THF solvent at -15°C for 2 hours, afforded the corresponding racemic α -substituted, α -hydroxymalonic esters in good yields. Various α -alkyl substrates such as, methyl, ethyl, n-butyl and isobutyl (Table 23, entries 1-3) were obtained in good yields, and aromatic α - substrates, like phenyl and benzyl as well as various ester substrates like ethyl, propyl, isopropyl, phenyl, 4-fluorophenyl and 1-naphthyl also (Table 23, entries 4-7) in good yields, the results are collected in Table 23.



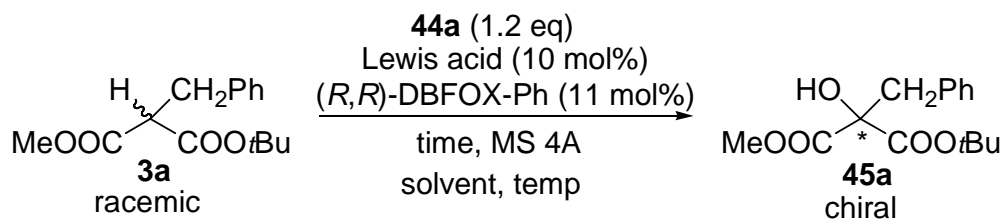
Scheme 91

Table 23

entry	3	R	R ¹	R ²	45	yield (%)
1	3a	CH ₂ Ph	Me	<i>t</i> Bu	45a	60
2	3b	Ph	Me	<i>t</i> Bu	45b	55
3	3c	Me	Me	<i>t</i> Bu	45c	71
4	3d	Et	Me	<i>t</i> Bu	45d	74
5	3e	Bu	Me	<i>t</i> Bu	45e	70
6	3f	<i>i</i> Bu	Me	<i>t</i> Bu	45f	60
7	3g	CH ₂ Ph	Et	<i>t</i> Bu	45g	77
8	3h	Ph	Et	<i>t</i> Bu	45h	66
9	3i	Me	Et	<i>t</i> Bu	45i	55
10	3j	Et	Et	<i>t</i> Bu	45j	68
11	3k	CH ₂ Ph	Pr	<i>t</i> Bu	45k	69
12	3l	CH ₂ Ph	<i>i</i> Pr	<i>t</i> Bu	45l	57
13	3m	CH ₂ Ph	Et	Me	45m	55
14	3n	Me	Et	Ph	45n	53
15	3o	Me	Et	4-FPh	45o	48
16	3p	Me	Et	1-Nap	45p	46

3. 4 Enantioselective Hydroxylation of Malonates (Screening for metal salts and solvents):

We first attempted the direct α -hydroxylation of racemic 2-benzyl-*tert*-butyl methyl malonate (**3a**) with oxaziridine **44a** under the best conditions previously reported for the desymmetrization-like enantioselective fluorination of malonates^[7] in the presence of Zn(OAc)₂ and 4 Å molecular sieves in CH₂Cl₂ at room temperature. However, even after 1 day of stirring, the reaction did not proceed (Table 24, run 1). Under the reflux condition the corresponding 2-hydroxy-2-benzyl-*tert*-butyl methyl malonate (**45a**) was obtained in 15% yield with 92% ee (run 2). When the reaction was performed in the presence of Ni(ClO₄)₂·6H₂O in CH₂Cl₂ under the reflux temperature, the yield was improved to 60% with 91% ee (run 3). The addition of 1 equiv of 2,6-lutidine as base to the reaction media dramatically improved the yield of **45a** even at lower temperatures, but the enantioselectivities were not excellent (83—91% yields, 82—84% ee, runs 4—5). Optimization experiments for both Lewis acid and solvent were carried out to improve both the yield and enantioselectivity of the transformations (runs 6—14), and we found that the combination of Ni(ClO₄)₂·6H₂O in 1,2-dichloroethane at reflux temperature was very effective for the desymmetrization-like catalytic enantioselective α -hydroxylation of malonates (run 6). The structure of the oxidant slightly affected the yield and enantioselectivity of **45a**. Changing the oxidant from cyclic oxaziridine **44a** to acyclic 3-(4-nitrophenyl)-2-(phenylsulfonyl)-1,2-oxaziridine (**44b**) resulted in lower yields with lower ees (runs 15 and 16).



Scheme 92

Table 24

run	Lewis acid	solvent	temp (°C)	T (h)	yield ^[b] (%)	ee ^[c] (%)
1	Zn(OAc) ₂	CH ₂ Cl ₂	rt	24	trace	—
2	Zn(OAc) ₂	CH ₂ Cl ₂	reflux	36	15	92
3	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	reflux	42	60	91
4 ^[d]	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	rt	24	91	82
5 ^[d]	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	−20	48	83	84
6	Ni(ClO ₄) ₂ ·6H ₂ O	ClCH ₂ CH ₂ Cl	reflux	48	82	91

7	Zn(OAc) ₂	ClCH ₂ CH ₂ Cl	reflux	80	trace	—
8	Zn(OTf) ₂	ClCH ₂ CH ₂ Cl	reflux	48	77	89
9	Ni(OAc) ₂ ·4H ₂ O	ClCH ₂ CH ₂ Cl	reflux	48	0	—
10	Sc(OTf) ₂	ClCH ₂ CH ₂ Cl	reflux	60	trace	53
11	Mg(ClO ₄) ₂	ClCH ₂ CH ₂ Cl	reflux	60	trace	7
12	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	reflux	60	19	0
13	Ni(ClO ₄) ₂ ·6H ₂ O	EtOH	reflux	60	0	—
14	Ni(ClO ₄) ₂ ·6H ₂ O	toluene	85	60	20	85
15 ^[e]	Ni(ClO ₄) ₂ ·6H ₂ O	CH ₂ Cl ₂	reflux	62	28	87
16 ^[e]	Zn(OAc) ₂	CH ₂ Cl ₂	reflux	48	41	49

a) Reaction **3a** with oxaziridine **45a** was carried out in the presence of Lewis acid (10 mol%), (*R,R*)-DBFOX-Ph (11 mol%), and molecular sieves (4Å) in solvent

b) Yield of isolated product

c) Determined by chiral HPLC analysis

d) 2,6-Lutidine (1.0 equiv) was added

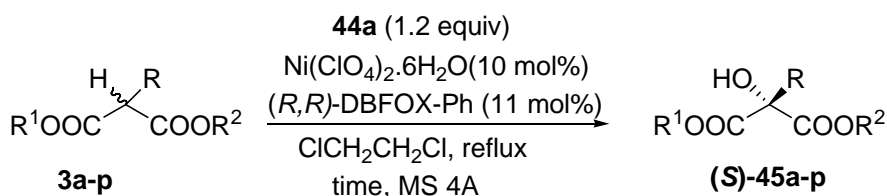
e) Oxaziridine **44b** was used instead of **44a**.

3.5 Preparation of Optically Active Hydroxylated Malonic Esters (various substrates and various ester groups):

With the conditions now optimized, we next explored the scope of the hydroxylation reaction in terms of substrates (Scheme 93, Table 25). First we examined the effect of substitutions on the stereogenic centre at the α -position of malonates to the enantioselective transformation. The results showed that the aryl and alkyl substitutions at the α -position of **3** have less effect on the yields and enantioselectivities and they were indeed good substrates to afford **45a—e** in high enantioselectivities (91—98% ees, entries 1—5). The hydroxylation of the malonate **3f** with a sterically demanding *i*Bu group also proceeded nicely to give **45f** with 88% ee (entry 6). We next investigated the scope, limitation and ability of the present method to sterically discriminate the ester moieties. As shown in Table 25, the DBFOX/Ni(II) catalyst can efficiently discriminate not only the Me/*t*Bu-ester system (entries 1—6) but also the Et/*t*Bu-ester system (entries 7—10) as well as the Pr/*t*Bu-esters (entry 11) at a level of more than 90% ee. *It should be noted that the discrimination between both sterically hindered iPr and tBu esters is possible to give the product 39l with 82% ee (entry 12).*

We further attempted the discrimination between Me and Et esters by using malonate **3m**. However, the desired product **45m** was obtained in 98% yield with 12% ee

(entry 13). These results indicate that the *tert*-butyl ester moiety in malonate **3** should be responsible for the enantioselective transformation. Steric discrimination between Ph and Et esters of **3n** have also been possible by the DBFOX/Ni(II) catalyst at 66% ee to give **45n** (entry 14), but the level of ee was not quite satisfactory. When oxaziridine **44b** was used, 60% ee of **3n** was obtained (entry 15). In order to improve its enantioselectivity, we further attempted the same reaction of **1n** using 2 equiv of the oxaziridines **44a** and **44b**, but the results were slightly worse (entries 16 and 17). These results could be explained in light of the matched/mismatched concept for this reaction between two chiral molecules, DBFOX-Ph and oxaziridines. To see the matched/mismatched effect of **3** more clearly, we investigated the reaction of **3n** with an alternated oxaziridine **44c** that is available in both enantiomeric forms. Although the reactivity of oxaziridine **3c** was very low, the reaction of **3n** with (+)-**44c** proceeded with high enantioselectivity of 81% ee to produce **45n** in the matched case. The mismatched case with (-)-**44c** provided a trace amount of product (entries 18 and 19). We next undertook the reaction of aryl ethyl malonates larger substituents on the benzene ring to overcome the low discrimination problem between ph and Et esters. It should be noted that the enantioselectivity was finally improved to 88% ee and 90% ee by the use of larger aryl-substituents, an *o*-fluorophenyl ester **45o** and 1-naphthyl ester **45p**, respectively (entries 20 and 21), in Scheme 93, Table 25.



Scheme 93

Table 25

entry	3	R	R ¹	R ²	time (h)	45	yield (%)	ee ^[a] (%)
1	3a	CH ₂ Ph	Me	<i>t</i> Bu	48	45a	82	91
2	3b	Ph	Me	<i>t</i> Bu	12	45b	83	93
3	3c	Me	Me	<i>t</i> Bu	16	45c	84	98
4	3d	Et	Me	<i>t</i> Bu	36	45d	74	95
5	3e	Bu	Me	<i>t</i> Bu	36	45e	80	94

6	3f	<i>i</i> Bu	Me	<i>t</i> Bu	48	45f	65	88
7	3g	CH ₂ Ph	Et	<i>t</i> Bu	48	45g	71	91
8	3h	Ph	Et	<i>t</i> Bu	16	45h	74	90
9	3i	Me	Et	<i>t</i> Bu	14	45i	72	94
10	3j	Et	Et	<i>t</i> Bu	62	45j	52	90
11	3k	CH ₂ Ph	Pr	<i>t</i> Bu	48	45k	63	90
12	3l	CH ₂ Ph	<i>i</i> Pr	<i>t</i> Bu	62	45l	48	82
13	3m	CH ₂ Ph	Et	Me	14	45m	98	12
14	3n	Me	Et	Ph	3	45n	80	66
15 ^b	3n	Me	Et	Ph	2	45n	55	60
16 ^c	3n	Me	Et	Ph	3	45n	79	54
17 ^{b,c}	3n	Me	Et	Ph	1	45n	59	47
18 ^d	3n	Me	Et	Ph	16	45n	24	81
19 ^e	3n	Me	Et	Ph	24	45n	trace	–
20	3o	Me	Et	<i>o</i> -F-Ph	2	45o	91	88
21	3p	Me	Et	1-naphthyl	2	45p	93	90

a) Determined by chiral HPLC analysis. The absolute configuration of **45n** was determined to be *S* by comparing the optical rotation of the known (*S*)-1-ethyl 3-phenyl-2-hydroxy-2-methylmalonate, and the stereochemistry of the other malonate **45** was tentatively assumed by analogy.

b) Oxaziridine **44b** was used instead of **44a**.

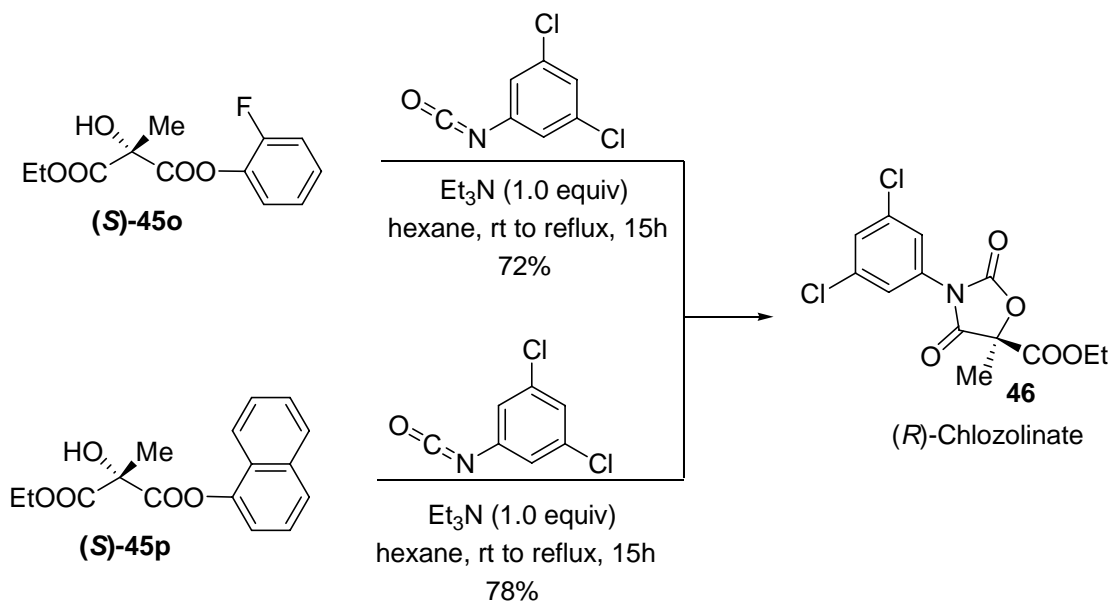
c) The reaction was performed at rt.

d) Oxaziridine (+)-**44c** was used instead of **44a**.

e) Oxaziridine (-)-**44c** was used instead of **44a**.

3.6 Synthesis of (*R*)-Chlozolate (46):

The utility of 2-hydroxy malonate **45** was next demonstrated by the synthesis of chlozolate (**46**), an important antifungal agent.⁷⁴ Previously (*R*)-chlozolate **46** was synthesized by Guanti and co-workers based on enzymatic desymmetrization,⁷⁵ However, the synthesis requires multiple-step transformations. They were synthesized by using phenylester compound, our method allowed access to **46** by only a two-step from the racemic malonate **45o** and **45p** via chiral **45o** and **45p** (Scheme 82). Namely, treatment of (*S*)-**45p** (90% ee) or (*S*)-**45o** (88% ee) with 3,5-dichlorophenyl isocyanate in the presence of triethylamine at rt in hexane, afforded enantiomerically enriched (*R*)-chlozolate **46**.

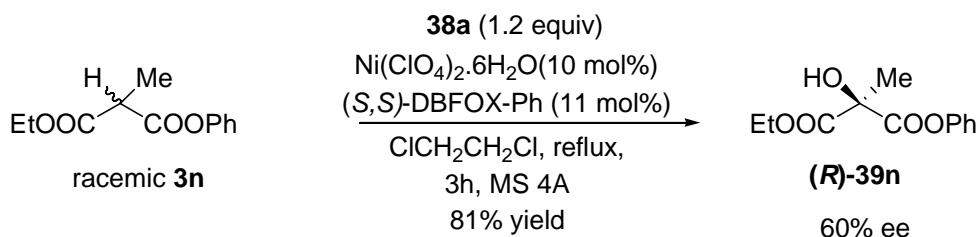


Scheme 94

⁷⁴ a) D. T. Vincenzo, G. Franco, M. Cecere, S. Lorusso, C. Garavaglia, *Ger. Offen.* **1979**, 2906574, *Chem. Abstr.* 92, 41923w. b) C. Lentza-Rizos, E. J. Avramides, A. Argyropoulou, V. Papadimitriou, K. Kokkinaki, *J. Agric. Food Chem.* **2000**, 48, 2522. c) T. M. Stewart, P. G. Long, *New Zeal J Exp Agr.* **1987**, 15, 97

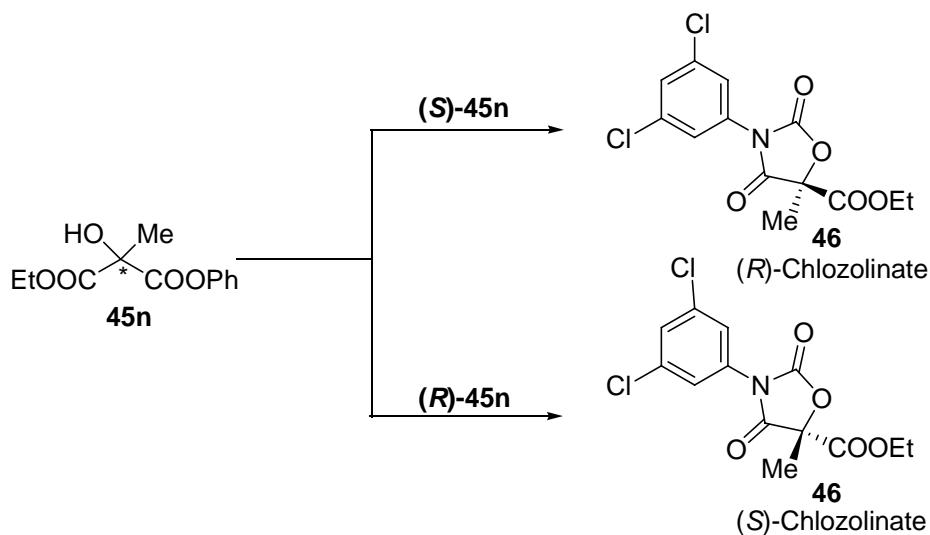
⁷⁵ G. Guanti, L. Banfi, K. Powels, M. Rasparini, C. Scolastico, N. Fossati, *Tetrahedron: Asymmetry* **2001**, 12, 271

We also prepared opposite enantiomer of the product phenylester was prepared by using (*S,S*) DBFOX-Ph was used instead of (*R,R*) DBFOX-Ph used as in same condition, the product was obtained in 81% yield and 60% enantioselectivity (Scheme 95).



Scheme 95

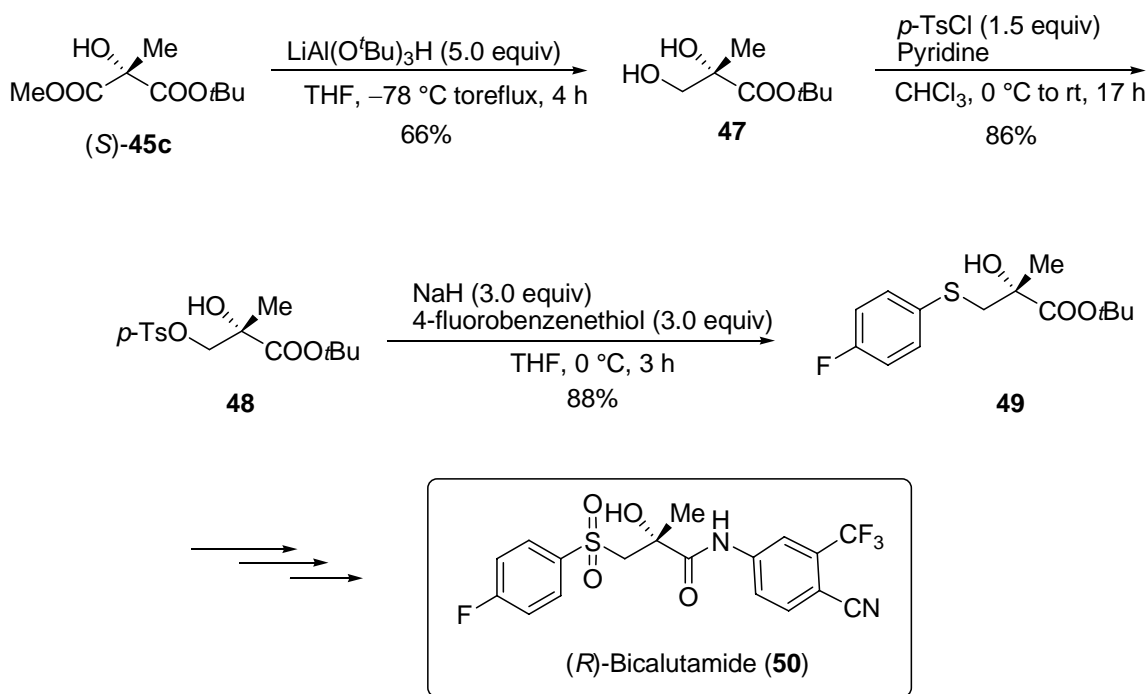
R and *S* chlozolinates (**46**) were synthesized using malonate hydroxylated both enantiomers with the same reported condition, in single step, such as the treatment of 3,5-dichlorophenyl isocyanate (1.5 equiv), in the presence of triethylamine (1.0 equiv), afforded chlozolate 3 in good yields, after a single recrystallization **46**(*R*) from absolute ethanol gave in 64% yield with high optical purity (scheme 96).



Scheme 96

3.7 Synthesis of bicalutamide (50)

We also considered the synthesis of a key intermediate of bicalutamide derivatives.⁷⁶ Bicalutamide (**50**) sold under the trade name Casodex[®] is the leading antiandrogen used for the treatment of prostate cancer. Bicalutamide is a racemic mixture with most of its activity residing in (*R*)-isomer. The chemoselective reduction of (*S*)-**45c** was successfully achieved by using $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$ ⁷⁷ to yield 66% of (*S*)-*tert*-butyl-2-hydroxy-2-(hydroxymethyl)propanoate (**47**). The primary hydroxyl group of **47** was then protected using *p*-toluenesulfonyl chloride and pyridine in CHCl_3 to give the tosylate **48**. Nucleophilic substitution of **48** by sodium 4-fluorobenzenethiol furnished (*R*)-**49**, which should be useful as a common intermediate for the syntheses of (*R*)-bicalutamide as well as its derivatives (Scheme 97).



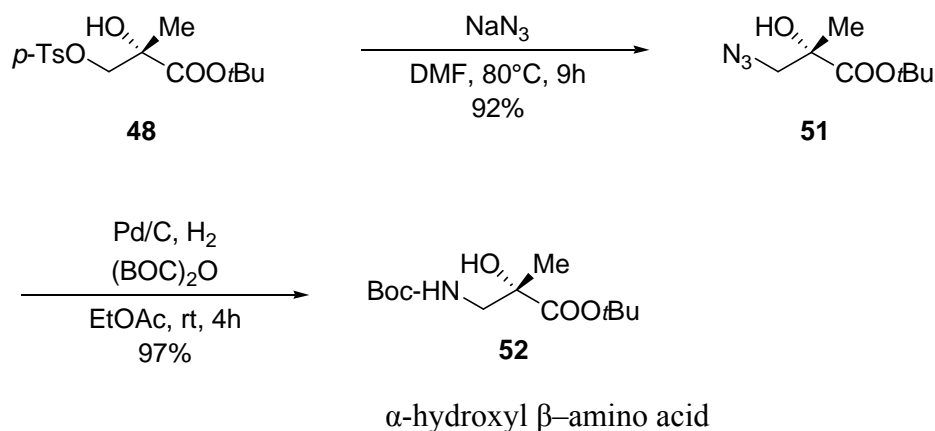
Scheme 97

⁷⁶ a) A. Fujino, M. Asano, H. Yamaguchi, N. Shirasaka, A. Sakoda, M. Ikunaka, R. Obata, S. Nishiyama, T. Sugai, *Tetrahedron Lett.* **2007**, 48, 979-983; b) K. D. James, N. N. Ekwuribe, *Tetrahedron* **2002**, 58, 5905; c) G. Blackledge, G. Kolvenbag, A. Nash, *Anticancer Drugs* **1996**, 7, 27; d) P. Iversen, M. A. Roder, *Expert Rev. Anticancer Ther.* **2008**, 8, 361; e) H. Tucker, J. W. Crook, G. J. Chesterson, *J. Med. Chem.* **1988**, 31, 954; f) T. Sugai, M. Ikunaka, H. Yamaguchi, *Jpn. Kokai Tokkyo Koho*, **2007**, JP 2007204420; g) A. Bor, G. Orosz, F. Lukacs, G. Schneider, *Eur. Pat. Appl.* **2006**, EP 1669347.

⁷⁷ T. A. Ayers, *Tetrahedron Lett.* **1999**, 40, 5467

3.8 Synthesis of (*S*)-2-methyl isoserine derivative (α -hydroxyl β -amino acid):

A methodology for the synthesis of hydroxylated α -methyl- β -serine (**52**) amino acid has been synthesized from compound (*S*)-*t*-Butyl 2-hydroxy-2-(hydroxymethyl)-3-propionate (**47**). Nucleophilic azidation of tosyl protected compound (**48**) with NaN₃ (3.0 equiv) in DMF at 80°C for 9 hours, obtained (*S*)-*t*-Butyl 3-azido-2-methyl-2-hydroxy (**51**) compound in 92% yield, and which was subsequent hydrogenolysis and in situ Boc protection under H₂ in the presence of Pd/C and (Boc)₂O in AcOEt solvent afforded the α -hydroxy- α -methyl- β -amino acid target compound (**52**) in 97% yield (Scheme 98).



Scheme 98

3.9 Determination of the absolute configuration of (45):

The stereochemistry of the resulting hydroxy-malonate **45** can be explained by the preferential approach of hydroxylating agent **44** from the less hindered *Si* face of the substrates/Ni(II)/DBFOX-Ph complex, based on the mechanism of the previous paper for the enantioselective fluorination of malonates by Zn(II)/DBFOX-Ph catalysis (Figure 7). The octahedral complex coordinated with a water molecule for **3c**/DBFOX-Ph/Ni(II) optimized using PM3 (Spartan '06) in the light of the X-ray structure of the DBFOX-Ph/Ni(II) complex was also shown (Figure 9).

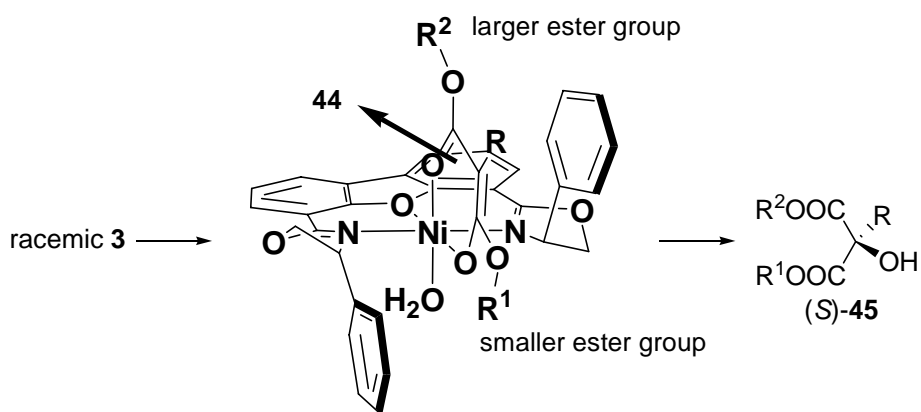


Figure 8. Transition state structure for the DBFOX-Ph/Ni(II)-catalyzed enantioselective hydroxylation of malonates **3** to *(S)*-**45**

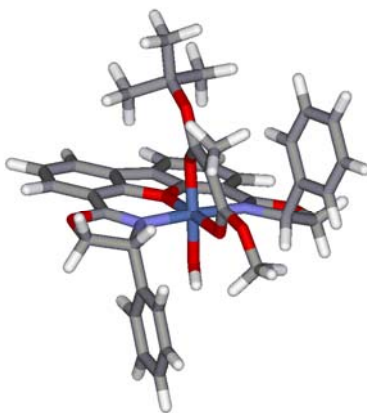
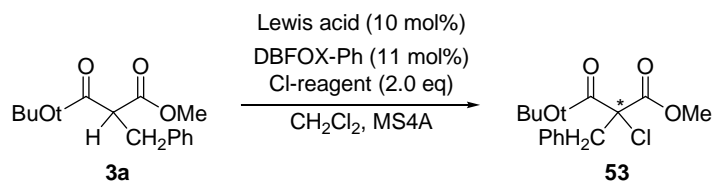


Figure 8. Optimized structure of the complex of **1c**/DBFOX-Ph/Ni(II)

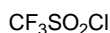
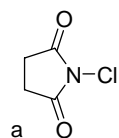
3.10 Enantioselective Chlorination of Malonic ester Compounds:



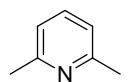
Scheme 99

Table 26

Entry	Cl-reagent	Lewis acid	base		temp(°C)	Time(h)	Yield(%)	Ee(%)
1	a	Zn(OAc) ₂	-	-	rt	48	trace	12
2	a	Zn(OAc) ₂	-	-	reflux	72	95	19
3	b	Ni(ClO ₄) ₂ ·6H ₂ O	-	-	rt	72	23	97
4	b	Ni(ClO ₄) ₂ ·6H ₂ O	1.0eq	-	rt	24	99	63
5	b	Ni(ClO ₄) ₂ ·6H ₂ O	-	seal tube	50	36	51	90
6	b	Zn(OAc) ₂	-	seal tube	50	36	35	65



b



base
(2,6-lutidine)

We attempted the asymmetric chlorination of malonates using DBFOX-Ph/Lewis acid metal complexes (Scheme x, Table xx), when we used NCS reagent, we got excellent yield but low ee. In case of CF₃SO₂Cl reagent the ee was increased up to 97% (entry 3). 2,6-lutidine was given high chemical yield and ee value up to 63% (entry 4). Zinc acetate was not effective for this malonate chlorination, and also we attempted in seal tube reaction, yields were only moderate but enantioselectivity was excellent (entry 5 and 6).

3.11 Conclusion

In conclusion, we have achieved the highly enantioselective direct hydroxylation of malonate (**45**) by the use of DBFOX-Ni(II) complex for the first time ever. The biologically attractive optically active molecules including (*R*)-chlozolate were synthesized from corresponding chiral malonates. Dynamic kinetic asymmetric transformation in the functionalization of racemic malonate based on this strategy.

Chapter 4. Summary

The thesis consists of design and synthesis of asymmetric enantioselective fluorinated malonates using DBFOX-Ph/Lewis acid complexes and further its application to synthesized various fluorinated biologically active molecules, and development of enantioselective fluorination of α -aryl acetyl thiazolidinones were studied. Development of direct α -hydroxylation of asymmetric malonates was also studied.

In Chapter 1, desymmetrization-like catalytic enantioselective fluorination of malonates were described. The using of DBFOX-Ph/Ni(II) or Zn(II) complexes in catalytic amount and achiral NFSI as a fluorinating agent in presence of molecular sieves obtained high yields with excellent enantioselectivity of various substrate malonic esters were obtained. These 2-fluorinated malonates can be easily converted in to the corresponding hydroxylated fluorine compounds in good yields by chemoselective reduction. The 2-fluoromalonates can also converted in to the unsymmetrical ester- amide exchange reaction. We have demonstrated valuable starting materials for the preparation of pharmaceutically attractive molecules, such as fluorinated β -amino acids, β -lactam and total synthesis of the ACE inhibitor fluoro-alacepril was synthesized by the first time. HIV-1 protease inhibitor fluorinated retroamide isostere also we synthesized.

In Chapter 2, we demonstrated that DBFOX-Ph/Ni(II) complex catalyzed asymmetric enantioselective fluorination of α -arylacetyl thiazolidinones with or without 2,6-lutidine and achiral NFSI to produced for the electrophilic fluorine to afford chiral 2-fluoro 2-arylacetates derivatives in good yields with up to 78% ee. In order to determine suitable reaction conditions for the catalytic enantioselective fluorination of α -aryl acetates. We further investigated and found addition of HFIP as a additive is beneficial to furnish high chemical yields excellent enantioselectivity up to 99% ee of the chiral monifluorinated compounds. We also succeeded enantioselective fluorination of allyl aryl thiazolidinones in high chemical yields with excellent enantioselectivities.

In Chapter 3, dynamic kinetic asymmetric transformation in the α -hydroxylated malonates were described. The using of DBFOX-Ph/Ni(II) complexe in catalytic, with oxaziridine as the electrophilic oxidizing agent. This procedure provides a novel highly enantioselective direct α -hydroxylation of malonic esters with various substrates as well as the various ester groups such as alkyl or aryl esters, the chiral 2-hydroxylated malonates in high yields with high enantioselectivity up to 98% ee. Changing the oxidant cyclic oxaziridine to acyclic oxaziridine and enantiomeric oxaziridines also investigated for asymmetric hydroxylation of malonates. Chiral α -hydroxy malonates and their equivalents are a valuable class of compounds utilized in the synthesis of drug candidates. The utility of 2-hydroxy malonate was next demonstrated by the synthesis of chlozolate by only single step, it is an important antifungal agent and also synthesized a key intermediate of bicalutamide derivatives, which is used in drug therapy to treat prostate cancer.

Experimental Section:

Chapter 1

General procedure for the Catalytic Enantioselective Fluorination of Malonic esters :

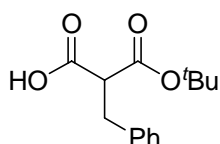
Zn(OAc)₂ (10 mol%) and the (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) (11 mol%) were stirred under vacuum for 2 h at room temperature. Dry CH₂Cl₂ (0.3 mL) and MS 4A (substrate/MS 4A=1:500 mol/g) were added under nitrogen atmosphere and stirred for 1 h. Then a solution of malonic esters (0.10-0.25 mmol) in dry CH₂Cl₂ (0.2 mL) was added to catalyst solution. After stirring for another 30 min, *N*-fluorobenzenesulfonimide (1.2 equiv) was added directly to the reaction mixture. The reaction was stirred under reflux for 15-48 h with monitoring by TLC, it was stopped by the addition of water. The reaction mixture was then diluted with CH₂Cl₂, washed with saturated aqueous sodium bicarbonate solution, washed with brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. Crude product was purified by column chromatography on silica gel eluting with hexane/AcOEt to give compound **9**. The ee of the product **9** was determined by chiral HPLC on CHIRALCEL OJ-H or CHIRALCEL OD-H column and GC.

Malonic esters were prepared according to literature.⁷⁸ (*R,R*)-4,6-Dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) (DBFOX-Ph) was prepared following a literature procedure.⁷⁹

General procedure for the preparation of malonic esters:

Malonic acid (1.0 equiv) was dissolved in acetonitrile solvent (10 ml) and alcohol (1.0 equiv) was added to this solution, and cooled to 0°C. *N,N'*-Dicyclohexylcarbodiimide (1.0 equiv) (DCC) in acetonitrile (10 ml) was added to the above dropwise, which was stirred overnight at rt for several hours. Filtered the reaction mass, washed with the solvent and evaporated solvent, obtained crude product as a syrup, which was proceeded next step without any purification.

t-Butyl 2-benzylmalonic acid (**2a**)



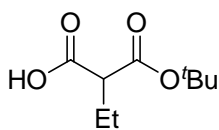
The reaction of **1a** (1.0 g, 5.15 mmol) acetonitrile (10 ml), *tert*-Butylalcohol (0.47 ml, 5.15 mmol) and (1.06 g, 5.15 mmol) DCC in acetonitrile (10 ml) which was stirred overnight at rt for 20 hours. Filtered and evaporated solvent, gave **2a** as a colorless syrup.

⁷⁸ R. Shelkov, M. Nahmany, A. Melman, *J. Org. Chem.* **2002**, 67, 8975-8982.

⁷⁹ U. Iserloh, D. P. Curran, S. Kanemasa, *Tetrahedron: Asymmetry* **1999**, 10, 2417-2428.

Molecular formula: C₁₄H₁₈O₄

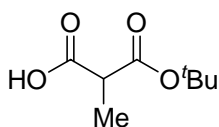
***t*-Butyl 2-ethylmalonic acid (2b)**



The reaction of **1b** (1.0 g, 7.57 mmol) acetonitrile (10 ml), *tert*-Butylalcohol (0.72 ml, 7.57 mmol) and (1.56 g, 7.57 mmol) DCC in acetonitrile (10 ml) which was stirred overnight at rt for 15 hours. Filtered and evaporated solvent, gave **2b** as a colorless syrup.

Molecular formula: C₉H₁₆O₄

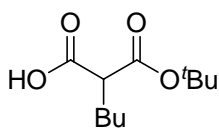
***t*-Butyl 2-methylmalonic acid (2c)**



The reaction of **1c** (2.0 g, 16.9 mmol) acetonitrile (10 ml), *tert*-Butylalcohol (1.60 ml, 16.9 mmol) and (3.49 g, 16.9 mmol) DCC in acetonitrile (10 ml) which was stirred overnight at rt for 15 hours. Filtered and evaporated solvent, gave **2c** as a colorless syrup.

Molecular formula: C₈H₁₄O₄

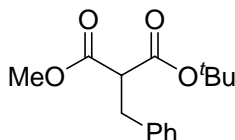
***t*-Butyl 2-butylmalonic acid (2d)**



The reaction of **1d** (1.0 g, 6.24 mmol) acetonitrile (10 ml), *tert*-Butylalcohol (0.47 ml, 6.24 mmol) and (1.06 g, 6.24 mmol) DCC in acetonitrile (10 ml) which was stirred overnight at rt for 16 hours. Filtered and evaporated solvent, gave **2d** as a colorless syrup.

Molecular formula: C₁₁H₂₀O₄

1-*tert*-Butyl 3-methyl 2-benzylmalonate (3a)



40% yield).

The reaction of **2a** (1.29 g, 5.15 mmol) dichloromethane (10 ml), methanol (0.42 ml, 10.3 mmol) and (1.06 g, 5.15 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 3 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3a** in (549.7 mg, after 2 steps

Color less liquid

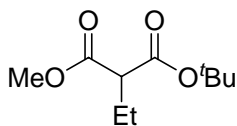
Molecular formula: C₁₅H₂₀O₄

M. W.: 264.32

R_f=0.44 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.38 (s, 9H), 3.17 (d, *J*=8.0 Hz, 2H), 3.56 (d, *J*=8.2 Hz, 1H), 3.59 (d, *J*=8.2 Hz, 1H), 3.69 (s, 3H), 7.17-7.27 (m, 5H)

1-*tert*-Butyl 3-methyl 2-ethylmalonate (**3b**)



The reaction of **2b** (1.42 g, 7.57 mmol) dichloromethane (10 ml), methanol (0.62 ml, 15.1 mmol) and (1.56 g, 7.57 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 15 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=95: 5) obtained **3a** in (300 mg, after 2 steps 21% yield).

Color less liquid

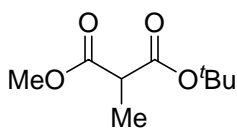
Molecular formula: C₁₀H₁₈O₄

M.W.: 202.11

R_f=0.56 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 0.99 (t, *J*=7.2 Hz, 3H), 1.46 (s, 9H), 1.89 (t, *J*=7.4 Hz, 2H), 3.17 (t, *J*=8.0 Hz, 1H), 3.72 (s, 3H)

1-*tert*-Butyl 3-methyl 2-methylmalonate (**3c**)



The reaction of **2c** (2.94 g, 16.9 mmol) dichloromethane (10 ml), methanol (1.39 ml, 33.8 mmol) and (3.49 g, 16.9 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 15 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3c** in (2.37 g, after 2 steps 39% yield).

Color less liquid

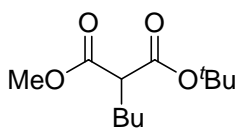
Molecular formula: C₉H₁₆O₄

M.W.: 188.11

R_f=0.46 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.38 (d, *J*=7.2 Hz, 2H), 1.46 (s, 9H), 3.35 (q, *J*=7.2 Hz, 1H), 3.73 (s, 3H)

1-*tert*-Butyl 3-methyl 2-butylmalonate (**3d**)



The reaction of **2d** (1.29 g, 16.9 mmol) dichloromethane (10 ml), methanol (0.51 ml, 12.5 mmol) and (1.06 g, 6.24 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 3 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3d** in (355.2 mg, after 2 steps 26% yield).

Color less liquid

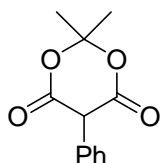
Molecular formula: C₁₂H₂₂O₄

M.W.: 230.13

R_f=0.61 (Hexane: AcOEt=80: 20)

¹H-NMR (CDCl₃, 200 MHz): δ 0.90 (t, *J*=6.8 Hz, 3H), 1.26-1.39 (m, 4H), 1.45 (s, 9H), 1.79-1.91 (m, 2H), 3.23 (t, *J*=7.6 Hz, 1H), 3.17 (s, 3H), 3.69 (s, 3H)

2,2-Dimethyl-5-phenyl-1,3-dioxane-4,6-dione (4)



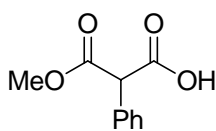
2-phenylmalonic acid (2.0 g, 11.1 mmol), was charged into a flask and cooled to 0°C, acetic anhydride (1.26 ml, 13.3 mmol), H₂SO₄ (2 drops), and acetone (1.07 ml, 14.4 mmol) was added, which was stirred for 2 hours and added cold water then filtered, afforded (1.18 g, 48%).

White solid

Molecular formula: C₁₂H₁₂O₄

M.W.: 220.22

3-Methyl 2-phenylmalonic acid (5)

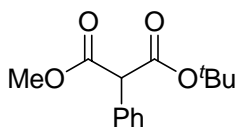


2,2-Dimethyl-5-phenyl-1,3-dioxane-4,6-dione (1.0 g, 4.54 mmol) was dissolved in methanol (10 ml), and refluxed for 19 hours obtained carboxylic acid compound as a syrup in quantitative, which was used next step without purification.

Molecular formula: C₁₀H₁₀O₄

M.W.: 194.18

1-*tert*-Butyl 3-methyl 2-phenylmalonate (3e)



The reaction of Methyl 2-phenylmalonic acid **5** (881 mg, 4.54 mmol) dichloromethane (10 ml), *tert*-Butylalcohol (0.43 ml, 9.08 mmol) and (1.87 g, 4.54 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 3 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=95: 5) obtained **3e** in (497.1 mg, after 2 steps 44% yield).

Colorless oil

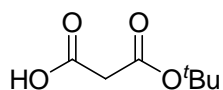
Molecular formula: C₁₀H₁₈O₄

M.W.: 250.29

R_f=0.51 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.45 (s, 9H), 3.74 (s, 3H), 4.54 (s, 1H), 7.32-7.35 (m, 5H)

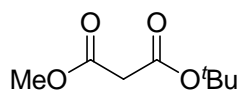
t-Butyl malonic acid (6)



Malonic acid (2.0 g, 19.2 mmol) in acetonitrile (20 ml), *tert*-Butylalcohol (1.76 ml, 19.2 mmol) and DCC (3.97 g, 19.2) in acetonitrile (10.0 ml) as per the general procedure for 15h, in quantitative yield as a syrup.

Molecular formula: C₇H₁₂O₄

1-*tert*-Butyl 3-methyl malonate (7)



The reaction of *t*-Butyl malonic acid **6** (3.08 g, 19.2 mmol) dichloromethane (20 ml), methanol (1.56 ml, 38.5 mmol) and (3.97 g, 19.2 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 3 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **7** in (1.28 g, after 2 steps 38% yield).

Colorless liquid

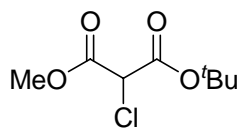
Molecular formula: C₈H₁₄O₄

M.W.: 174.19

R_f=0.64 (Hexane: AcOEt=80: 20)

¹H-NMR (CDCl₃, 200 MHz): δ 1.47 (s, 9H), 3.29 (s, 2H), 3.74 (s, 3H)

1-*tert*-Butyl 3-methyl 2-chloromalonate (8)



t-Butyl methyl malonate (**7**) (601.0 mg, 3.45 mmol), was dissolved in dichloromethane, and cooled to 10°C, sulfuryl chloride (0.28 ml, 3.45 mmol) was added to the reaction mass at 10°C, which was stirred for 1 hour at same temperature and evaporated solvent, purified by column eluted with (Hexane: AcOEt=90: 10) obtained **8** in (630.3 mg, 88% yield).

Colorless liquid

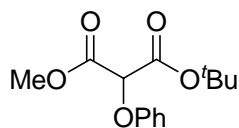
Molecular formula: C₈H₁₃ClO₄

M.W.: 208.64

R_f=0.22 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.50 (s, 9H), 3.91 (s, 3H), 4.76 (s, 1H)

1-*tert*-Butyl 3-methyl 2-(phenoxy)malonate (3f)



Sodium hydride (NaH 60%) 57.6 mg, 1.44 mmol) was charged in to a flask, and added dry THF solvent, which was cooled to 0°C, phenol (135.5 mg, 1.44 mmol) was in THF (0.5 ml) was added to above. Then *t*-Butyl methyl 2-chloromalonate (**8**) (300 mg, 1.44 mmol), TMEDA (0.21 ml, 1.44 mmol) in THF (0.5 ml) was to above reaction mixture, which was refluxed for 6 hours. Which was cooled and quench with saturated sodium

bicarbonate solution and extracted with dichloromethane solvent, organic layer washed with brine and evaporated solvent, purified by column eluted with (Hexane: AcOEt=90: 10) obtained **3f** in (110 mg, 25% yield).

Colorless oil

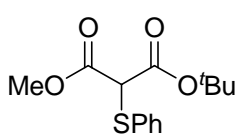
Molecular formula: C₁₄H₁₈O₅

M.W.: 301.11

R_f=0.33 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.48 (s, 9H), 3.84 (s, 3H), 5.11 (s, 1H), 6.92-6.97 (m, 3H), 7.24-7.29 (m, 2H)

1-*tert*-Butyl 3-methyl 2-(phenylthio)malonate (**3g**)



t-Butyl methyl 2-chloromalonate (**8**) (300 mg, 1.44 mmol), was charged in to a flask, and added dry CH₂Cl₂ solvent, which was cooled to 0°C, thiophenol (0.15 ml, 1.44 mmol), and TEA (0.21 ml, 1.51 mmol) was to above reaction mixture, which was stirred at rt for 24 hours. Which was cooled and quench with saturated sodium bicarbonate solution and extracted with dichloromethane solvent, organic layer washed with brine and evaporated solvent, purified by column eluted with (Hexane: AcOEt=90: 10) obtained **3g** in (260 mg, 57% yield).

Pale yellow liquid

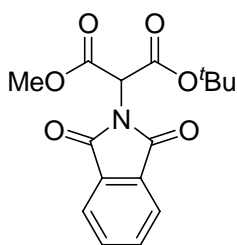
Molecular formula: C₁₄H₁₈O₄S

M.W.: 317.60

R_f=0.32 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.47 (s, 9H), 3.29 (s, 1H), 3.74 (s, 3H), 7.28-7.54 (m, 5H)

1-*tert*-Butyl 3-methyl 2-(*N*-phthalimido)malonate (**3h**)



t-Butyl methyl 2-chloromalonate (**8**) (463.2 mg, 2.22 mmol), was charged in to a flask, and dissolved in dry DMF (7.5 ml) solvent, added Potassium phthalimide (555.1 mg, 3.00 mmol), 18-Crown 6-ether (58.6 mg, 0.222 mmol), which was stirred at 40°C for 17 hours. The reaction mixture was quench with water and extracted with dichloromethane solvent, organic layer washed with brine and evaporated solvent, purified by column eluted with (Hexane: AcOEt=90: 10) obtained **3h** in (446.6 mg, 63% yield).

White solid

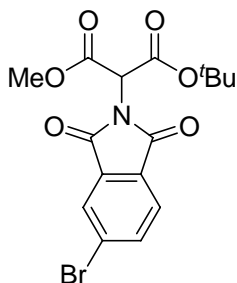
Molecular formula: C₁₆H₁₇NO₆

M.W.: 319.31

R_f=0.38 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.50 (s, 9H), 3.83 (s, 3H), 5.41 (s, 1H), 7.73-7.77 (m, 2H), 7.87-7.91 (m, 2H)

1-*tert*-Butyl 3-methyl 2-(*N*-(4-bromophthalimido))malonate (3i)



t-Butyl methyl 2-chloromalonate (**8**) (300 mg, 1.44 mmol), was charged in to a flask, and dissolved in dry DMF (5.0 ml) solvent, added Potassium 4-bromophthalimide (512 mg, 1.94 mmol), which was stirred at 70°C for 17 hours. The reaction mixture was quenched with water and extracted with dichloromethane solvent, organic layer washed with brine and evaporated solvent, purified by column eluted with (Hexane: AcOEt=90: 10) obtained **3i** in (300 mg, 52% yield).

White solid

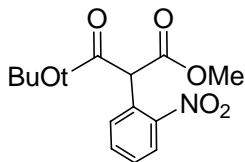
M.W.: 397.22

Molecular formula: C₁₆H₁₆BrNO₆

R_f=0.50 (Hexane: AcOEt=80: 20)

¹H-NMR (CDCl₃, 200 MHz): δ 1.50 (s, 9H), 3.83 (s, 3H), 5.39 (s, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.89 (d, *J*=8.2 Hz, 1H), 8.02 (s, 2H)

1-*tert*-Butyl 3-methyl 2-(*ortho*-nitrophenyl)malonate (3j)



Sodium hydride (NaH 60%) 152 mg, 3.79 mmol) was charged in to a flask, and added dry THF solvent, which was cooled to 0°C, the *t*-Butyl malonic acid **6** (600 mg, 3.44 mmol) in THF (5.0 ml) was added to the above and stirred for 1 h, and 1-fluoro 2-nitrobenzene (390 mg, 3.61 mmol) was added which was stirred at 70°C for 48 hours. The reaction mixture was quenched with water and extracted with dichloromethane solvent, organic layer washed with brine and evaporated solvent, purified by column eluted with (Hexane: AcOEt=90: 10) obtained **3j** in (605 mg, 60% yield).

Pale yellow syrup

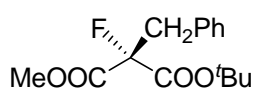
Molecular formula: C₁₄H₁₇NO₆

M.W.: 295.28

R_f=0.32 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.47 (s, 9H), 3.79 (s, 1H), 5.20 (s, 3H), 7.47-7.60 (m, 3H), 8.02 (d, 1H)

(S)-1-*tert*-Butyl 3-methyl 2-benzyl-2-fluoromalonate (9a)



The reaction of 1-*t*-Butyl 3-methyl 2-benzylmalonate **3a** (40.0 mg, 0.151 mmol) with DBFOX-Ph (7.5 mg, 0.016 mmol), Zn(OAc)₂ (2.4 mg, 0.015 mmol) and *N*-Fluorobenzenesulfonimide (57.2 mg, 0.186 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 15 h, gave **9a** in (38.0 mg, 90% yield) obtained.

Colorless oil

Molecular formula: C₁₅H₁₉FO₄

M.W.: 282.31

R_f=0.46 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.41 (s, 9H), 3.42 (d, *J*=25.8 Hz, 2H), 3.76 (s, 3H), 7.16-7.25 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -163.4 (t, *J*=26.3 Hz)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.9, 40.2 (d, *J*=20.8 Hz), 53.1, 84.1, 95.1 (d, *J*=200 Hz), 127.2, 128.1, 130.1, 133.0, 164.1 (d, *J*=26.4 Hz), 166.3 (d, *J*=25.5 Hz)

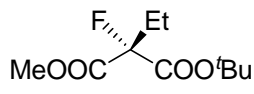
IR (neat): 2980, 1753, 1604, 1497, 1455, 1437, 1395, 1371, 1307, 1254, 1157, 1085, 1056, 841, 744, 700 cm⁻¹

MS (EI): *m/z* 263 (M⁺)

HPLC: (CHIRALCEL OJ-H Hexane/ ⁱPrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (major) = 13.6 min, t_R (minor) = 11.4 min (98% ee)

[α]_D²⁵ +13.92 (*c*=1.0, MeOH 98% ee)

(S)-1-*t*-Butyl 3-methyl 2-ethyl-2-fluoromalonate (9b)



The reaction of *t*-Butyl methyl 2-ethylmalonate **3b** (50.0 mg, 0.247 mmol) with DBFOX-Ph (12.3 mg, 0.027 mmol), Zn(OAc)₂ (4.0 mg, 0.024 mmol) and *N*-Fluorobenzenesulfonimide (93.0 mg, 0.296 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 24 h, gave **2b** (51.0 mg, 94% yield) obtained.

Colorless oil

Molecular formula: C₁₀H₁₇FO₄

M.W.: 220.24

R_f=0.42 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 0.99 (t, *J*=7.6 Hz, 3H), 1.49 (s, 9H), 1.85-1.92 (m, 2H), 3.82 (s, 3H)

¹⁹F NMR (188 MHz, CDCl₃): δ -167.24 (t, *J*=23.7 Hz)

¹³C NMR (50.3 MHz, CDCl₃): δ 7.14 (d, *J*=4.4 Hz), 27.4, 27.8, 52.9, 83.6, 95.0 (d, *J*=197 Hz), 164.6 (d, *J*=25.2 Hz), 166.6 (d, *J*=25.6 Hz)

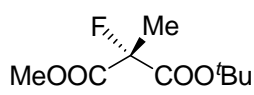
IR (neat): 2981, 1752, 1458, 1371, 1315, 1243, 1139, 1101, 1022, 842, 805 cm⁻¹

MS (EI): *m/z* 220 (M⁺)

GC: (CHIRALDEX G-TA, 30 m x 0.25 mm, 100□) t_R (major) = 20.6 min, t_R (minor) = 22.7 min (96% ee)

[α]_D²⁵ +15.5 (*c*=1.0, CHCl₃ 96% ee)

(S)-1-tert-Butyl 3-methyl-2-fluoro-2-methylmalonate (9c)



The reaction of *t*-Butyl methyl 2-methylmalonate **3c** (40.0 mg, 0.212 mmol) with DBFOX-Ph (10.6 mg, 0.023 mmol), Zn(OAc)₂ (3.3 mg, 0.021 mmol) and *N*-Fluorobenzenesulfonimide (80.0 mg, 0.255 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 24 h, gave **9c** (39.0 mg, 90% yield) obtained.

Colorless oil

Molecular formula: C₉H₁₅FO₄

M.W.: 206.21

R_f=0.42 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.49 (s, 9H), 1.74 (d, *J*=22.0 Hz, 3H), 3.82 (s, 3H)

¹⁹F NMR (188 MHz, CDCl₃): δ -155.8 (q, *J*=22.3 Hz)

¹³C NMR (50.3 MHz, CDCl₃): δ 20.6 (d, *J*=23.1 Hz), 27.7, 52.9, 83.6, 92.3 (d, *J*=194 Hz), 165.1 (d, *J*=24.7 Hz), 167.1 (d, *J*=25.2 Hz)

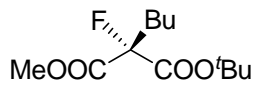
IR (neat): 2982, 1753, 1448, 1396, 1372, 1305, 1257, 1124, 982, 944, 841, 794 cm⁻¹

MS (EI): *m/z* 206 (M⁺)

GC: (HYDRODEX- β-TBDac, 25 m x 0.25 mm, 65 μm) t_R (major) = 60.5 min, t_R (minor) = 58.6 min (99% ee)

[α]_D²³ +11.4 (*c*=1.0, CHCl₃ 99% ee)

(S)-1-tert-Butyl 3-methyl 2-butyl-2-fluoromalonate (9d)



The reaction of *t*-Butyl methyl 2-butylmalonate **3d** (40.0 mg, 0.173 mmol) with DBFOX-Ph (8.6 mg, 0.019 mmol), Zn(OAc)₂ (2.7 mg, 0.017 mmol) and *N*-Fluorobenzenesulfonimide (65.7 mg, 0.208 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 36 h, gave **9d** (40.0 mg, 93% yield).

Colorless oil

Molecular formula: C₁₂H₂₁FO₄

M.W.: 248.29

R_f=0.42 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 0.91 (t, *J*=6.6 Hz, 3H), 1.33-1.46 (m, 4H), 1.49 (s, 9H), 2.01-2.20 (m, 2H), 3.82 (s, 3H)

¹⁹F NMR (188 MHz, CDCl₃): δ -165.4 (t, *J*=22.3 Hz)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.0, 22.7, 25.0 (d, *J*=2.8 Hz), 28.0, 34.0 (d, *J*=21.6 Hz), 53.1, 83.8, 95.0 (d, *J*=197 Hz), 164.8 (d, *J*=25.1 Hz), 166.9 (d, *J*=25.9 Hz)

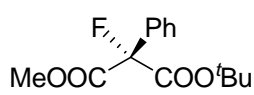
IR (neat): 2960, 2874, 1753, 1457, 1370, 1287, 1248, 1142, 1047, 842 cm⁻¹

MS (EI): *m/z* 248 (M⁺)

GC: (CP-CHIRASIL-DEX CB, 25 m x 0.25 mm, 85 μm) t_R (major) = 118.1 min, t_R (minor) = 122.7 min (99% ee)

[α]_D²⁵ +5.7 (*c*=0.50, CHCl₃ 99% ee)

(S)-1- tert-Butyl 3-methyl 2-fluoro-2-phenylmalonate (9e)



The reaction of *t*-Butyl methyl 2-phenylmalonate **3e** (40.0 mg, 0.15 mmol) with DBFOX-Ph (8.0 mg, 0.017 mmol), Zn(OAc)₂ (2.5 mg, 0.015 mmol) and *N*-Fluorobenzenesulfonimide (56.3 mg, 0.178 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 24 h, gave **9e** (40.0 mg, 95% yield).

Colorless oil

Molecular formula: C₁₄H₁₇FO₄

M.W.: 268.28

R_f=0.47 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.49 (s, 9H), 3.84 (s, 3H), 7.38-7.43 (m, 3H), 7.55-7.60 (m, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -159.2 (s)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.9, 53.5, 84.5, 94.2 (d, *J*=200 Hz), 125.5, 128.0, 129.0, 133.7 (d, *J*=21.9 Hz), 163.9 (d, *J*=25.6 Hz), 166.1 (d, *J*=26.0 Hz)

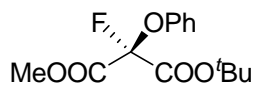
IR (neat): 2981, 1754, 1451, 1395, 1371, 1281, 1157, 1120, 1071, 1050, 840, 737 cm⁻¹

MS (EI): *m/z* 268 (M⁺)

HPLC: (CHIRALCEL OJ-H, Hexane/ *i*PrOH=95/ 5, 0.5 ml/ min, 254 nm) t_R (major) = 24.0 min, t_R (minor) = 22.9 min (99% ee)

[α]_D²⁵ +5.7 (*c* =1.0, MeOH 99% ee)

(S)-1-tert-Butyl 3-methyl-2-fluoro-2-(phenoxy)malonate (9f)



The reaction of *t*-Butyl methyl 2-(phenoxy)malonate **3f** (40.0 mg, 0.132 mmol) with DBFOX-Ph (6.0 mg, 0.014 mmol), Zn(OAc)₂ (2.2 mg, 0.013 mmol) and *N*-Fluorobenzenesulfonimide (52.0 mg, 0.159 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 15 h, gave **9f** (36.0 mg, 85% yield).

Colorless oil

Molecular formula: C₁₄H₁₇FO₅

M.W.: 284.28

R_f=0.29 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.37 (s, 9H), 3.87 (s, 3H), 7.15-7.31 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -110.8 (s)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.7, 53.6, 85.0, 104.1 (d, *J*=243 Hz), 119.9, 124.9, 129.2, 153.0 (d, *J*=2.4 Hz), 160.6 (d, *J*=34.3 Hz), 162.8 (d, *J*=33.6 Hz)

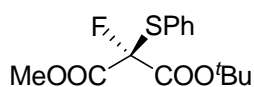
IR (neat): 2981, 1767, 1591, 1491, 1457, 1396, 1372, 1321, 1259, 1210, 1144, 1082, 949, 863, 837, 758, 692, 642 cm⁻¹

MS (EI): *m/z* 284 (M⁺)

HPLC: (CHIRALCEL OD-H, Hexane/ *i*PrOH=98/ 2, 0.5 ml/ min, 254 nm) t_R (major) = 14.4 min, t_R (minor) = 16.2 min (98% ee)

[α]_D²⁵ +6.44 (*c*=0.50, MeOH, 98% ee)

(S)-1-tert-Butyl 3-methyl-2-fluoro-2-(phenylthio)malonate (9g)



The reaction of *t*-Butyl methyl 2-(phenylthio)malonate **3g** (40.0 mg, 0.126 mmol) with DBFOX-Ph (6.3 mg, 0.013 mmol), Zn(OAc)₂ (2.0 mg, 0.012 mmol) and *N*-Fluorobenzenesulfonimide (47.7 mg, 0.151 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 24 h, gave **9g** (35.0 mg, 81%, 90% ee yield).

Colorless oil

Molecular formula: C₁₄H₁₇FO₄S

M.W.: 300.35

R_f=0.34 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.39 (s, 9H), 3.75 (s, 3H), 7.33-7.41 (m, 3H), 7.54-7.59 (m, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -130.7 (s)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.7, 53.7, 85.2, 101.0 (d, *J*=242 Hz), 127.3, 128.8, 129.9, 135.6, 161.5 (d, *J*=28.0 Hz), 163.7 (d, *J*=29.1 Hz)

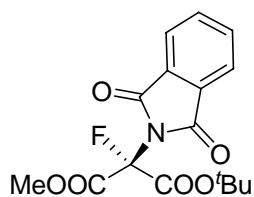
IR (neat): 2980, 1752, 1439, 1371, 1288, 1154, 1048, 837, 792, 749, 691 cm⁻¹

MS (EI): *m/z* 300 (M⁺)

HPLC: (CHIRALCEL OJ-H Hexane/ ⁱPrOH=90/ 10, 0.5 ml/ min, 254 nm) t_R (major) = 44.2 min, t_R (minor) = 41.3 min (90% ee)

[α]_D²⁵ +13.39 (*c*=0.50, MeOH 90% ee)

(S)-1- tert-Butyl 3-methyl 2-fluoro-2-(N-phthalimido)malonate (9h)



The reaction of *t*-Butyl methyl 2-(*N*-phthalimido)malonate **3h** (50.0 mg, 0.15 mmol) with DBFOX-Ph (7.5 mg, 0.016 mmol), Zn(OAc)₂ (2.4 mg, 0.015 mmol) and *N*-Fluorobenzenesulfonimide (56.0 mg, 0.18 mmol) in CH₂Cl₂ (0.5 mL) at reflux for 18 h, gave **9h** (47.5 mg, 91% yield).

White solid

Molecular formula: C₁₆H₁₆FNO₆

M.W.: 337.30

R_f=0.26 (Hexane: AcOEt=70: 30)

¹H NMR (200 MHz, CDCl₃): δ 1.56 (s, 9H), 3.95 (s, 3H), 7.80-7.91 (m, 4H)

¹⁹F NMR (188 MHz, CDCl₃): δ -127.4 (s)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.7, 54.2, 85.8, 89.2 (d, *J*=229 Hz), 124.0, 130.9, 134.90, 159.5 (d, *J*=30.7 Hz), 162.2 (d, *J*=31.3 Hz), 164.8 (d, *J*=2.0 Hz)

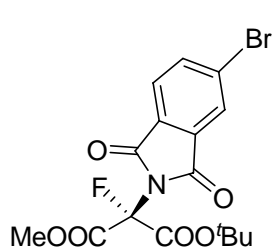
IR (KBr): 2982, 1776, 1742, 1582, 1450, 1400, 1371, 1295, 1188, 1141, 1113, 1082, 948, 794, 754, 724, 682, 625 cm⁻¹

MS (EI): *m/z* 337 (M⁺)

HPLC: (CHIRALCEL OJ-H Hexane/ ⁱPrOH=90/ 10, 0.5 ml/ min, 254 nm) t_R (major) = 48.1 min, t_R (minor) = 42.5 min (93% ee)

[α]_D²⁵ +4.5 (*c*=0.50, MeOH 93% ee)

(S)-1- tert-Butyl 3-methyl 2-fluoro-2-(N-(4-bromophthalimido))malonate (9i)



The reaction of *t*-Butyl methyl 2-(*N*-(4-bromophthalimido))malonate **3i** (40.0 mg, 0.096 mmol) with DBFOX-Ph (4.5 mg, 0.010 mmol), Zn(OAc)₂ (1.7 mg, 0.009 mmol) and *N*-Fluorobenzenesulfonimide (36.4 mg, 0.115mmol) in CH₂Cl₂ (0.5 mL) at reflux for 24 h, gave **9i** (39.0 mg, 93% yield).
White solid

Molecular formula: C₁₆H₁₅BrFNO₆

M.W.: 416.20

R_f=0.53 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.55 (s, 9H), 3.94 (s, 3H), 7.79 (t, *J*=7.4 Hz, 1H), 7.96 (dd, *J*=8.0, 1.6 Hz, 1H), 8.04 (d, *J*=1.2 Hz, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -127.8 (s)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.7, 54.3, 86.1, 89.2 (d, *J*=230 Hz), 125.4, 127.4, 129.4, 130.1, 132.4, 138.0, 159.3, (d, *J*=30.3 Hz), 161.9 (d, *J*=31.1 Hz), 163.5, 164.1

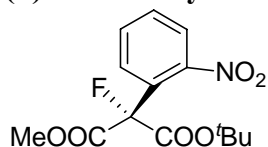
IR (KBr): 2981, 1740, 1604, 1420, 1359, 1296, 1143, 946, 838, 745, 647 cm⁻¹

MS (EI): *m/z* 416 (M⁺)

HPLC: (CHIRALCEL OJ-H Hexane/ ⁱPrOH=95/ 5, 1.0 ml/ min, 254 nm) *t*_R (major) = 43.8 min, *t*_R (minor) = 34.8 min (97% ee)

[α]_D²⁴ +15.38 (*c*=1.0, MeOH 97% ee)

(S)-1-tert-butyl 3-methyl 2-fluoro-2-(2-nitrophenyl)malonate (9j)



yellowish syrup

Molecular formula: C₁₄H₁₆FNO₆

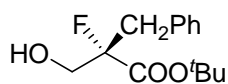
M.W.: 313.27

R_f=0.24 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.51 (s, 9H), 3.89 (s, 3H), 7.5-7.63 (m, 3H), 8.01 (d, *J*=7.2 Hz, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -150.27 (s, 1F)

(S)-tert-Butyl 2-fluoro-2-(hydroxybenzyl)propionate (10a)



To a solution of **3a** (50.0 mg, 0.177 mmol) in dry THF (1.0 mL) was added a solution of LiAl(O^{*t*}Bu)₃H (1.0 M in THF, 0.88 mL, 0.885 mmol) at -78 °C by syringe over 10 min. The solution was allowed to

warm to room temperature, which was stirred for 1 h at that temperature, gave **10a** (40.0 mg, 89% yield).

Colorless oil

Molecular formula: C₁₄H₁₉FO₃

M.W.: 254.30

R_f=0.19 (Hexane: AcOEt=70: 30)

¹H NMR (200 MHz, CDCl₃): δ 1.38 (s, 9H), 2.02-2.10 (m, 1H), 3.13 (d, *J*=24.0 Hz, 2H), 3.74-3.99 (m, 2H), 7.24-7.27 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -169.2- -168.9 (m)

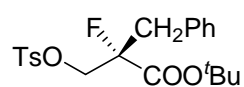
¹³C NMR (150.9 MHz, CDCl₃): δ 27.8, 39.4 (d, *J*=21.3 Hz), 66.2 (d, *J*=24.0 Hz), 83.1, 97.2 (d, *J*=190 Hz), 127.2, 128.3, 130.2 (d, *J*=0.9 Hz), 134.0, 168.6 (d, *J*=25.2 Hz)

IR (neat): 3455, 2979, 2932, 1732, 1496, 1456, 1370, 1252, 1161, 1093, 1044, 842, 742, 701 cm⁻¹

MS (EI): *m/z* 254 (M⁺)

[α]_D²⁵ +9.05 (*c*=0.35, CHCl₃)

(*S*)-2-(*tert*-Butoxycarbonyl)-2-fluoropropyl-4-methylbenzenesulfonate (**11a**)



To a solution of alcohol **10a** (390.0 mg 1.624 mmol) in dry pyridine (1.0 mL) and dry CHCl₃ (2.0 mL) was cooled to 0 °C, and *p*-tosyl chloride (371.0 mg, 1.948 mmol) was added directly. After stirring for 10 min at 0 °C, the solution was stirred at room temperature for 12 h. 1N HCl was added, and the product was extracted three times with CH₂Cl₂, the combined organic layers were washed with water and brine. The organic solution was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The product was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give compound **11a** in (590.0 mg, 90% yield).

White solid

Molecular formula: C₂₁H₂₅FO₅S

M.W.: 408.48

R_f=0.22 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.34 (s, 9H), 2.45 (s, 3H), 3.04 (d, *J*=3.0 Hz, 1H), 3.16 (s, 1H), 4.16-4.39 (m, 2H), 7.17-7.35 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -167.5- -167.0 (m)

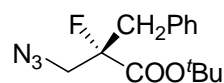
¹³C NMR (150.9 MHz, CDCl₃): δ 21.6, 27.7, 70.9 (d, *J*=23.1 Hz), 83.8, 94.3 (d, *J*=197 Hz), 127.4, 128.0, 128.4, 130.0, 130.2, 132.5, 132.9, 145.1, 166.4 (d, *J*=25.0 Hz)

IR (KBr): 3060, 3032, 2979, 2928, 1760, 1596, 1496, 1445, 1371, 1246, 1193, 987, 943, 861, 818, 764, 697, 666 cm⁻¹

MS (EI): *m/z* 408 (M⁺), 352 (M⁺-*t*Bu)

[α]_D²⁴ -1.08 (*c*=0.23, CHCl₃)

(*S*)-*tert*-Butyl 3-azido-2-benzyl-2-fluoro propionate (**12**)



To a solution of (*S*)-2-(*t*-Butoxycarbonyl)-2-fluoro-3-phenylpropyl 4-methylbenzenesulfonate **11a** (48.2 mg, 0.118 mmol) in DMF (2.0 mL)

was added NaN₃ (23.0 mg, 0.354 mmol) and resulting mixture was stirred at 80 °C for 24 h. The reaction mixture was diluted with CH₂Cl₂, washed with water, brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. The purified by column chromatography on silica gel eluting with hexane/AcOEt = 90/10 to give **12** in 95% yield. Colorless syrup

Molecular formula: C₁₄H₁₈FN₃O₂

M.W.: 279.31

R_f=0.32 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.39 (s, 9H), 3.08 (d, *J*=2.2 Hz, 1H), 3.20 (s, 1H), 3.50-3.70 (m, 2H), 7.20-7.30 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -164.1- -163.6 (m)

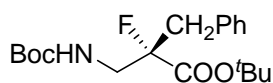
¹³C NMR (150.9 MHz, CDCl₃): δ 27.8, 40.6 (d, *J*=21.1 Hz), 55.6 (d, *J*=22.1 Hz), 83.5, 95.8, 96.4 (d, *J*=195 Hz), 127.4, 128.4, 130.2 (d, *J*=0.9 Hz), 133.4, 167.6 (d, *J*=24.9 Hz)

IR (neat): 2981, 2932, 2107, 1758, 1731, 1496, 1456, 1095, 950, 843, 700 cm⁻¹

MS (EI): *m/z* 279 (M⁺)

[α]_D²⁴ -40.5 (*c*=0.31, CHCl₃)

***tert*-Butyl (*S*)-2-(*tert*-butoxycarbonyl)-2-fluoro-3-phenylpropylcarbamate (**13**)**



To a solution of (*S*)-*t*-Butyl 3-azido-2-benzyl-2-fluoropropionate **12** (47.7 mg, 0.171 mmol) in ethyl acetate (2.5 mL), (Boc)₂O (56.1 mg, 0.257 mmol), Pd-C (5.0 mg) were added and resulting mixture was stirred under hydrogen atmosphere for 2 h at room temperature. This reaction mixture was filtered through celite to remove Pd-C. After removal of the solvent, the crude product was purified by column chromatography on silica gel eluting with hexane/AcOEt = 80/20 to give **13** (95% yield).

Colorless oil

Molecular formula: C₁₉H₂₈FNO₄

M.W.: 353.43

R_f=0.25 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.36 (s, 9H), 1.43 (s, 9H), 3.07 (s, 1H), 3.19 (d, *J*=2.2 Hz, 1H), 3.41 (td, *J*=14.8, 4.8 Hz, 1H), 3.70-3.79 (m, 1H), 4.84 (s, 1H), 7.24-7.25 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -165.0- -164.5 (m)

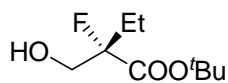
¹³C NMR (100.6 MHz, CDCl₃): δ 27.7, 28.3, 40.5 (d, *J*=21.3 Hz), 46.1 (d, *J*=21.7 Hz), 79.7, 83.0, 96.5 (d, *J*=189 Hz), 127.1, 128.2, 130.2, 134.0, 155.4, 167.9 (d, *J*=25.7 Hz)

IR (neat): 3383, 3033, 2979, 2932, 1722, 1514, 1456, 1393, 1368, 1250, 1166, 1108, 1037, 999, 913, 843, 741, 700 cm⁻¹

MS (EI): *m/z* 353 (M⁺), 277 (M⁺-*t*Bu)

[α]_D²⁴ +23.6 (*c*=0.35, CHCl₃)

(*S*)-*t*-Butyl 2-fluoro-2-(hydroxymethyl)butanoate (10b**)**



To a solution of (*S*)-1-*t*-Butyl 3-methyl 2-ethyl-2-fluoromalonate **9b** (180.0 mg, 0.818 mmol) in dry THF (2.0 mL) was added a solution of LiAl(O^{*t*}Bu)₃H (1.0 M in THF, 4.0 mL, 4.09 mmol) at -78 °C by

syringe over 10 min. The solution was allowed to warm to room temperature, which was stirred for 1 h at that temperature, gave **10b** (126.0 mg, 80% yield).

Colorless oil

Molecular formula: C₉H₁₇FO₃

M.W.: 192.23

R_f=0.36 (Hexane: AcOEt=70: 30)

¹H NMR (200 MHz, CDCl₃): δ 0.98 (t, *J*=7.4 Hz, 3H), 1.52 (s, 9H), 1.72-1.97 (m, 2H), 2.02-2.04 (m, 1H), 3.75-3.92 (m, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -173.9- -173.4 (m)

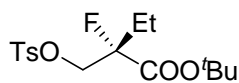
¹³C NMR (50.3 MHz, CDCl₃): δ 7.22 (d, *J*=4.4 Hz), 26.5 (d, *J*=22.3 Hz), 28.0, 66.2 (d, *J*=23.1 Hz), 82.6, 98.0 (d, *J*=186 Hz), 168.8 (d, *J*=26.0 Hz)

IR (neat): 3441, 2978, 2938, 2284, 1732, 1459, 1394, 1370, 1323, 1254, 1139, 1072, 1010, 963, 909, 841, 746 cm⁻¹

MS (EI): *m/z* 192 (M⁺)

[α]_D²⁵ -5.42 (*c*=1.0, CHCl₃)

(*S*)-2-(*t*-Butoxycarbonyl)-2-fluorobutyl 4-methylbenzenesulfonate (**11b**)



To a solution of (*S*)-*t*-Butyl 2-fluoro-2-(hydroxymethyl)butanoate **10b** (120.0 mg 0.625 mmol) in dry pyridine (2.0 mL) and dry CHCl₃ (2.0 mL) was cooled to 0 °C, and *p*-tosyl chloride (142.0 mg, 0.75 mmol) was added directly. After stirring for 10 min at 0 °C, the solution was stirred at room temperature for 12 h. 1N HCl was added, and the product was extracted three times with CH₂Cl₂, the combined organic layers were washed with water and brine. The organic solution was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The product was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give compound **11b** in (185.0 mg, 85% yield).

White solid

Molecular formula: C₁₆H₂₃FO₅S

M.W.: 346.13

R_f=0.42 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 0.93 (t, *J*=7.4 Hz, 3H), 1.47 (s, 9H), 1.74-1.87 (m, 2H), 2.44 (s, 3H), 4.15-4.34 (m, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 7.77 (d, *J*=8.4 Hz, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -171.1- -170.6 (m)

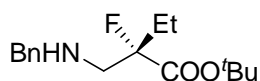
¹³C NMR (50.3 MHz, CDCl₃): δ 7.03 (d, *J*=4.4 Hz), 21.7, 26.8 (d, *J*=22.3 Hz), 27.9, 71.1 (d, *J*=22.7 Hz), 83.4, 94.6 (d, *J*=193 Hz), 127.6, 129.6, 132.1, 144.8, 166.3 (d, *J*=26.0 Hz)

IR (KBr): 2982, 1758, 1597, 1455, 1369, 1249, 1190, 178, 1141, 1097, 1005, 939, 910, 826, 760 cm⁻¹

MS (EI): *m/z* 346 (M⁺)

[α]_D²⁴ +0.63 (*c*=1.0, CHCl₃)

(*S*)-*tert*-Butyl 2-((benzylamino)methyl)-2-fluorobutanoate (**14**)



Tosyl derivative compound **9** (180 mg, 0.520 mmol) was dissolved in toluene (0.5 mL) and sodium bicarbonate (131 mg, 1.56 mmol) was added. To the resulting suspension benzyl amine (0.28 mL, 2.601 mmol) was added, and the mixture was left stirring at 80 °C for 48 h. More toluene (0.4 mL) was added and also benzyl amine (0.28 mL, 2.601 mmol) and the mixture was stirred at 80 °C another 24 h. The reaction mixture was then cooled to room temperature, filtered, and evaporated. The crude product was purified by column chromatography on silica gel eluted (hexane/AcOEt = 10/1) **14** in 72% yield.

Light yellow oil

Molecular formula: C₁₆H₂₄FNO₂

M.W.: 281.37

R_f=0.29 (Hexane: AcOEt=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 0.94 (t, *J*=7.6 Hz, 3H), 1.49 (s, 9H), 1.74-1.91 (m, 2H), 2.87 (s, 1H), 2.93 (d, *J*=14.8 Hz, 1H), 3.04 (d, *J*=14.8 Hz, 1H), 3.74 (d, *J*=13.4 Hz, 1H), 3.87 (d, *J*=13.4 Hz, 1H), 7.24-7.31 (m, 5H)

¹⁹F NMR (188 MHz, CDCl₃): δ -170.54- -170.1 (m)

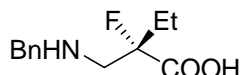
¹³C NMR (50.3 MHz, CDCl₃): δ 7.45 (d, *J*=4.4 Hz), 28.1, 53.7, 54.4 (d, *J*=21.2 Hz), 81.9, 98.2 (d, *J*=186 Hz), 126.6, 127.7, 128.0, 139.8, 169.3 (d, *J*=26.3 Hz)

IR (neat): 3344, 3063, 3027, 2952, 2929, 1735, 1495, 1461, 1368, 1250, 1168, 1136, 1028, 914, 843, 737, 638 cm⁻¹

MS (EI): *m/z* 281 (M⁺)

[α]_D²⁴ = -12.1 (*c*=1.0, EtOH)

(*S*)-2-((Benzylamino)methyl)-2-fluorobutanoic acid (**15**)



Under the similar procedure described for the synthesis of **17**, the reaction of (*S*)-*t*-Butyl 2-((benzylamino)methyl)-2-fluorobutanoate **14** (100.0 mg, 0.355 mmol) with TFA (0.27 ml, 3.554 mmol) in CH₂Cl₂ (1.0 mL) at room temperature for 3 h, gave **15** (70.2 mg, 87% yield).

White solid

Molecular formula: C₁₂H₁₆FNO₂

M.W.: 225.26

R_f=0.45 (CH₂Cl₂: MeOH=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 0.78 (t, *J*=7.2 Hz, 3H), 1.55-1.85 (m, 2H), 3.10-3.46 (m, 2H), 4.19 (d, *J*=12.8 Hz, 1H), 4.33 (d, *J*=12.6 Hz, 1H), 7.25-7.44 (m, 5H), 9.00 (bs, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -167.8 (br)

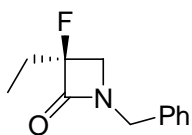
¹³C NMR (100.6 MHz, CDCl₃): δ 6.85 (d, *J*=3.7 Hz), 27.7, 28.7 (d, *J*=21.7 Hz), 51.7 (d, *J*=21.7 Hz), 52.4, 85.0, 94.7 (d, *J*=193 Hz), 128.7, 129.4, 129.9, 130.8, 172.4 (d, *J*=21.7 Hz)

IR (neat): 3362, 2974, 1723, 1606, 1499, 1455, 1212, 1133, 1090, 912, 733, 700 cm⁻¹

MS (EI): *m/z* 225 (M⁺)

[α]_D²³ = -1.72 (*c*=1.0, MeOH)

(S)-1-Benzyl-3-ethyl-3-fluoroazetidin-2-one (16)



To a 20 mL round-bottomed flask charged with carboxylic compound (S)-2-((Benzylamino)methyl)-2-fluorobutanoic acid **11** (50.0 mg, 0.222 mmol) was added CH₂Cl₂ (10.0 mL) and 2-chloro-1-methylpyridinium iodide (62.4 mg, 0.244 mmol) in CH₂Cl₂ under high-dilution conditions and the mixture was stirred at room temperature for 15 min, then added TEA (0.09 mL, 0.666 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction progress was assessed by TLC, the mixture was concentrated in vacuum and which was purified on column chromatography on silica gel eluted with (hexane/AcOEt = 15/1), **16** in 70% yield.

Colorless oil

Molecular formula: C₁₂H₁₄FNO

M.W.: 207.24

R_f=0.65 (Hexane: AcOEt=60: 40)

¹H NMR (300 MHz, CDCl₃): δ 1.05 (t, *J*=7.5 Hz, 3H), 1.87-2.04 (m, 2H), 3.28 (dddd, *J*=37.5, 6.3, 8.4, 11.1 Hz, 2H), 4.39 (d, *J*=17.7 Hz, 1H), 4.46 (d, *J*=11.4 Hz, 1H), 7.22-7.25 (m, 2H), 7.32-7.40 (m, 3H)

¹⁹F NMR (188 MHz, CDCl₃): δ -165.0- -164.7 (m)

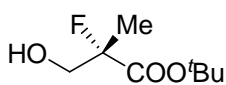
¹³C NMR (100.6 MHz, CDCl₃): δ 7.35 (d, *J*=6.4 Hz), 25.0 (d, *J*=23.6 Hz), 45.6 (d, *J*=1.9 Hz), 51.5 (d, *J*=26.4 Hz), 102.7 (d, *J*=216 Hz), 128.0, 128.2, 128.9, 134.6, 165.8 (d, *J*=24.4 Hz)

IR (neat): 2975, 1766, 1455, 1406, 1309, 1196, 1076, 970, 910, 852, 725, 700 cm⁻¹

MS (EI): *m/z* 207 (M⁺)

[α]_D²⁴ -70.1 (*c*=1.0, MeOH)

(S)-tert-Butyl 2-fluoro-2-(hydroxymethyl)propionate (10c)



To a solution of (S)-1-*t*-Butyl 3-methyl 2-fluoro-2-methylmalonate **9c** (200 mg, 0.970 mmol) in dry THF (5.0 mL) was added a solution of LiAl(O^{*t*}Bu)₃H⁸⁰ (1.0 M in THF, 3.8 mL, 3.81 mmol) at -78 °C by syringe over 20 min. The solution was allowed to warm to room temperature, which was stirred for 1 h at that temperature. After addition of a saturated solution of potassium sodium tartrate, the organic materials were extracted with ethyl acetate three times and the combined organic phase was washed with brine three times and dried over Na₂SO₄, and concentrated, the crude materials were purified by column chromatography using (hexane/AcOEt = 5/1) to afford alcohol **10c** quantitatively in 85% yield.

Colorless oil

Molecular formula: C₈H₁₅FO₃

M.W.: 178.20

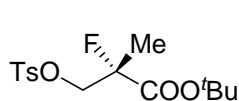
R_f=0.24 (Hexane: AcOEt=70: 30)

¹H NMR (200 MHz, CDCl₃): δ 1.50 (d, *J*=20.2 Hz, 3H), 1.51 (s, 9H), 2.07-2.13 (m, 1H), 3.70-3.94 (m, 2H)

⁸⁰ T. A. Ayers, *Tetrahedron Lett.* **1999**, 40, 5467-5470.

^{19}F NMR (188 MHz, CDCl_3): δ -163.4- -162.9 (m)
 ^{13}C NMR (50.3 MHz, CDCl_3): δ 19.7 (d, $J=23.6$ Hz), 27.9, 66.8 (d, $J=23.5$ Hz), 82.7, 95.0 (d, $J=184$ Hz), 169.3 (d, $J=25.6$ Hz)
 IR (neat): 3450, 2981, 2938, 2293, 1735, 1476, 1457, 1395, 1370, 1318, 1251, 1139, 1065, 955, 928, 901, 843, 748, 701 cm^{-1}
 MS (EI): m/z 178 (M^+)
 $[\alpha]_{\text{D}}^{22}$ -12.48 ($c=1.0$, CHCl_3)

(S)-2-(tert-Butoxycarbonyl)-2-fluoropropyl-4-methylbenzenesulfonate (**11c**)



To a solution of alcohol **10c** (250 mg 1.302 mmol) in dry CHCl_3 (3.0 mL) and pyridine (0.20 mL, 2.604 mmol) was added. The solution was cooled to 0 °C, and *p*-tosyl chloride⁸¹ (290 mg, 1.56 mmol) was added directly. After stirring for 10 min at 0 °C, the cooling bath was removed, and the solution was stirred at room temperature for 12 h. 1N HCl was added, and the product was extracted three times with CH_2Cl_2 , the combined organic layers were washed with water and brine. The organic solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuum. The product was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give a colourless gummy syrup compound **11c** in 81% yield.

White solid

Molecular formula: $\text{C}_{15}\text{H}_{21}\text{FO}_5\text{S}$

M.W.: 332.39

$R_f=0.46$ (Hexane: AcOEt=70: 30)

^1H NMR (200 MHz, CDCl_3): δ 1.44 (s, 9H), 1.49 (d, $J=20.8$ Hz, 3H), 2.45 (s, 3H), 4.06-4.38 (m, 2H), 7.34 (d, $J=8.6$ Hz, 2H), 7.78 (d, $J=8.6$ Hz, 2H)

^{19}F NMR (188 MHz, CDCl_3): δ -160.3- -159.7 (m)

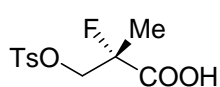
^{13}C NMR (50.3 MHz, CDCl_3): δ 20.0 (d, $J=23.5$ Hz), 21.7, 27.8, 71.5 (d, $J=23.1$ Hz), 83.5, 91.9 (d, $J=187$ Hz), 127.6, 129.6, 132.1, 144.8, 167.0 (d, $J=25.5$ Hz)

IR (neat): 2982, 1758, 1597, 1455, 1369, 1249, 1190, 178, 1141, 1097, 1005, 939, 910, 826, 760 cm^{-1}

MS (EI): m/z 332 (M^+)

$[\alpha]_{\text{D}}^{23}$ -6.50 ($c=1.0$, CHCl_3)

(S)-3-(4-Methylbenzenesulfonyl)-2-fluoro-2-methylpropionic acid (**17**)



To a 30 ml round-bottomed flask charged with (S)-2-(tert-Butoxycarbonyl)-2-fluoropropyl-4-methylbenzenesulfonate **11c** (100 mg, 0.300 mmol) was added CH_2Cl_2 (1.0 mL) and TFA (0.17 mL, 1.504 mmol), and the mixture was stirred at room temperature for 3 h, reaction progress was assessed by TLC, since the starting material had been consumed. The mixture was concentrated in vacuum and subsequently co-evaporated with toluene (2 x 10 mL) to

⁸¹ P. Schwerdtfeger, G. A. Heath, M. Dolg, M. A. Bennett, *J. Am. Chem. Soc.* **1992**, 118, 7517-7528.

afforded carboxylic compound, which was purified on column chromatography on silica gel eluted with (hexane/AcOEt = 1/1), **17** in 90% yield.

White solid

Molecular formula: C₁₁H₁₃FO₅S

M.W.: 276.28

R_f=0.12 (Hexane: AcOEt=50: 50)

¹H NMR (200 MHz, CDCl₃): δ 1.60 (d, *J*=21.0 Hz, 3H), 2.45 (s, 3H), 4.19-4.35 (m, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.78 (d, *J*=8.2 Hz, 2H), 8.15 (bs, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -161.2- -160.8 (m)

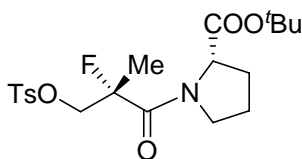
¹³C NMR (50.3 MHz, CDCl₃): δ 19.9 (d, *J*=23.1 Hz), 21.6, 71.4 (d, *J*=22.3 Hz), 92.5 (d, *J*=190 Hz), 127.6, 129.6, 131.7, 145.0, 170.3 (d, *J*=24.7 Hz)

IR (KBr): 3340, 3070, 1931, 1776, 1733, 1592, 1491, 1453, 1372, 1304, 1290, 1271, 1188, 1121, 1011, 940, 892, 826 cm⁻¹

MS (EI): *m/z* 276 (M⁺)

[α]_D²⁴ +6.55 (*c*=1.0, EtOH)

(*S*)-*tert*-Butyl 3-(4-methylbenzenesulfonyl)-2-fluoro-2-(methylpropanoyl)-1-pyrrolidine-2-carboxylate (18**)**



To a 10 mL round-bottomed flask equipped with a nitrogen balloon and charged with (*S*)-3-(4-Methylbenzenesulfonyl)-2-fluoro-2-methylpropanoic acid **17** (120 mg, 0.508 mmol) in CH₂Cl₂ (1.0 mL) was added a solution of L-proline *tert*-butyl ester⁸² (83.8 mg, 0.508 mmol) in CH₂Cl₂ (0.5 mL) at room temperature, then EDC·HCl (116 mg, 0.609 mmol) was added and HOBT (83 mg, 0.609 mmol) added

at under nitrogen atmosphere. The solution was cooled to 0 °C, then DIPEA (0.17 mL, 1.016 mmol) was added dropwise, the reaction was stirred at room temperature for 24 h. This solution was diluted with CH₂Cl₂, washed with 1N HCl and water, the organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (hexane/AcOEt = 2/1) **18** in 67% yield.

Colorless syrup

Molecular formula: C₂₀H₂₈FO₆S

M.W.: 429.50

R_f=0.35 (Hexane: AcOEt=60: 40)

¹H NMR (200 MHz CDCl₃): δ 1.43 (s, 9H), 1.57 (d, *J*=21.2 Hz, 3H), 1.87-2.04 (m, 4H), 2.44 (s, 3H), 3.74-3.76 (m, 2H), 4.18-4.44 (m, 2H), 4.57 (t, *J*=7.8 Hz, 1H), 7.32 (d, *J*=8.2 Hz, 2H), 7.76 (d, *J*=8.4 Hz, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -160.5 (q, *J*=21.1 Hz, major), -158.3 (q, *J*=20.5 Hz, minor)

¹³C NMR (50.3 MHz, CDCl₃): δ 20.3 (d, *J*=23.2 Hz), 21.7, 25.3 (d, *J*=4.8 Hz), 28.0, 47.6 (d, *J*=15.5 Hz), 61.2, 72.3 (d, *J*=21.2 Hz), 81.1, 95.1 (d, *J*=194 Hz), 127.7, 129.6, 132.3, 144.7, 166.6 (d, *J*=22.3 Hz), 170.3

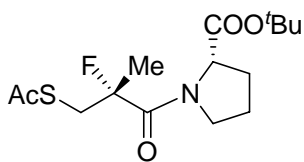
⁸² (a) A. J. Vernall, A. D. Abell, *Org. Biomol. Chem.* **2004**, 2, 2555-2557; (b) V. D. Bock, R. Perciaccante, T. P. Jansen, H. Hiemstra, J. H. van Maarseveen, *Org. Lett.* **2006**, 8, 919-922.

IR (neat): 3648, 2978, 2255, 1736, 1641, 1597, 1455, 1429, 1367, 1290, 1225, 1178, 1153, 1096, 1004, 916, 884, 833, 732, 680 cm^{-1}

MS (EI): m/z 429 (M^+)

$[\alpha]_D^{25}$ -39.44 ($c=1.0$, EtOH)

**(S)-tert-Butyl
carboxylate (19)**



Sodium hydride⁸³ (13.0 mg, 0.325 mmol) was placed into a 20 mL flask and added dry hexane (1.0 mL), stirred for 10 min, then hexane was removed by syringe under nitrogen condition, then DMF (0.5 mL) was added. The solution was cooled to 0 °C, thioacetic acid (8.2 mg, 0.108 mmol) was added drop wise with syringe at 0 °C, which was stirred for 30 min at room temperature, then (S)-*t*-Butyl 3-(4-methylbenzenesulfonyl)-2-fluoro-2-(methylpropanoyl)-1-pyrrolidine-2-carboxylate **18** (42 mg, 0.108 mmol) in DMF (0.5 mL) was added to the above mixture, raised the temperature up to 70 °C for 4 h. The reaction mixture cooled to room temperature, added water and ethyl acetate, extracted organic layer, washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (hexane/AcOEt = 2/1) **19** in 77% yield.

Light yellow syrup

Molecular formula: $\text{C}_{15}\text{H}_{24}\text{FNO}_4\text{S}$

M.W.: 333.42

$R_f=0.50$ (Hexane: AcOEt=60: 40)

^1H NMR (200 MHz, CDCl_3): δ 1.45 (s, 9H), 1.66 (d, $J=21.4$ Hz, 3H), 2.02-2.13 (m, 4H), 2.35 (s, 3H), 3.39-3.80 (m, 4H), 4.53-4.58 (m, 1H)

^{19}F NMR (188 MHz, CDCl_3): δ -154.8 (q, $J=21.1$ Hz, major), -151.6 (q, $J=21.1$ Hz, minor)

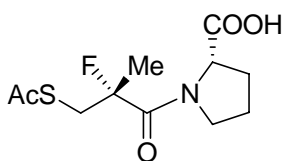
^{13}C NMR (50.3 MHz, CDCl_3): δ 23.0 (d, $J=23.1$ Hz), 25.4, 28.0, 30.5, 47.8 (d, $J=15.1$ Hz), 61.2, 81.0, 96.5 (d, $J=190$ Hz), 168.6 (d, $J=23.5$ Hz), 170.5, 193.7

IR (neat): 2978, 2936, 1737, 1698, 1639, 1455, 1425, 1368, 1289, 1222, 1155, 1093, 845, 919, 846, 761, 731, 652 cm^{-1}

MS (EI): m/z 334 (M^+)

$[\alpha]_D^{25}$ -84.5 ($c = 1.0$, EtOH)

**(S)-3-(Acetylthio)-2-fluoro-2-(methylpropanoyl)-1-pyrrolidine -2-carboxylic acid
(20)**



Under the similar procedure described for the synthesis of **17**, the reaction of (S)-*t*-Butyl 3-(acetylthio)-2-fluoro-2-(methylpropanoyl)-1-pyrrolidine-2-carboxylate **19** (100.0 mg,

⁸³ M. Chmielewski, R. L. Whistler, *J. Org. Chem.* **1975**, *40*, 639-643.

0.299 mmol) with TFA (0.113 ml, 1.495 mmol) in CH₂Cl₂ (1.0 mL) at room temperature for 3 h, gave **20** (78.0 mg, 95% yield).

Brown solid

Molecular formula: C₁₁H₁₆FNO₄S

M.W.: 277.31

R_f=0.22 (Hexane: AcOEt=50: 50)

¹H NMR (200 MHz, CDCl₃): δ 1.65 (d, *J*=21.4 Hz, 3H), 2.01-2.15 (m, 4H), 2.36 (s, 3H), 3.49 (d, *J*=20.6 Hz, 2H), 3.76-3.85 (m, 2H), 4.54-4.59 (m, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -154.3 (q, *J*=19.7 Hz, major), -151.4 (q, *J*=21.8 Hz, minor)

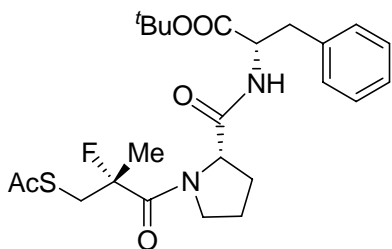
¹³C NMR (50.3 MHz, CDCl₃): δ 23.0 (d, *J*=23.2 Hz), 25.6, 27.8, 30.4, 48.0 (d, *J*=15.7 Hz), 59.6 (d, *J*=14.7 Hz), 60.7, 96.6 (d, *J*=190 Hz), 169.5 (d, *J*=23.1 Hz), 175.6, 193.8

IR (KBr): 2985, 1698, 1634, 1428, 1374, 1354, 1180, 1132, 958, 916, 731, 650, 624 cm⁻¹

MS (EI): *m/z* 277 (M⁺)

[α]_D²⁵ -77.3 (*c*=1.0, EtOH)

1-[(*S*)-3-(Acetylthio)-2-fluoro-2-methylpropanoyl]-L-prolyl-L-phenylalanine *t*-butyl ester (**21**)



A solution of (*S*)-3-(Acetylthio)-2-fluoro-2-(methylpropanoyl)-1-pyrrolidine-2-carboxylic acid **20** (48.2 mg, 0.174 mmol) in CH₂Cl₂ (2.0 mL) was added L-phenylalanine *tert*-butyl ester hydrochloride (44.9 mg, 0.174 mmol), HOBT (30.5 mg, 0.226 mmol), TEA (0.061 mL, 0.435 mmol), and EDC·HCl (43.3 mg, 0.226 mmol) at 0 °C and stirred for 5 h at room temperature. The reaction mixture was diluted with CH₂Cl₂, washed with

saturated sodium bicarbonate solution, brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. The purified by column chromatography on silica gel eluting with CH₂Cl₂/MeOH = 95/5 to give **21** (82% yield).

Brown oil

Molecular formula: C₂₄H₃₃FN₂O₅S

M.W.: 480.59

R_f=0.58 (CH₂Cl₂: MeOH=90: 10)

¹H NMR (200 MHz, CDCl₃): δ 1.55 (d, *J*=21.6 Hz, 3H), 1.87-1.98 (m, 4H), 2.35 (s, 3H), 3.06-3.10 (m, 2H), 3.46 (d, *J*=20.4 Hz, 2H), 3.67-3.79 (m, 2H), 4.54-4.70 (m, 2H), 6.82 (d, *J*=7.4 Hz, 1H), 7.12-7.26 (m, 5H)

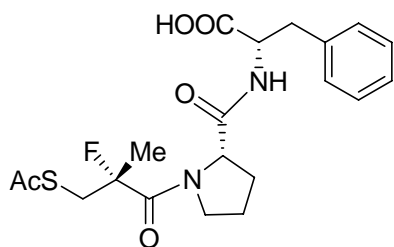
¹⁹F NMR (188 MHz, CDCl₃): δ -153.7 (q, *J*=19.7 Hz, major), -150.5 (q, *J*=21.1 Hz, minor)

¹³C NMR (100.6 MHz, CDCl₃): δ 23.2 (d, *J*=23.6 Hz), 25.4 (d, *J*=4.6 Hz), 27.0, 27.9, 30.4, 36.0 (d, *J*=24.0 Hz), 37.9, 47.9 (d, *J*=15.6 Hz), 53.7, 61.6, 82.2, 96.8 (d, *J*=191 Hz), 126.8, 128.2, 129.5, 136.3, 169.9 (d, *J*=23.0 Hz), 170.4, 170.5, 194.1

IR (neat): 3323, 3062, 2978, 2934, 1730, 1695, 1633, 1519, 1455, 1427, 1369, 1253, 1156, 957, 845, 741, 702 cm⁻¹

MS (EI): m/z 480 (M^+), 424 ($M^+ - t\text{Bu}$), 381 ($M^+ - \text{COO}^t\text{Bu}$)
[α]_D²⁵ -59.9 ($c=0.82$, EtOH)

1-[(S)-3-(Acetylthio)-2-fluoro-2-methylpropanoyl]-L-prolyl-L-phenylalanine (22)



To CH_2Cl_2 (1.0 mL) solution of 1-[(S)-3-(Acetylthio)-2-fluoro-2-methylpropanoyl]-L-prolyl-L-phenylalanine *t*-butyl ester **21** (68.4 mg, 0.142 mmol) was added TFA (0.1 mL) at room temperature, and stirred for 16 h. The solvent was removed under reduced pressure. The purified by column chromatography on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH} = 90/10$ to give **22** (73% yield).

Yellow oil

Molecular formula: $\text{C}_{20}\text{H}_{25}\text{FN}_2\text{O}_5\text{S}$

M.W.: 424.49

$R_f=0.32$ (CH_2Cl_2 : MeOH=90: 10)

^1H NMR (200 MHz, CDCl_3): δ 1.50 (d, $J=21.8$ Hz, 3H), 1.91-2.17 (m, 4H), 3.01-3.27 (m, 2H), 3.44 (d, $J=20.8$ Hz, 2H), 3.65-3.74 (m, 2H), 4.52-4.76 (m, 2H), 6.92 (d, $J=7.4$ Hz, 1H), 7.14-7.25 (m, 5H)

^{19}F NMR (188 MHz, CDCl_3): δ -153.6 (q, $J=21.1$ Hz, major), -150.5 (q, $J=19.7$ Hz, minor)

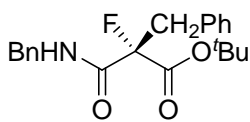
^{13}C NMR (150.9 MHz, CDCl_3): δ 23.1 (d, $J=23.4$ Hz), 25.3 (d, $J=4.7$ Hz), 27.1, 30.4, 35.9 (d, $J=24.3$ Hz), 37.2, 48.1 (d, $J=15.7$ Hz), 53.4, 61.8, 96.8 (d, $J=191$ Hz), 126.9, 128.4, 129.4, 136.1, 170.2 (d, $J=23.4$ Hz), 171.2, 174.3, 194.2

IR (neat): 3325, 2981, 2933, 1738, 1636, 1524, 1456, 1422, 1192, 1131, 958, 702 cm^{-1}

MS (EI): m/z 424 (M^+)

[α]_D²⁵ -22.8 ($c=0.88$, EtOH)

(S)-tert-Butyl 2-fluoro-2-(hydroxymethyl)-3-phenylpropionate (23)



To a solution of (S)-1-*t*-Butyl 3-methyl 2-benzyl-2-fluoromalonate **22** (100 mg, 0.354 mmol) and benzylamine (36.0 mg, 0.337 mmol) in 1.0 mL (1.00 M in ester substrate) of toluene was added HOAt (24.0 mg, 0.177 mmol) followed by $\text{Zr}(\text{O}^t\text{Bu})_4$ (67.0 mg, 0.177 mmol). The reaction was stirred at the 60 °C for 24 h and quenched by addition of MeOH (2 mL) and CH_2Cl_2 (2 mL). The reaction mixture was filtered through a silica gel pad and concentrated in *vacuo*. Amide products were isolated by column chromatography using silica gel, eluted in hexane/AcOEt = 85/15 in 55% yield of compound **23**.

White solid

Molecular formula: $\text{C}_{21}\text{H}_{24}\text{FNO}_3$

M.W.: 357.42

$R_f=0.19$ (Hexane: AcOEt=90: 10)

^1H NMR (200 MHz, CDCl_3): δ 1.46 (s, 9H), 3.48 (dd, $J=10.0, 20.4$ Hz, 2H), 4.36 (d, $J=5.8$ Hz, 2H), 6.48 (s, 1H), 6.96-7.01 (m, 2H), 7.20-7.25 (m, 8H)

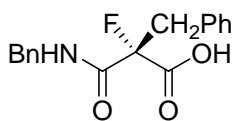
^{19}F NMR (188 MHz, CDCl_3): δ -163.17 (ddd, $J=22.2, 11.0, 3.9$ Hz)

^{13}C NMR (50.3 MHz, CDCl_3): δ 27.9, 39.8 (d, $J=19.9$ Hz), 43.3, 84.0, 96.8 (d, $J=200$ Hz), 127.0, 127.2, 127.3, 128.1, 128.4, 130.3, 133.4, 164.7 (d, $J=24.7$ Hz), 165.4 (d, $J=21.5$ Hz)

IR (KBr): 3374, 2979, 1743, 1677, 1533, 1455, 1370, 1258, 1158, 1085, 841, 737, 699 cm^{-1}

MS (EI): m/z 357 (M^+)

(S)-2-Fluoro-2-bezylamide-3-phenylpropanoic acid (**24**)



The reaction of (*S*)-*t*-Butyl 2-fluoro-2-bezylamide-3-phenylpropanate **23** (28.0 mg, 0.072 mmol) with TFA (0.054 ml, 0.727 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 3 h, reaction progress was assessed by TLC. The reaction mixture was concentrated in vacuum and subsequently co-evaporated with toluene (2 x 10 mL) to afford carboxylic compound, which was purified on column chromatography on silica gel eluted ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 9/1$), in 74% yield of **24**.

White solid

Molecular formula: $\text{C}_{12}\text{H}_{16}\text{FNO}_2$

M.W.: 225.26

$R_f=0.51$ (CH_2Cl_2 : $\text{MeOH}=90:10$)

^1H NMR (200 MHz, CD_3OD): δ 3.13-3.57 (m, 2H), 4.11 (d, $J=16.6$ Hz, 1H), 4.31 (d, $J=15.4$ Hz, 1H), 6.89 (s, 2H), 7.08-7.21 (m, 8H), 8.53 (bs, 1H)

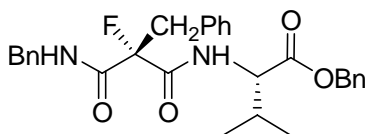
^{19}F NMR (188 MHz, CDCl_3): δ -163.17 (ddd, $J=22.2, 11.0, 3.9$ Hz)

IR (KBr): 3280, 3029, 2965, 1758, 1671, 1530, 1495, 1454, 1383, 1358, 1299 cm^{-1}

MS (EI): m/z 301 (M^+)

$[\alpha]_D^{25} +20.11$ ($c=0.50$, CH_2Cl_2)

(S)-2-Fluoro-2-(bezyloxy-L-valylcarbonyl)-3-phenylpropanoic acid benzylamide (**25**)



A solution of acid **24** (16.0 mg, 0.053 mmol), L-valine benzyl ester *p*-toluenesulfonate (15.3 mg, 0.053 mmol), HOBt (7.3 mg, 0.053 mmol) and *N*-methylmorpholine (0.05 mg, 0.053 mmol) in dry THF (2 mL) was stirred and cooled in an ice-water bath while DCC (10.9 mg, 0.053 mmol) was added. Stirring was continued for 2 h at 0 °C and additional 20 h at room temperature. The *N,N'*-dicyclohexylurea formed during the reaction was removed by filtration and the filtrate was poured in to a mixture of AcOEt (10 mL) and an aqueous saturated solution of NaHCO_3 (5 mL). The organic phase was extracted with 10% solution citric acid in water (5 mL), then washed with saturated NaHCO_3 and water. The

solution was dried over Na₂SO₄ and concentrated. The resulting residue was chromatographed (hexane/AcOEt) to afford 20.5 mg of compound **25** (77% yield).

White solid

Molecular formula: C₂₉H₃₁FN₂O₄

M.W.: 490.57

R_f=0.47 (Hexane: AcOEt=70: 30)

¹H NMR (200 MHz, CDCl₃): δ 0.87 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 2.13-2.29 (m, 1H), 3.37 (d, *J*=4.4 Hz, 1H), 3.49 (d, *J*=15.2 Hz, 1H), 4.24 (dd, *J*=14.8, 5.2 Hz, 1H), 4.44 (dd, *J*=14.9, 6.4 Hz, 1H), 4.53 (dd, *J*=8.8, 5.0 Hz, 1H), 5.12 (s, 2H), 6.82 (bs, 1H), 6.93-6.98 (m, 2H), 7.23-7.36 (m, 12H), 7.55 (d, *J*=8.6 Hz, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -168.20 (dd, *J*=30.9, 21.1 Hz)

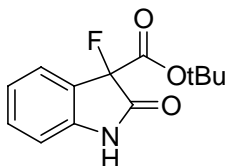
¹³C NMR (50.3 MHz, CDCl₃): δ 17.6, 19.2, 31.4, 43.4 (d, *J*=21.2 Hz), 43.5, 57.3, 67.1, 96.2 (d, *J*=199 Hz), 127.3, 127.4, 128.11, 128.17, 128.24, 128.36, 128.42, 130.1, 132.6, 135.0, 136.6, 166.4 (d, *J*=23.1 Hz), 166.5 (d, *J*=22.3 Hz), 170.2

IR (KBr): 3341, 3032, 2965, 1740, 1687, 1539, 1455, 1216, 1148, 1086, 1050, 746, 698 cm⁻¹

MS (EI): *m/z* 357 (M⁺)

[α]_D²⁵ -3.09 (*c*=0.50, CH₂Cl₂) [lit.⁸⁴ [α]_D +7.3 (*c*=1.5, CH₂Cl₂)]

(S)-*tert*-butyl 3-fluoro-2-oxindoline-3-carboxylate (**26**)



White solid

Molecular formula: C₁₃H₁₄FN₂O₃

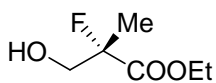
M.W.: 251.25

R_f=0.37 (Hexane: AcOEt=60: 40)

¹H NMR (200 MHz, CDCl₃): δ 1.43 (s, 9H), 6.90-7.40 (m, 4H), 8.25 (s, br, 1H)

¹⁹F NMR (188 MHz, CDCl₃): δ -162.97 (s, 1F)

(S)-Ethyl- 2-fluoro-3-hydroxy-2-methyl propionate (**27**)



H₂SO₄ (2 drops) was added into a solution of (*S*)-*tert*-Butyl 2-fluoro-2-(hydroxymethyl)propionate **10c** (21.9 mg, 0.114 mmol) in ethanol (2.0 mL) at room temperature and the resulting mixture was stirred for 9 h at 80 °C. The reaction mixture was concentrated in vacuo to about 1/6 of its original volume, and then ether was added. The ether solution was washed with saturated sodium bicarbonate solution, brine, and dried over MgSO₄ and the solvent was evaporated under

⁸⁴ Abouabdellah, A.; Welch, J. T. *Tetrahedron: Asymmetry* **1994**, 5, 1005-1013.

reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/AcOEt = 70/30 to give **27** (85% yield).

Colorless oil

Molecular formula: C₆H₁₁FO₃

M.W.: 150.15

R_f=0.24 (Hexane: AcOEt=70: 30)

¹H NMR (200 MHz, CDCl₃): δ 1.32 (t, *J*=7.2 Hz, 3H), 1.54 (d, *J*=21.6 Hz, 3H), 2.20 (s, 1H), 3.73-4.01 (m, 2H), 4.28 (q, *J*=7.2 Hz, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -164.2- -163.6 (m)

¹³C NMR (150.9 MHz, CDCl₃): δ 14.1, 19.7 (d, *J*=23.5 Hz), 61.9, 67.0 (d, *J*=23.4 Hz), 95.4 (d, *J*=184 Hz), 170.6 (d, *J*=25.5 Hz)

IR (neat): 3443, 2987, 2939, 1740, 1665, 1454, 1384, 1308, 1228, 1136, 1067, 1019, 901 cm⁻¹

MS (EI): *m/z* 120 (M⁺-Et)

[α]_D²⁵ -13.1 (*c*=0.24, MeOH) [lit.⁸⁵ [α]_D -8.87 (*c*=1.81, MeOH)]

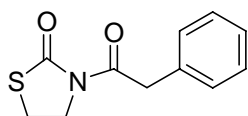
⁸⁵ Kitazume, T.; Yamamoto, T. *J. Fluorine Chem.* **1987**, 35, 467.

Chapter 2

General procedure for the preparation of Thiazolidinone aryl esters:

Thiazolidin-2-one (1.0 equiv) was dissolved in CH₂Cl₂ solvent (10 ml) and carboxylic compound (1.2 equiv), DMAP (0.13 equiv) was added to this solution, and cooled to 0°C. *N,N'*-Dicyclohexylcarbodiimide (1.3 equiv) (DCC) in CH₂Cl₂ (10 ml) was added to the above dropwise, which was stirred overnight at rt for several hours. Filtered the reaction mass, washed with the solvent and evaporated solvent, obtained crude product, which was purified by silica gel column chromatography.

3-(2-phenylacetyl)thiazolidin-2-one (30a)



Thiazolidin-2-one was dissolved in (1.0 equiv) in dry THF, which was cooled to -80°C. *n*-BuLi (1.1 equiv) was added dropwise to the reaction mixture, stirred for 30 mins at same temperature, then phenyl acetyl chloride (1.0 equiv) was added, further stirred at rt for 1 hour, and quench the reaction mixture then general workup. Purified by column eluted with (Hexane: AcOEt=70:30) afforded 59% yield.

White solid

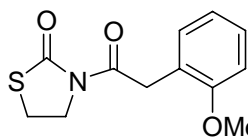
Molecular formula: C₁₁H₁₁NO₂S

M.W.: 221.27

R_f=0.46 (Hexane: AcOEt=60: 40)

¹H-NMR (CDCl₃, 200 MHz): δ 4.01 (t, *J*=8.2 Hz, 2H), 4.27 (s, 2H), 4.39 (t, *J*=7.6 Hz, 2H), 7.24-7.31 (m, 5H)

3-[2-(2-methoxyphenyl)acetyl]-2-thiazolidinone (30b)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 2-methoxy phenylacetic acid (0.360 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 1 hour. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30b** in 475 mg, 95% yield.

White solid

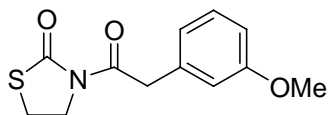
Molecular formula: C₁₂H₁₃NO₃S

M.W.: 251.30

R_f=0.62 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.29 (t, *J*=7.2 Hz, 2H), 3.79 (s, 3H), 4.16 (t, *J*=7.4 Hz, 2H), 4.17 (s, 2H), 6.90 (t, *J*=7.4 Hz, 2H), 7.09 (d, *J*=7.2 Hz, 1H), 7.24 (t, *J*=8.8 Hz, 1H)

3-[2-(3-methoxyphenyl)acetyl]-2-thiazolidinone (30c)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 3-methoxy phenylacetic acid (0.360 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 2 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30c** in 480 mg, 96% yield.

White solid

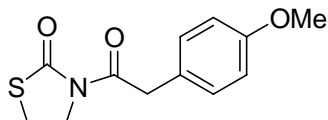
Molecular formula: C₁₂H₁₃NO₃S

M.W.: 251.30

R_f=0.60 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.26 (t, *J*=6.8 Hz, 2H), 3.78 (s, 3H), 4.17 (t, *J*=7.4 Hz, 2H), 4.19 (s, 2H), 6.81 (t, *J*=8.8 Hz, 2H), 7.24 (t, *J*=4.4 Hz, 2H)

3-[2-(4-methoxyphenyl)acetyl]-2-thiazolidinone (30d)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 4-methoxy phenylacetic acid (0.360 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 1 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30d** in 486 mg, 99% yield.

White solid

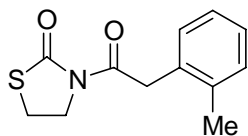
Molecular formula: C₁₂H₁₃NO₃S

M.W.: 251.30

R_f=0.61 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.26 (t, *J*=7.2 Hz, 2H), 3.78 (s, 3H), 4.16 (t, *J*=7.4 Hz, 2H), 4.14 (s, 2H), 6.83 (t, *J*=6.6 Hz, 2H), 7.19 (t, *J*=8.8 Hz, 2H)

3-[2-(2-methylphenyl)acetyl]-2-thiazolidinone (30e)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 2-methyl phenylacetic acid (0.349 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 5 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30e** in 419 mg, 91% yield.

White solid

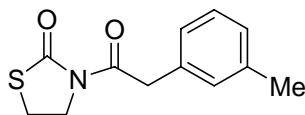
Molecular formula: C₁₂H₁₃NO₂S

M.W.: 235.30

R_f=0.59 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 2.25 (s, 3H), 3.29 (t, *J*=7.4 Hz, 2H), 4.18 (t, *J*=7.4 Hz, 2H), 4.19 (s, 2H), 7.09-7.24 (m, 4H)

3-[2-(3-methylphenyl)acetyl]-2-thiazolidinone (30f)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 3-methyl phenylacetic acid (0.349 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 6 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30f** in 427 mg, 93% yield.

White solid

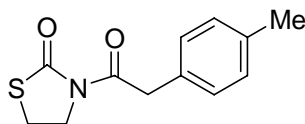
Molecular formula: C₁₂H₁₃NO₂S

M.W.: 235.30

R_f=0.63 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 2.32 (s, 3H), 3.26 (t, *J*=7.4 Hz, 2H), 4.17 (t, *J*=7.4 Hz, 2H), 4.18 (s, 2H), 7.03 (t, *J*=6.0 Hz, 2H), 7.19 (t, *J*=8.0 Hz, 2H)

3-[2-(4-methoxyphenyl)acetyl]-2-thiazolidinone (30g)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 4-methyl phenylacetic acid (0.349 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 5 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30g** in 331 mg, 73% yield.

White solid

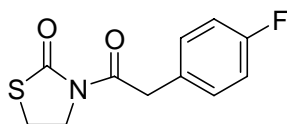
Molecular formula: C₁₂H₁₃NO₂S

M.W.: 235.30

R_f=0.60 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 2.32 (s, 3H), 3.25 (t, *J*=7.2 Hz, 2H), 4.16 (t, *J*=7.4 Hz, 2H), 4.17 (s, 2H), 7.12-7.24 (m, 4H), 7.19 (t, *J*=4H)

3-[2-(4-fluorophenyl)acetyl]-2-thiazolidinone (30h)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 4-fluoro phenylacetic acid (0.358 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 4 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30h** in 382 mg, 83% yield.

White solid

Molecular formula: C₁₁H₁₀FO₂S

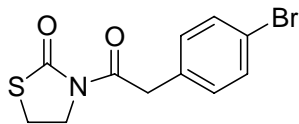
M.W.: 239.26

R_f=0.55 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.28 (t, *J*=7.4 Hz, 2H), 4.17 (t, *J*=7.4 Hz, 2H), 4.18 (s, 2H), 6.99 (t, *J*=8.8 Hz, 2H), 7.24 (t, *J*=8.0 Hz, 2H)

¹⁹F-NMR (CDCl₃, 188 MHz): -115.1 – -115.3 (m, 1F)

3-[2-(4-bromophenyl)acetyl]-2-thiazolidinone (30i)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 4-bromo phenylacetic acid (0.501 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 1 hour. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30i** in 345 mg, 58% yield.

White solid

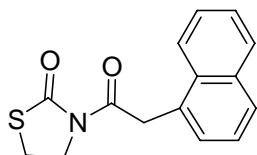
Molecular formula: C₁₁H₁₀BrNO₂S

M.W.: 300.17

R_f=0.55 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.28 (t, *J*=7.4 Hz, 2H), 4.15 (t, *J*=7.4 Hz, 2H), 4.16 (s, 2H), 7.12 (dd, *J*=1.8, 8.4 Hz, 2H), 7.32 (dd, *J*=1.8, 8.4 Hz, 2H)

3-[2-(1-naphthyl)acetyl]-2-thiazolidinone (30j)



The reaction of **29** (0.245 g, 2.38 mmol) in dichloromethane (10 ml), 1-naphthyl acetic acid (0.575 g, 3.08 mmol), DMAP (37.7 mg, 0.30 mmol) and DCC (0.64 g, 3.088 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 1 hour. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30j** in 625 mg, 96% yield.

Pale yellow solid

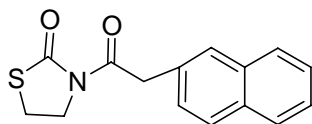
Molecular formula: C₁₅H₁₃NO₂S

M.W.: 271.33

R_f=0.50 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.30 (t, *J*=7.4 Hz, 2H), 4.19 (t, *J*=7.0 Hz, 2H), 4.65 (s, 2H), 7.33-7.51 (m, 4H), 7.76-7.87 (m, 3H)

3-[2-(2-naphthyl)acetyl]-2-thiazolidinone (30k)



The reaction of **29** (0.245 g, 2.38 mmol) in dichloromethane (10 ml), 2-naphthyl acetic acid (0.575 g, 3.08 mmol), DMAP (37.7 mg, 0.30 mmol) and DCC (0.64 g, 3.088 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 1 hour. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30k** in 623 mg, 96% yield.

White solid

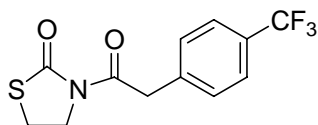
Molecular formula: C₁₅H₁₃NO₂S

M.W.: 271.33

R_f=0.52 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.30 (t, *J*=7.4 Hz, 2H), 4.19 (t, *J*=7.0 Hz, 2H), 4.65 (s, 2H), 7.50–7.55 (m, 2H), 7.62 (d, *J*=1.2, 8.4 Hz, 1H), 7.84–7.89 (m, 3H), 8.02 (s, 1H)

3-[2-(4-trifluoromethylphenyl)acetyl]-2-thiazolidinone (30l)



The reaction of **29** (0.1 g, 0.96 mmol) in dichloromethane (10 ml), 4-trifluoromethyl phenylacetic acid (0.237 g, 1.16 mmol), DMAP (15.3 mg, 0.12 mmol) and DCC (0.26 g, 1.26 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 24 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30l** in 130 mg, 46% yield.

White solid

Molecular formula: C₁₂H₁₀F₃NO₂S

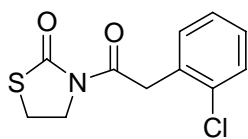
M.W.: 289.27

R_f=0.65 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.29 (t, *J*=7.2 Hz, 2H), 4.18 (t, *J*=7.2 Hz, 2H), 4.27 (s, 2H), 7.37 (d, *J*=8.2 Hz, 2H), 7.56 (d, *J*=8.4 Hz, 2H)

¹⁹F-NMR (CDCl₃, 188 MHz): -63.33 (s, 3F)

3-[2-(2-chlorophenyl)acetyl]-2-thiazolidinone (30m)



The reaction of **29** (0.2 g, 1.93 mmol) in dichloromethane (10 ml), 2-chloro phenylacetic acid (0.396 g, 2.32 mmol), DMAP (30.7 mg, 0.25 mmol) and DCC (0.52 g, 2.52 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 12 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30m** in 230 mg, 46% yield.

Colorless syrup

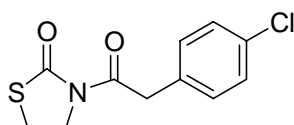
Molecular formula: C₁₁H₁₀ClNO₂S

M.W.: 255.72

R_f=0.62 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.33 (t, *J*=7.4 Hz, 2H), 4.22 (t, *J*=7.2 Hz, 2H), 4.31 (s, 2H), 7.17-7.25 (m, 3H), 7.34-7.40 (m, 1H)

3-[2-(4-chlorophenyl)acetyl]-2-thiazolidinone (30n)



The reaction of **29** (0.1 g, 0.96 mmol) in dichloromethane (10 ml), 4-chloro phenylacetic acid (0.237 g, 1.16 mmol), DMAP

(15.3 mg, 0.12 mmol) and DCC (0.26 g, 1.26 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 12 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **30n** in 480 mg, 96% yield.

White solid

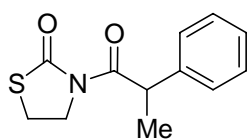
Molecular formula: C₁₁H₁₀ClNO₂S

M.W.: 255.72

R_f=0.66 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 3.28 (t, *J*=7.4 Hz, 2H), 4.16 (t, *J*=7.2 Hz, 2H), 4.17 (s, 2H), 7.15-7.30 (m, 4H)

3-[2-phenylpropanoyl]-2-thiazolidinone (**32**)



The reaction of **29** (0.1 g, 0.96 mmol) in dichloromethane (10 ml), 2-phenyl propinoic acid (0.174 g, 1.16 mmol), DMAP (15.3 mg, 0.12 mmol) and DCC (0.26 g, 1.26 mmol) in dichloromethane (10 ml) which was stirred overnight at 0°C-rt for 16 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=70: 30) obtained **32** in 220 mg, 96% yield.

Colorless syrup

Molecular formula: C₁₂H₁₃NO₂S

M.W.: 235.3

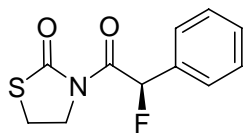
R_f=0.68 (Hexane: AcOEt=50: 50)

¹H-NMR (CDCl₃, 200 MHz): δ 1.47 (d, *J*=7.0 Hz, 3H), 3.19 (t, *J*=6.8 Hz, 2H), 4.15 (t, *J*=7.4 Hz, 2H), 4.96 (q, *J*=7.0 Hz, 1H), 7.21-7.30 (m, 5H)

General procedure for the Enantioselective Catalytic Fluorination

Ni(ClO₄)₂·6H₂O (10 mol%) and the (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) (DBFOX-Ph) (11 mol%) were stirred under vacuum for 2 h at room temperature. Dry dichloromethane (2.0 ml) and MS 4Å (substrate/ MS 4A=1: 500 mol/ g) were added under nitrogen atmosphere and stirred for 1 h. Then **1** (0.1 mmol) was added directly to the catalyst solution. After stirring for another 20 min at 0 °C, NFSI (1.2 equiv) and 2,6-lutidine (1.0 equiv) were added to the mixture. The reaction was stirred at 0 °C for 24—48 h with monitoring by TLC, it was stopped by the addition of water. The reaction mixture was then diluted with dichloromethane, washed with brine, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure, and purified by column chromatography on silica gel eluting with Hexane/AcOEt/CHCl₃ to give **2**. The ee of the product **2** was determined by chiral HPLC on CHIRALPAK AD-H or CHIRALCEL OJ-H column.

3-[2-Fluoro-2-(phenyl)acetyl]-2-thiazolidinone (31a)



White solid

Molecular formula: C₁₁H₁₀FNO₂S

M. W.: 239.26

R_f=0.31 (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 3.26–3.33 (m, 2H), 4.13–4.17 (m, 1H), 4.21–4.25 (m, 1H), 6.81 (d, *J*=48.6 Hz, 1H), 7.40–7.41 (m, 3H), 7.51–7.53 (m, 2H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.5, 168.1 (d, *J*=26.7 Hz), 133.6 (d, *J*=20.1 Hz), 129.9 (d, *J*=3.0 Hz), 128.7 (d, *J*=1.5 Hz), 128.5 (d, *J*=4.6 Hz), 89.6 (d, *J*=179.3 Hz), 46.6, 25.6

¹⁹F-NMR (CDCl₃, 188 MHz): –170.3 (d, *J*=48.7 Hz, 1F)

IR (KBr): 2924, 2853, 1695, 1496, 1472, 1458, 1360, 1291, 1247, 1182, 1069, 1012, 967, 928, 858, 790, 768, 701, 654, 616 cm^{–1}

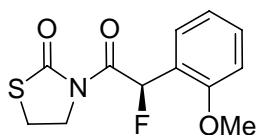
MS (EI): *m/z* 239 (M⁺)

HPLC: (AD-H, hexane/*i*PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R ((*R*)-isomer)=15.1 min, t_R ((*S*)-isomer)=17.5 min

[α]_D²⁵ –69.2 (*c*=0.500, CHCl₃ 74% ee), Lit. [1] [α]_D³¹ –92.1 (*c*=1.0, CHCl₃ 82% ee, *R*)

Mp: 125–126 °C

3-[2-Fluoro-2-(2-methoxyphenyl)acetyl]-2-thiazolidinone (31b)



White solid

Molecular formula: C₁₂H₁₂FNO₃S

M. W.: 269.29

R_f=0.30 (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 3.27–3.34 (m, 2H), 3.89 (s, 3H), 4.18–4.27 (m, 2H), 6.98 (d, *J*=48.6 Hz, 1H), 6.94–6.97 (m, 2H), 7.24 (dt, *J*=7.8, 1.2 Hz, 1H), 7.37 (tt, *J*=8.1, 1.2 Hz, 1H)

¹³C-NMR (CDCl₃, 150.9 MHz): 171.8, 168.4 (d, *J*=25.8 Hz), 157.9 (d, *J*=13.2 Hz), 131.4 (d, *J*=3.6 Hz), 129.0 (d, *J*=4.4 Hz), 122.4 (d, *J*=18.7 Hz), 120.6 (d, *J*=2.6 Hz), 111.4 (d, *J*=2.1 Hz), 85.9 (d, *J*=178.1 Hz), 55.9, 46.6, 25.7

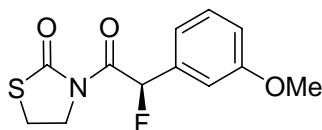
¹⁹F-NMR (CDCl₃, 188 MHz): –173.7 (d, *J*=49.8 Hz, 1F)

IR (KBr): 3017, 2984, 2951, 2898, 2845, 1700, 1601, 1587, 1496, 1467, 1441, 1367, 1330, 1294, 1254, 1189, 1165, 1110, 1075, 1050, 1024, 1008, 967, 931, 865, 810, 769, 749, 685, 656, 607 cm^{–1}

MS (EI): *m/z* 269 (M⁺)

HPLC: (AD-H, hexane/ⁱPrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (minor-isomer)=21.5 min,
 t_R (major-isomer)=26.0 min
 $[\alpha]_D^{25}$ -208.1 ($c=0.500$, CHCl_3 78% ee)
Mp: 119–120 °C

3-[2-Fluoro-2-(3-methoxyphenyl)acetyl]-2-thiazolidinone (31c)



White solid

Molecular formula: $\text{C}_{12}\text{H}_{12}\text{FNO}_3\text{S}$

M. W.: 269.29

$R_f=0.33$ (Hexane: AcOEt: $\text{CHCl}_3=5: 1: 1$)

$^1\text{H-NMR}$ (CDCl_3 , 600 MHz): 3.27–3.32 (m, 2H), 3.82 (d, $J=4.2$ Hz, 3H), 4.13–4.17 (m, 1H), 4.22 (dt, $J=12.0$, 7.8 Hz, 1H), 6.80 (d, $J=48.6$ Hz, 1H), 6.94 (d, $J=7.2$ Hz, 1H), 7.06 (t, $J=1.2$ Hz, 1H), 7.10 (d, $J=7.2$ Hz, 1H), 7.30 (t, $J=7.8$ Hz, 1H)

$^{13}\text{C-NMR}$ (CDCl_3 , 150.9 MHz): 172.5, 168.0 (d, $J=26.6$ Hz), 159.7, 134.9 (d, $J=20.2$ Hz), 129.8, 120.7 (d, $J=5.0$ Hz), 115.8 (d, $J=2.9$ Hz), 113.5 (d, $J=4.8$ Hz), 89.3 (d, $J=179.7$ Hz), 55.3, 46.7, 25.5

$^{19}\text{F-NMR}$ (CDCl_3 , 188 MHz): -171.8 (d, $J=47.2$ Hz, 1F)

IR (KBr): 3019, 2969, 2938, 2883, 2716, 1688, 1600, 1490, 1472, 1454, 1434, 1362, 1326, 1288, 1250, 1204, 1169, 1079, 1035, 1013, 957, 890, 858, 825, 800, 759, 701, 687, 665, 653 cm^{-1}

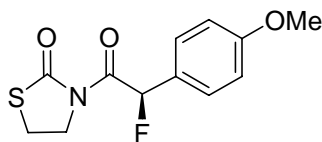
MS (EI): m/z 269 (M^+)

HPLC: (AD-H, hexane/ⁱPrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (minor-isomer)=20.9 min,
 t_R (major-isomer)=23.0 min

$[\alpha]_D^{25}$ -54.8 ($c=0.500$, CHCl_3 66% ee)

Mp: 97–98 °C

3-[2-Fluoro-2-(4-methoxyphenyl)acetyl]-2-thiazolidinone (31d)



White solid

Molecular formula: $\text{C}_{12}\text{H}_{12}\text{FNO}_3\text{S}$

M. W.: 269.29

$R_f=0.33$ (Hexane: AcOEt: $\text{CHCl}_3=5: 1: 1$)

^1H -NMR (CDCl_3 , 600 MHz): 3.25–3.32 (m, 2H), 4.13–4.17 (m, 1H), 4.23 (dt, $J=12.0$, 7.8 Hz, 1H), 6.73 (d, $J=48.6$ Hz, 1H), 6.91 (d, $J=7.8$ Hz, 2H), 7.44 (dd, $J=1.2$, 8.4 Hz, 1H)

^{13}C -NMR (CDCl_3 , 150.9 MHz): 172.3, 168.3 (d, $J=27.5$ Hz), 160.8 (d, $J=2.9$ Hz), 130.2 (d, $J=4.1$ Hz), 125.6 (d, $J=21.0$ Hz), 114.1 (d, $J=1.8$ Hz), 89.3 (d, $J=179.0$ Hz), 55.3, 46.6, 25.6

^{19}F -NMR (CDCl_3 , 188 MHz): -167.3 (d, $J=48.7$ Hz, 1F)

IR (KBr): 3052, 1970, 2932, 1720, 1686, 1610, 1586, 1512, 1456, 1370, 1326, 1309, 1280, 1242, 1200, 1178, 1116, 1075, 1034, 1005, 966, 926, 838, 825, 800, 769, 660, 626 cm^{-1}

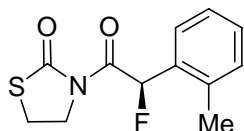
MS (EI): m/z 269 (M^+)

HPLC: (AD-H, hexane/ i PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (minor-isomer)=23.2 min, t_R (major-isomer)=28.1 min

$[\alpha]_D^{25} -84.5$ ($c=0.500$, CHCl_3 65% ee)

Mp: 142–143 $^\circ\text{C}$

3-[2-Fluoro-2-(2-methylphenyl)acetyl]-2-thiazolidinone (31e)



White solid

Molecular formula: $\text{C}_{12}\text{H}_{12}\text{FNO}_2\text{S}$

M. W.: 253.29

$R_f=0.31$ (Hexane: AcOEt: $\text{CHCl}_3=5: 1: 1$)

^1H -NMR (CDCl_3 , 600 MHz): 2.53 (d, $J=1.8$ Hz, 3H), 3.32 (t, $J=7.8$ Hz, 2H), 4.24–4.30 (m, 2H), 6.90 (d, $J=49.8$ Hz, 1H), 7.16–7.20 (m, 2H), 7.26 (d, $J=7.2$ Hz, 1H), 7.31 (tt, $J=2.4$, 7.2 Hz, 1H)

^{13}C -NMR (CDCl_3 , 150.9 MHz): 172.2, 168.4 (d, $J=25.5$ Hz), 138.9 (d, $J=3.3$ Hz), 131.8 (d, $J=17.7$ Hz), 131.1 (d, $J=2.7$ Hz), 130.1 (d, $J=4.1$ Hz), 127.4 (d, $J=3.6$ Hz), 126.3 (d, $J=2.9$ Hz), 87.9 (d, $J=178.8$ Hz), 46.5, 25.7, 18.9

^{19}F -NMR (CDCl_3 , 188 MHz): -170.9 (d, $J=48.5$ Hz, 1F)

IR (KBr): 2970, 2932, 2855, 1699, 1495, 1471, 1450, 1361, 1316, 1291, 1248, 1174, 1068, 1006, 965, 929, 863, 813, 762, 730, 654, 605 cm^{-1}

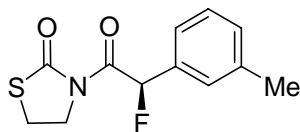
MS (EI): m/z 253 (M^+)

HPLC: (AD-H, hexane/ i PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (minor-isomer)=11.3 min, t_R (major-isomer)=14.0 min

$[\alpha]_D^{25} -193.6$ ($c=0.500$, CHCl_3 76% ee)

Mp: 114–115 $^\circ\text{C}$

3-[2-Fluoro-2-(3-methylphenyl)acetyl]-2-thiazolidinone (31f)



White solid

Molecular formula: C₁₂H₁₂FNO₂S

M. W.: 253.29

R_f=0.32 (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 2.37 (s, 3H), 3.26–3.32 (m, 2H), 4.13–4.18 (m, 1H), 4.23 (dt, *J*=12.6, 7.8 Hz, 1H), 6.77 (d, *J*=49.2 Hz, 1H), 7.21 (dd, *J*=0.6, 7.2 Hz, 1H), 7.28 (dd, *J*=7.2, 7.8 Hz, 1H), 7.30–7.33 (m, 2H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.4, 168.2 (d, *J*=26.7 Hz), 138.6 (d, *J*=1.7 Hz), 133.4 (d, *J*=19.9 Hz), 130.7 (d, *J*=3.2 Hz), 129.0 (d, *J*=4.5 Hz), 128.6 (d, *J*=1.5 Hz), 125.6 (d, *J*=4.7 Hz), 89.6 (d, *J*=179.0 Hz), 46.6, 25.5, 21.3

¹⁹F-NMR (CDCl₃, 188 MHz): –169.9 (d, *J*=48.7 Hz, 1F)

IR (KBr): 3003, 2970, 2925, 2855, 1699, 1495, 1471, 1450, 1361, 1291, 1248, 1174, 1068, 1006, 929, 863, 813, 762, 730, 654, 605 cm^{–1};

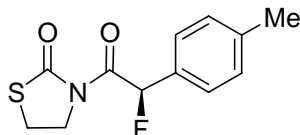
MS (EI): *m/z* 253 (M⁺)

HPLC: (OJ-H, hexane/*i*PrOH=90/ 10, 1.0 ml/ min, 254 nm) *t*_R (major-isomer)=32.7 min, *t*_R (minor-isomer)=39.2 min

[α]_D²⁵ –77.5 (*c*=0.500, CHCl₃ 73 % ee)

Mp: 93–94 °C

3-[2-Fluoro-2-(4-methylphenyl)acetyl]-2-thiazolidinone (31g)



White solid

Molecular formula: C₁₂H₁₂FNO₂S

M. W.: 253.29

R_f=0.33 (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 2.36 (d, *J*=1.8 Hz, 3H), 3.25–3.32 (m, 2H), 4.12–4.18 (m, 1H), 4.22 (dt, *J*=12.0, 7.8 Hz, 1H), 6.76 (d, *J*=48.6 Hz, 1H), 7.20 (d, *J*=7.8 Hz, 2H), 7.40 (dd, *J*=1.2, 7.8 Hz, 1H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.4, 168.3 (d, *J*=31.1 Hz), 140.1 (d, *J*=3.2 Hz), 130.6 (d, *J*=20.4 Hz), 129.4 (d, *J*=1.7 Hz), 128.5 (d, *J*=4.5 Hz), 89.5 (d, *J*=89.5 Hz), 46.6, 25.6, 21.3

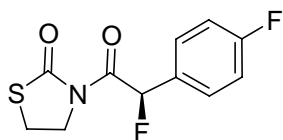
¹⁹F-NMR (CDCl₃, 188 MHz): –169.1 (d, *J*=48.7 Hz, 1F)

IR (KBr): 2994, 2961, 2922, 1717, 1698, 1610, 1513, 1472, 1446, 1364, 1287, 1266, 1241, 1183, 1066, 1008, 926, 860, 847, 827, 797, 766, 723, 661, 653 cm^{–1}

MS (EI): *m/z* 253 (M⁺)

HPLC: (AD-H, hexane/*i*PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (major-isomer)=12.3 min,
 t_R (minor-isomer)=13.9 min
 $[\alpha]_D^{25}$ -72.9 ($c=0.500$, CHCl₃ 77 % ee)
Mp: 92–93 °C

3-[2-Fluoro-2-(4-fluorophenyl)acetyl]-2-thiazolidinone (31h)



White solid

Molecular formula: C₁₁H₉F₂NO₂S

M. W.: 257.25

$R_f=0.35$ (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 3.28–3.35 (m, 2H), 4.15 (ddd, $J=5.4$, 7.8, 12.0 Hz, 1H), 4.24 (td, $J=12.0$, 7.8 Hz, 1H), 6.77 (d, $J=48.0$ Hz, 1H), 7.08 (dt, $J=0.6$, 8.4 Hz, 2H), 7.51–7.53 (m, 2H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.6, 168.0 (d, $J=26.9$ Hz), 163.6 (dd, $J=3.2$, 249.7 Hz), 130.6 (dd, $J=4.5$, 8.6 Hz), 129.5 (dd, $J=3.3$, 20.8 Hz), 115.8 (dd, $J=1.7$, 21.7 Hz), 88.7 (d, $J=179.7$ Hz), 46.6, 25.6

¹⁹F-NMR (CDCl₃, 188 MHz): -169.2 (dd, $J=5.3$, 47.2 Hz 1F), -110.2 – -110.1 (m, 1F)

IR (neat): 2950, 1694, 1591, 1489, 1445, 1408, 1360, 1286, 1242, 1178, 1072, 1011, 968, 922, 859, 827, 782, 709, 657, 616 cm⁻¹

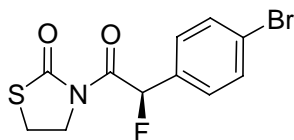
MS (EI): m/z 257 (M^+)

HPLC: (AD-H, hexane/*i*PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (major-isomer)=12.0 min,
 t_R (minor-isomer)=17.4 min

$[\alpha]_D^{25}$ -51.3 ($c=0.500$, CHCl₃ 62 % ee)

Mp: 84–85 °C

3-[2-Fluoro-2-(4-Bromophenyl)acetyl]-2-thiazolidinone (31i)



Pale yellow oil

Molecular formula: C₁₁H₉BrFNO₂S

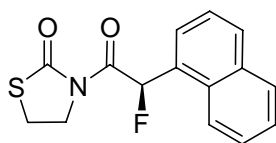
M. W.: 318.16

$R_f=0.34$ (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 3.29–3.35 (m, 2H), 4.12–4.18 (m, 1H), 4.24 (dt, $J=12.0$, 8.4 Hz, 1H), 6.76 (d, $J=48.6$, 1H), 7.41 (dd, $J=1.8$, 8.4 Hz, 2H), 7.54 (d, $J=8.4$ Hz, 2H)

^{13}C -NMR (CDCl_3 , 150.9 MHz): 172.7, 167.7 (d, $J=26.6$ Hz), 132.5 q(d, $J=20.7$ Hz), 132.0, 130.1 (d, $J=4.6$ Hz), 124.4 (d, $J=3.6$ Hz), 88.8 (d, $J=180.0$ Hz), 46.6, 25.6
 ^{19}F -NMR (CDCl_3 , 188 MHz): -171.1 (d, $J=47.4$ Hz, 1F)
 IR (neat): 3074, 2924, 2854, 1720, 1690, 1603, 1508, 1447, 1421, 1368, 1285, 1228, 1186, 1161, 1102, 1077, 1019, 928, 893, 867, 845, 810, 779, 725, 658 cm^{-1}
 MS (EI): m/z 317, 319 (M^+); HPLC: (AD-H, hexane/ i PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (major-isomer)=13.4 min, t_R (minor-isomer)=20.4 min
 $[\alpha]_D^{25}$ -33.8 ($c=0.400$, CHCl_3 56 % ee)

3-[2-Fluoro-2-(1-naphthyl)acetyl]-2-thiazolidinone (31j)



White solid

Molecular formula: $\text{C}_{15}\text{H}_{12}\text{FNO}_2\text{S}$

M. W.: 289.32

$R_f=0.34$ (Hexane: AcOEt: $\text{CHCl}_3=5: 1: 1$)

^1H -NMR (CDCl_3 , 600 MHz): 3.21–3.29 (m, 2H), 4.19–4.23 (m, 1H), 4.26 (dt, $J=12.0$, 8.4 Hz, 1H), 7.44 (d, $J=49.2$ Hz, 1H), 7.44 (dt, $J=1.2$, 7.8 Hz, 1H), 7.48–7.50 (m, 1H), 7.54 (dt, $J=0.6$, 7.5 Hz, 1H), 7.60–7.63 (m, 1H), 7.88 (d, $J=8.4$ Hz, 1H), 7.91 (d, $J=8.4$ Hz, 1H), 8.30 (d, $J=8.4$ Hz, 1H)

^{13}C -NMR (CDCl_3 , 150.9 MHz): 172.3, 168.5 (d, $J=25.7$ Hz), 133.9, 131.5, 131.0 (d, $J=3.8$ Hz), 129.5 (d, $J=18.1$ Hz), 128.7, 127.2, 127.0 (d, $J=5.6$ Hz), 126.3, 124.9 (d, $J=2.7$ Hz), 123.6, 88.1 (d, $J=180.0$ Hz), 46.7, 25.6

^{19}F -NMR (CDCl_3 , 188 MHz): -170.4 (d, $J=48.7$ Hz, 1F)

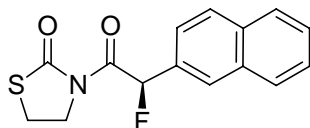
IR (KBr): 3060, 2966, 2632, 1717, 1698, 1599, 1510, 1471, 1446, 1361, 1346, 1289, 1240, 1131, 1004, 927, 858, 821, 807, 781, 750, 678, 638, 616 cm^{-1}

MS (EI): m/z 289 (M^+); HPLC: (AD-H, hexane/ i PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (minor-isomer)=16.2 min, t_R (major-isomer)=21.2 min

$[\alpha]_D^{25}$ -184.0 ($c=0.500$, CHCl_3 59 % ee)

Mp: 158–160 $^{\circ}\text{C}$

3-[2-Fluoro-2-(2-naphthyl)acetyl]-2-thiazolidinone (31k)



White solid

Molecular formula: C₁₅H₁₂FNO₂S

M. W.: 289.32

R_f=0.34 (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 3.24–3.31 (m, 2H), 4.16 (ddd, *J*=5.4, 7.8, 12.0 Hz, 1H), 4.24 (td, *J*=7.8, 12.0 Hz, 1H), 6.98 (d, *J*=48.6 Hz, 1H), 7.50–7.55 (m, 2H), 7.62 (d, *J*=1.2, 8.4 Hz, 1H), 7.84–7.89 (m, 3H), 8.02 (s, 1H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.5, 168.1 (d, *J*=26.7 Hz), 133.8, 132.9, 130.9 (d, *J*=19.9 Hz), 128.7 (d, *J*=5.9 Hz), 128.6, 128.5, 127.7, 127.1, 126.5, 125.1 (d, *J*=3.6 Hz), 89.7 (d, *J*=179.6 Hz), 46.7, 25.5

¹⁹F-NMR (CDCl₃, 188 MHz): –170.2 (d, *J*=48.7 Hz, 1F)

IR (neat): 3057, 2939, 1696, 1509, 1470, 1444, 1360, 1286, 1236, 1182, 1071, 1019, 957, 924, 862, 818, 799, 761, 657 cm^{–1}

MS (EI): *m/z* 289 (M⁺)

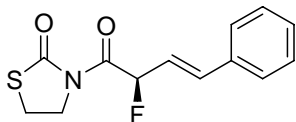
HPLC: (AD-H, hexane/*i*PrOH=98/ 2, 1.0 ml/ min, 254 nm) *t_R* (minor-isomer)=56.6 min, *t_R* (major-isomer)=63.3 min

[α]_D²⁵ –90.2 (*c*=0.500, CHCl₃ 60 % ee)

General procedure for the Catalytic Enantioselective Fluorination

Ni(ClO₄)₂·6H₂O (10 mol%) and the (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) (DBFOX-Ph) (11 mol%) were stirred under vacuum for 2 h at room temperature. Dry dichloromethane (1.0 ml) and MS 4Å (substrate/ MS 4A=1: 500 mol/ g) were added under nitrogen atmosphere and stirred for 1 h. Then **34** (1.0 equiv) was added directly to the catalyst solution. After stirring for another 30 min, then cooled to 0 °C, NFSI (1.2 equiv) and HFIP (30 mol%) were added to the reaction mixture, stirred for 10 min. The reaction mixture was cooled to –60 °C, 2,6-lutidine (2.0 equiv) were added to the mixture. The reaction was stirred at –60 °C for xx h with monitoring by TLC, it was stopped by the addition of NaHCO₃ solution. The reaction mixture was then diluted with dichloromethane, washed with brine, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure, and purified by the silica gel column chromatography or flash chromatography on eluting with Hexane/AcOEt/CHCl₃ (5:1:1) to give **35**. The ee of the product **35** was determined by chiral HPLC on CHIRALPAK AD-H or CHIRALCEL OJ-H or CHIRALCEL OD-H column.

3-((*R,E*)-2-Fluoro-4-phenylbut-3-enoyl)thiazolidin-2-one(35a)



White solid

Molecular formula: C₁₃H₁₂FNO₂S

M. W.: 265.30

R_f=0.36 (Hexane: AcOEt: CHCl₃=5:1:1)

¹H-NMR (CDCl₃, 200 MHz): 3.35 (t, *J*=7.2 Hz, 2H); 4.22 (t, *J*=7.2 Hz, 2H); 6.30 (ddq, *J*=0.8, 9.4, 1H); 6.55 (d, *J*=6.6 Hz, 1H); 6.90 (dd, *J*=9.4, 50.0 Hz, 1H); 7.32-7.87 (m, 5H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.7, 167.9 (d, *J*=25.4 Hz), 136.3 (d, *J*=11.2 Hz), 135.4 (d, *J*=1.2 Hz), 128.8, 128.7, 127.0 (d, *J*=1.1 Hz), 120.5 (d, *J*=18.9 Hz), 88.5 (d, *J*=179.3 Hz), 46.7, 25.8 (d, *J*=2.3 Hz)

¹⁹F-NMR (CDCl₃, CDCl₃, 188 MHz): -181.0 (ddq, *J*=5.0, 50.0 Hz, 1F)

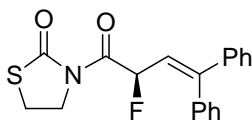
IR (KBr): 1869, 1772, 1734, 1699, 1685, 1654, 1636, 1558, 1541, 1522, 1508, 1489, 1473, 1457, 1418, 1363, 1238, 1117 cm⁻¹

MS (EI): *m/z* 265 (M⁺), 266 (M⁺+1), 267 (M⁺+2); HRMS: *m/z* calcd for C₁₃H₁₂FNO₂S: 265.0573 (M⁺); found: 265.0576

HPLC: (OJ-H, hexane/ⁱPrOH=90/10, 1.0 ml/ min, 254 nm) *t_R* (minor -isomer)=57.3 min, *t_R* (major-isomer)=85.1 min

[α]_D²⁵ -30.8 (*c*=0.093, CHCl₃ 78% ee)

3-((*R,E*)-2-Fluoro-4,4-diphenylbut-3-enoyl)thiazolidin-2-one(35b)



White solid

Molecular formula: C₁₉H₁₆FNO₂S

M. W.: 341.39

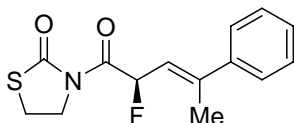
R_f=0.36 (Hexane: AcOEt: CHCl₃=5:1:1)

¹³C-NMR (CDCl₃, 150.9 MHz): 171.7, 168.5 (d, *J*=26.0 Hz), 152.8 (d, *J*=10.7 Hz), 141.0 (d, *J*=3.2 Hz), 137.9 (d, *J*=3.9 Hz), 130.0 (d, *J*=3.0 Hz), 128.7, 128.4, 128.2, 128.1, 128.0 (d, *J*=2.6 Hz), 118.9 (d, *J*=17.4 Hz), 86.3 (d, *J*=173.8 Hz), 46.7, 25.7, 17.5 (d, *J*=2.3 Hz)

IR (KBr): 1718, 1699, 1358, 1284, 1254, 1179, 1006, 801, 768, 701 cm⁻¹

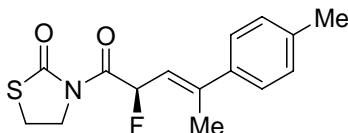
MS (EI): m/z 341 (M^+); HRMS: m/z calcd for $C_{19}H_{16}FNO_2S$: 341.0886 (M^+); found: 341.0888
HPLC: (AD-H, hexane/*i*PrOH=90/10, 1.0 ml/ min, 254 nm) t_R (minor -isomer)=12.8 min, t_R (major-isomer)=21.3 min
 $[\alpha]_D^{25}$ -32.0 ($c=0.208$, $CHCl_3$ 88% ee)

3-((*R,E*)-2-Fluoro-4-phenylpent-3-enoyl)thiazolidin-2-one(35c)



White solid
Molecular formula: $C_{14}H_{14}FNO_2S$
M. W.: 279.32
 $R_f=0.38$ (Hexane: AcOEt: $CHCl_3=5:1:1$)
 1H -NMR ($CDCl_3$, 200 MHz): 2.29 (dd, $J=1.0, 5.1$ Hz, 3H); 3.35 (brt, $J=7.3$ Hz, 2H); 4.20 (brt, $J=7.3$ Hz, 2H); 5.83 (ddq, $J=1.0, 9.4$, 1H); 6.59 (dd, $J=9.4, 50.0$ Hz, 1H); 7.30-7.45 (m, 5H)
 ^{13}C -NMR ($CDCl_3$, 150.9 MHz): 172.8, 169.3 (d, $J=25.8$ Hz), 147.9 (d, $J=9.8$ Hz), 142.3 (d, $J=3.5$ Hz), 128.8, 128.7, 126.5 (d, $J=2.6$ Hz), 118.7 (d, $J=17.4$ Hz), 85.8 (d, $J=175.3$ Hz), 47.2, 26.1, 17.5 (d, $J=2.3$ Hz)
 ^{19}F -NMR ($CDCl_3$, $CDCl_3$, 188 MHz): -173.3 (ddq, $J=5.1, 50.0$ Hz, 1F)
IR (KBr): 3385, 3057, 3025, 2955, 2925, 2857, 1955, 1888, 1696, 1495, 1445, 1360, 1229, 1179, 1119, 1065, 1003, 921, 863, 798, 761, 697, 658 cm^{-1}
MS (EI): m/z 279 (M^+), 280 (M^++1); HRMS: m/z calcd for $C_{14}H_{14}FNO_2S$: 279.0729 (M^+); found: 279.0726
HPLC: (OD-H, hexane/*i*PrOH=90/10, 1.0 ml/ min, 254 nm) t_R (major -isomer)=20.1 min, t_R (minor-isomer)=22.8 min
 $[\alpha]_D^{25}$ -73.1 ($c=0.113$, $CHCl_3$ 84% ee)

3-((*R,E*)-2-Fluoro-4-*p*-tolylpent-3-enoyl)thiazolidin-2-one(35d)



White solid
Molecular formula: $C_{15}H_{16}FNO_2S$
M. W.: 293.35

Rf=0.32 (Hexane: AcOEt: CHCl₃=5:1:1)

¹H-NMR (CDCl₃, 200 MHz): 2.27 (dd, *J*=1.0, 5.2 Hz, 3H); 2.35 (s, 3H); 3.35 (brt, *J*=7.4 Hz, 2H); 4.20 (brt, *J*=7.4 Hz, 2H); 5.81 (ddq, *J*=1.2, 9.4, 1H); 6.59 (dd, *J*=9.4, 50.0 Hz, 1H); 7.12-7.35 (m, 4H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.3, 169.0 (d, *J*=25.4 Hz), 147.4 (d, *J*=9.7 Hz), 138.9 (d, *J*=3.8 Hz), 138.3, 129.0, 126.0, 117.5 (d, *J*=17.5 Hz), 85.5 (d, *J*=175.0 Hz), 46.8, 25.7, 21.1, 17.0)

¹⁹F-NMR (CDCl₃, CDCl₃, 188 MHz): -172.9 (ddq, *J*=5.2, 50.0 Hz, 1F)

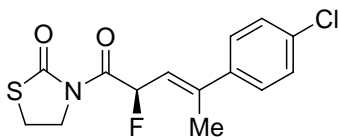
IR (KBr): 1726, 1691, 1628, 1513, 1450, 1362, 1285, 1254, 1233, 1184, 1158, 1118, 1064, 1022, 996, 925, 863, 812, 789, 660 cm⁻¹

MS (EI): *m/z* 293 (M⁺); HRMS: *m/z* calcd for C₁₅H₁₆FNO₂S: 293.0886 (M⁺); found: 293.0862

HPLC: (OJ-H, hexane/ⁱPrOH=90/10, 1.0 ml/ min, 254 nm) *t_R* (minor -isomer)=39.6 min, *t_R* (major-isomer)=50.5 min

[α]_D²⁵ -86.8 (*c*=0.100, CHCl₃ 85% ee)

3-((*R,E*)-4-(4-chlorophenyl)-2-fluoropent-3-enoyl)thiazolidin-2-one(35e)



White solid

Molecular formula: C₁₄H₁₃ClFNO₂S

M. W.: 313.77

Rf=0.35 (Hexane: AcOEt: CHCl₃=5:1:1)

¹H-NMR (CDCl₃, 200 MHz): 2.26 (dd, *J*=1.0, 5.1 Hz, 3H); 3.36 (brt, *J*=7.3 Hz, 2H); 4.21 (brt, *J*=7.3 Hz, 2H); 5.82 (ddq, *J*=1.0, 9.2 1H); 6.59 (dd, *J*=9.2, 50.0 Hz, 1H); 7.27-7.38 (m, 4H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.5, 168.7 (d, *J*=25.8 Hz), 146.3 (d, *J*=9.8 Hz), 140.2 (d, *J*=3.2 Hz), 134.2, 128.5, 127.3 (d, *J*=2.6 Hz), 118.7 (d, *J*=17.2 Hz), 85.3 (d, *J*=175.5 Hz), 46.7, 25.7, 17.0 (d, *J*=2.1 Hz)

¹⁹F-NMR (CDCl₃, CDCl₃, 188 MHz): -173.5 (ddq, *J*=5.1, 50.0 Hz, 1F)

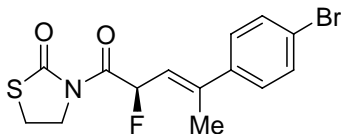
IR (KBr): 2921, 1689, 1489, 1449, 1347, 1283, 1230, 1180, 1062, 1004, 923, 822, 798, 758, 658 cm⁻¹

MS (EI): *m/z* 313, 315 (M⁺); HRMS: *m/z* calcd for C₁₄H₁₃ClFNO₂S: 313.0340 (M⁺); found: 313.0315

HPLC: (AD-H, hexane/ⁱPrOH=90/10, 1.0 ml/ min, 254 nm) *t_R* (major -isomer)=16.0 min, *t_R* (minor-isomer)=20.3 min

[α]_D²⁵ -89.4 (*c*=0.106, CHCl₃ 84% ee)

3-((*R,E*)-4-(4-bromophenyl)-2-fluoropent-3-enoyl)thiazolidin-2-one(35f)



White solid

Molecular formula: C₁₄H₁₃BrFNO₂S

M. W.: 358.22

R_f=0.34 (Hexane: AcOEt: CHCl₃=5:1:1)

¹H-NMR (CDCl₃, 200 MHz): 2.25 (dd, *J*=1.0, 5.1 Hz, 3H); 3.36 (brt, *J*=7.2 Hz, 2H); 4.21 (brt, *J*=7.2 Hz, 2H); 5.83 (ddq, *J*=1.0, 9.2, 1H); 6.55 (dd, *J*=9.2, 50.0 Hz, 1H); 7.25-7.48 (m, 4H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.5, 168.6 (d, *J*=25.5 Hz), 146.3 (d, *J*=9.7 Hz), 140.7 (d, *J*=3.3 Hz), 131.5, 127.7 (d, *J*=2.6 Hz), 122.4, 118.8 (d, *J*=17.4 Hz), 85.3 (d, *J*=175.6 Hz), 46.7, 25.7, 17.0 (d, *J*=2.3 Hz)

¹⁹F-NMR (CDCl₃, CDCl₃, 188 MHz): -173.6 (ddq, *J*=5.1, 50.0 Hz, 1F)

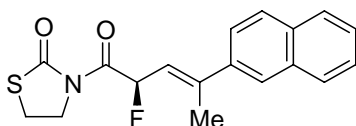
IR (KBr): 1722, 1694, 1487, 1447, 1402, 1360, 1282, 1250, 1229, 1180, 1155, 1119, 1062, 1004, 922, 864, 819, 797, 751, 657 cm⁻¹

MS (EI): *m/z* 357, 359 (M⁺); HRMS: *m/z* calcd for C₁₄H₁₃BrFNO₂S: 358.9814 (M⁺); found: 358.9791

HPLC: (AD-H, hexane/*i*PrOH=90/10, 1.0 ml/ min, 254 nm) *t_R* (major -isomer)=16.5 min, *t_R* (minor-isomer)=21.9 min

[α]_D²⁵ -56.5 (*c*=0.113, CHCl₃ 80% ee)

3-((*R,E*)-2-Fluoro-4-phenylpent-3-enoyl)thiazolidin-2-one(35g)



White solid

Molecular formula: C₁₈H₁₆FNO₂S

M. W.: 329.28

R_f=0.38 (Hexane: AcOEt: CHCl₃=5:1:1)

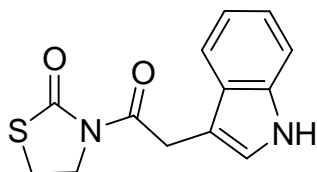
¹H-NMR (CDCl₃, 200 MHz): 2.40 (dd, *J*=0.8, 5.0 Hz, 3H); 3.36 (t, *J*=7.3 Hz, 2H); 4.23 (t, *J*=7.3 Hz, 2H); 5.99 (ddq, *J*=0.8, 9.4, 1H); 6.65 (dd, *J*=9.4, 50.0 Hz, 1H); 7.32-7.87 (m, 7H)

¹³C-NMR (CDCl₃, 150.9 MHz): 172.4, 168.9 (d, *J*=25.7 Hz), 147.3 (d, *J*=9.8 Hz), 139.0 (d, *J*=3.2 Hz), 133.2, 128.3, 128.0, 127.5, 126.3 (d, *J*=6.0 Hz), 125.4, 125.3, 124.0, 124.0, 118.8 (d, *J*=17.4 Hz), 85.4 (d, *J*=175.5 Hz), 46.8, 25.7, 17.1

¹⁹F-NMR (CDCl₃, CDCl₃, 188 MHz): -173.0 (ddq, *J*=5.0, 50.0 Hz, 1F)

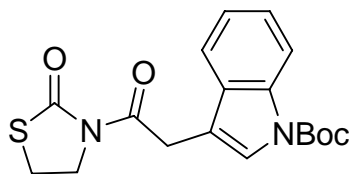
IR (KBr): 1688, 1354, 1243, 1243, 1183, 1133, 1068, 1002, 925, 819, 790, 748, 660 cm^{-1}
 MS (EI): m/z 329 (M^+); HRMS: m/z calcd for $\text{C}_{18}\text{H}_{16}\text{FNO}_2\text{S}$: 329.0886 (M^+); found: 329.0915
 HPLC: (AD-H, hexane/*i*PrOH=90/10, 1.0 ml/ min, 254 nm) t_R (major -isomer)=17.7 min, t_R (minor-isomer)=21.8 min
 $[\alpha]_D^{25}$ -76.4 ($c=0.106$, CHCl_3 85% ee)

3-[3-(1H-Indole-3-yl) acetyl]thiazolidin-2-one (36)



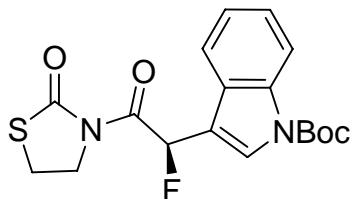
White solid
 Molecular formula: $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$
 M. W.: 260.31
 $R_f=0.35$ (Hexane: AcOEt 6: 4)
 ^1H -NMR (CDCl_3 , 600 MHz): 3.21 (t, $J=7.2$ Hz, 2H), 4.14 (t, $J=14.4$ Hz, 2H), 4.35 (s, 2H), 7.06–7.34 (m, 4H), 7.66 (d, $J=7.2$ Hz 1H), 8.09 (br, 1H)

3-[3-(1Boc-Indole-3-yl) acetyl]thiazolidin-2-one (37)



White solid
 Molecular formula: $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$
 M. W.: 360.42
 $R_f=0.69$ (Hexane: AcOEt 6: 4)
 ^1H -NMR (CDCl_3 , 600 MHz): 1.66 (s, 9H), 3.31 (t, $J=7.2$ Hz, 2H), 4.19 (t, $J=14.4$ Hz, 2H), 4.31 (s, 2H), 5.84 (s, 1H), 7.21–7.31 (m, 3H), 7.52–7.64 (m, 1H), 8.13 (d, $J=7.8$ Hz 1H)

3-[2-Fluoro 3-(1Boc-Indole-3-yl) acetyl]thiazolidin-2-one (37)



White solid

Molecular formula: C₁₈H₂₉FN₂O₄S

M. W.: 378.41

R_f=0.32 (Hexane: AcOEt: CHCl₃=5: 1: 1)

¹H-NMR (CDCl₃, 600 MHz): 1.67 (s, 9H), 3.24-3.32 (m, 2H), 4.14-4.25 (m, 2H), 7.00 (d, *J*=48.2 Hz, 1H), 7.24-7.34 (m, 3H), 7.76-7.81 (m, 1H), 8.12 (d, *J*=7.8 Hz 1H)

¹⁹F-NMR (CDCl₃, 188 MHz): -175.09 (d, *J*=51.8 Hz, 1F)

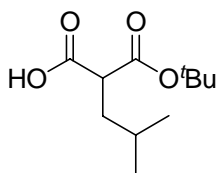
HPLC: (AD-H, hexane/ *i*PrOH=90/ 10, 1.0 ml/ min, 254 nm) t_R (major-isomer)=11.14 min, t_R (minor-isomer)=10.35 min (96.6% ee).

Chapter 3

General procedure for the preparation of malonic esters:

Malonic acid (1.0 equiv) was dissolved in acetonitrile solvent (10 ml) and alcohol (1.0 equiv) was added to this solution, and cooled to 0°C. *N,N'*-Dicyclohexylcarbodiimide (1.0 equiv) (DCC) in acetonitrile (10 ml) was added to the above dropwise, which was stirred overnight at rt for several hours. Filtered the reaction mass, washed with the solvent and evaporated solvent, obtained crude product as a syrup, which was proceeded to the next step without any purification.

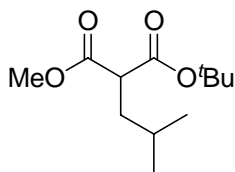
t-Butyl 2-isobutylmalonic acid (**2k**)



The reaction of **1k** (1.0 g, 6.24 mmol) acetonitrile (10 ml), *tert*-Butylalcohol (0.57 ml, 6.24 mmol) and (1.28 g, 6.24 mmol) DCC in acetonitrile (10 ml) which was stirred overnight at rt for 20 hours. Filtered and evaporated solvent, gave **2k** as a colorless syrup.

Molecular formula: C₁₁H₂₀O₄

t-Butyl methyl 2-isobutylmalonate (**3k**)



The reaction of **2k** (1.42 g, 6.55 mmol) dichloromethane (10 ml), methanol (0.58 ml, 13.1 mmol) and (1.35 g, 6.55 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 6 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=95: 5) obtained **3k** in (460 mg, after 2 steps 31%

yield).

Color less liquid

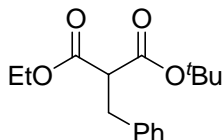
Molecular formula: C₁₂H₂₂O₄

M.W.: 230.17

R_f=0.56 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 0.91 (d, *J*=6.4 Hz, 6H), 1.45 (s, 9H), 1.56 (m, 1H), 1.78 (m, 2H), 3.33 (t, *J*=7.4 Hz, 1H), 3.71 (s, 3H)

1-*tert*-Butyl 3-ethyl 2-benzylmalonate (**3l**)



The reaction of **2a** (0.30 g, 1.20 mmol) dichloromethane (10 ml), ethanol (0.085 ml, 1.44 mmol) and DCC (0.248 g, 1.20 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 6 hours. Filtered and evaporated purified by column, eluted with (Hexane:

AcOEt=90: 10) obtained **3l** in (211 mg, after 2 steps 44% yield).

Color less liquid

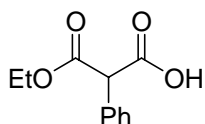
Molecular formula: C₁₆H₂₂O₄

M. W.: 278.34

R_f=0.45 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.21 (t, *J*=7.0 Hz, 3H), 1.39 (s, 9H), 3.16 (d, *J*=7.8 Hz, 2H), 3.55 (t, *J*=7.4 Hz, 1H), 4.15 (q, *J*=7.0 Hz, 2H), 7.17-7.26 (m, 5H).

Ethyl 2-phenylmalonic acid (**35**)

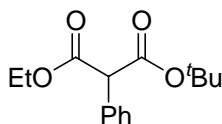


2,2-Dimethyl-5-phenyl-1,3-dioxane-4,6-dione **4** (1.0 g, 4.54 mmol) was dissolved in ethanol (10 ml), and refluxed for 19 hours obtained carboxylic acid compound as a syrup in quantitative, which was used next step without purification.

Molecular formula: C₁₁H₁₂O₄

M.W.: 208.21

t-Butyl methyl 2-phenylmalonate (**3o**)



The reaction of Methyl 2-phenylmalonic acid **35** (800 mg, 3.84 mmol) dichloromethane (10 ml), *tert*-Butylalcohol (0.72 ml, 7.68 mmol) and (0.79 g, 3.84 mmol) DCC in dichloromethane (10 ml) which was stirred overnight at rt for 3 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=95: 5) obtained **3o** in (600 mg, after 2 steps 42 % yield).

Colorless oil

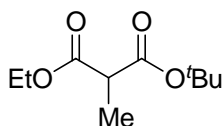
Molecular formula: C₁₅H₂₀O₄

M.W.: 264.31

R_f=0.51 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.26 (t, *J*=7.0 Hz, 3H), 1.45 (s, 9H), 3.21 (q, *J*=7.0 Hz, 2H), 4.51 (s, 1H), 7.24-7.38 (m, 5H).

1-*tert*-Butyl 3-methyl 2-ethylmalonate (**3m**)



The reaction of **2c** (0.50 g, 2.87 mmol) dichloromethane (10 ml), ethanol (0.20 ml, 3.44 mmol) and DCC (0.59 g, 2.87 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 9 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3m** in (189 mg, after 2 steps 26% yield).

Color less liquid

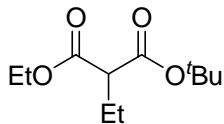
Molecular formula: C₁₀H₁₈O₄

M. W.: 202.24

R_f=0.49 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.27 (t, *J*=7.0 Hz, 3H), 1.34 (d, *J*=8.8 Hz, 3H), 1.45 (s, 9H), 3.31 (t, *J*=7.4 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H).

1-*tert*-Butyl 3-ethyl 2-ethylmalonate (3n)



The reaction of **2b** (0.50 g, 2.65 mmol) dichloromethane (10 ml), ethanol (0.19 ml, 3.18 mmol) and DCC (0.55 g, 2.65 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 9 hours. Filtered and evaporated purified by column, eluted with (Hexane:

AcOEt=90: 10) obtained **3n** in (300 mg, after 2 steps 40% yield).

Color less liquid

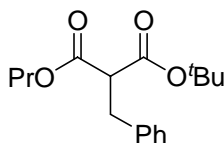
Molecular formula: C₁₁H₂₀O₄

M. W.: 216.27

R_f=0.47 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 0.96 (t, *J*=7.6 Hz, 3H), 1.28 (t, *J*=6.2 Hz, 3H), 1.46 (s, 9H), 1.86 (q, *J*=7.2 Hz, 2H), 3.14 (t, *J*=7.6 Hz, 1H), 4.18 (q, *J*=6.8 Hz, 2H).

1-*tert*-Butyl 3-propyl 2-benzylmalonate (3p)



The reaction of **2a** (0.485 g, 1.94 mmol) dichloromethane (10 ml), 1-propanol (0.18 ml, 2.32 mmol) and DCC (0.40 g, 1.94 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 8 hours. Filtered and evaporated purified by column, eluted with (Hexane:

AcOEt=90: 10) obtained **3p** in (360 mg, after 2 steps 36% yield).

Color less liquid

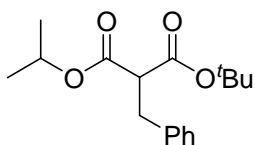
Molecular formula: C₁₇H₂₄O₄

M. W.: 292.37

R_f=0.44 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 0.89 (t, *J*=7.0 Hz, 3H), 1.54 (s, 9H), 1.63 (m, 2H), 3.16 (d, *J*=7.8 Hz, 2H), 3.56 (t, *J*=7.4 Hz, 1H), 4.10 (q, *J*=7.0 Hz, 2H), 7.17-7.25 (m, 5H).

1-*tert*-Butyl 3-isopropyl 2-benzylmalonate (3q)



The reaction of **2a** (0.30 g, 1.20 mmol) dichloromethane (10 ml), isopropanol (0.11 ml, 1.44 mmol) and DCC (0.248 g, 1.20 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 8 hours. Filtered and evaporated purified by column, eluted with

(Hexane: AcOEt=90: 10) obtained **3q** in (193 mg, after 2 steps 33% yield).

Color less liquid

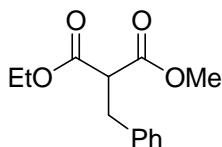
Molecular formula: C₁₇H₂₄O₄

M. W.: 292.37

R_f=0.42 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.18 (dd, *J*=6.2 Hz, 6H), 1.39 (s, 9H), 3.15 (d, *J*=7.8 Hz, 2H), 3.52 (t, *J*=7.4 Hz, 1H), 4.99 (m, 1H), 7.16-7.26 (m, 5H).

1-methyl 3-ethyl 2-benzylmalonate (3r)



The reaction of **2r** (0.450 g, 2.16 mmol) dichloromethane (10 ml), methanol (0.17 ml, 4.32 mmol) and DCC (0.445 g, 2.16 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 8 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3r** in (350 mg, after 2 steps 41% yield).

Color less liquid

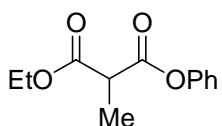
Molecular formula: C₁₃H₁₆O₄

M. W.: 236.26

R_f=0.24 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.19 (t, *J*=7.0 Hz, 3H), 3.21 (d, *J*=8.0 Hz, 2H), 3.65 (t, *J*=7.4 Hz, 1H), 3.69 (s, 3H), 4.14 (q, *J*=7.0 Hz, 2H), 7.17-7.27 (m, 5H).

1-phenyl 3-ethyl 2-methylmalonate (3s)



The reaction of **2s** (0.30 g, 2.05 mmol) dichloromethane (10 ml), phenol (0.289 g, 3.07 mmol) and DCC (0.423 g, 2.05 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 6 hours. Filtered and evaporated purified by column, eluted with (Hexane:

AcOEt=90: 10) obtained **3s** in (189 mg, after 2 steps 36% yield).

Color less liquid

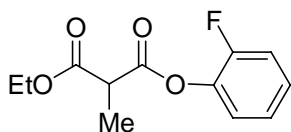
Molecular formula: C₁₂H₁₄O₄

M. W.: 222.23

R_f=0.45 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.36 (t, *J*=7.0 Hz, 3H), 1.66 (d, *J*=7.2 Hz, 3H), 3.84 (q, *J*=7.2 Hz, 1H), 4.32 (q, *J*=7.0 Hz, 2H), 7.11-7.56 (m, 5H).

1-ethyl 3-(2-fluorophenyl) 2-methylmalonate (3t)



The reaction of **2s** (0.30 g, 2.05 mmol) dichloromethane (10 ml), phenol (0.345 g, 3.07 mmol) and DCC (0.423 g, 2.05 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 12 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3t** in (165 mg, after 2 steps 39% yield).

Color less liquid

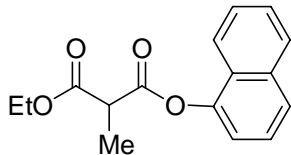
Molecular formula: C₁₂H₁₃FO₄

M. W.: 240.22

R_f=0.46 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.32 (t, *J*=7.0 Hz, 3H), 1.57 (d, *J*=7.2 Hz, 3H), 3.71 (q, *J*=7.2 Hz, 1H), 4.26 (q, *J*=7.0 Hz, 2H), 7.08-7.24 (m, 4H).

1-ethyl 3-naphthalen-1-yl 2-methylmalonate (**3u**)



The reaction of **2s** (0.20 g, 1.36 mmol) dichloromethane (10 ml), 1-naphthyl (0.295 g, 2.05 mmol) and DCC (0.282 g, 1.36 mmol) in dichloromethane (10 ml) which was stirred overnight at rt for 12 hours. Filtered and evaporated purified by column, eluted with (Hexane: AcOEt=90: 10) obtained **3u** in (170 mg, after 2

steps 41% yield).

Color less liquid

Molecular formula: C₁₆H₁₆O₄

M. W.: 272.29

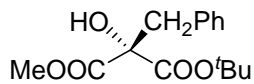
R_f=0.44 (Hexane: AcOEt=90: 10)

¹H-NMR (CDCl₃, 200 MHz): δ 1.36 (t, *J*=7.0 Hz, 3H), 1.66 (d, *J*=7.2 Hz, 3H), 3.84 (q, *J*=7.2 Hz, 1H), 4.32 (q, *J*=7.0 Hz, 2H), 7.21-7.86 (m, 4H), 7.76-7.95 (m, 3H).

General procedure for the Catalytic Enantioselective Hydroxylation of Malonic esters:

Ni(ClO₄)₂·6H₂O (10 mol%) and DBFOX-Ph (11 mol%) were stirred under vacuum for 2 h at room temperature. Dry ClCH₂CH₂Cl (0.5 mL) and MS 4A (substrate/MS 4A=1:500 mol/g) were added under nitrogen atmosphere and stirred for 1 h. Then a solution of malonic esters (0.15—0.25 mmol) in dry ClCH₂CH₂Cl (0.5 mL) was added to catalyst solution. After stirring for another 30 min, **44a** (1.2 equiv) was added directly to the reaction mixture. The reaction was stirred under reflux for 3—48 h with monitoring by TLC, it was stopped by the addition of water. The reaction mixture was then diluted with CH₂Cl₂, washed with saturated aqueous sodium bicarbonate solution, washed with brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. Crude product was purified by column chromatography on silica gel eluting with hexane/AcOEt to give compound. The ee of the product was determined by chiral HPLC on CHIRALPAK AD-H, CHIRALCEL OJ-H or CHIRALCEL OD-H column and GC.

(*S*)-1-*tert*-Butyl 3-methyl 2-benzyl-2-hydroxymalonate (**45a**)



The reaction of 1-*t*-Butyl 3-methyl 2-benzylmalonate **3a** (50.0 mg, 0.189 mmol) with DBFOX-Ph (10.4 mg, 0.0228 mmol), Ni(ClO₄)₂·6H₂O (6.7 mg, 0.0189 mmol) and **44a** (41.0 mg, 0.208 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 48 h, gave **45a** (43.5

mg, 82% yield) was obtained.

Colorless oil

Molecular formula: C₁₅H₂₀O₅

M.W.: 280.31

R_f=0.49 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.42 (s, 9H), 3.30 (s, 2H), 3.74 (s, 1H), 3.78 (s, 3H), 7.22-7.25 (m, 5H)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.9, 40.4, 53.0, 79.3, 83.9, 126.8, 127.8, 130.2, 134.6, 168.7, 170.1

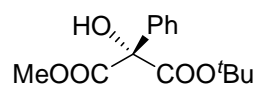
MS (EI): *m/z* 280 (M⁺), 262 (M⁺-OH); HRMS calcd for C₁₅H₂₀O₅ 280.1311, found 280.1280

IR (neat): 3477, 3032, 2979, 1735, 1637, 1455, 1370, 1296, 1154, 1120, 745, 701 cm⁻¹

HPLC: (CHIRALCEL OJ-H hexane/*i*PrOH = 90/10, 0.5 mL/min, 254 nm) t_R (major) = 15.5 min, t_R (minor) = 18.4 min

[α]_D²³ +21.89 (*c*=1.01, CHCl₃), 91% ee.

(*S*)-1- *tert*-Butyl 3-methyl 2-hydroxy-2-phenylmalonate (**45b**)

The reaction of 1-*t*-Butyl 3-methyl 2-phenylmalonate **3b** (40.0 mg, 0.160 mmol) with DBFOX-Ph (8.0 mg, 0.0176 mmol), Ni(ClO₄)₂·6H₂O (5.9 mg, 0.0160 mmol) and oxaziridine **44a** (37.8 mg, 0.192 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 12 h, gave **45b** (35.4 mg, 83% yield) was obtained.

Colorless oil

Molecular formula: C₁₄H₁₈O₅

M.W.: 266.28

R_f=0.47 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.47, (s, 9H), 3.81 (s, 3H), 4.33 (s, 1H), 7.32-7.38 (m, 3H), 7.60-7.65 (m, 2H)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.9, 53.4, 80.2, 84.4, 126.4, 127.6, 128.2, 135.9, 168.6, 170.0

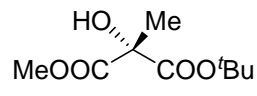
IR (neat): 3474, 2980, 1735, 1450, 1435, 1371, 1254, 1153, 1072, 1023, 839, 738, 697 cm⁻¹

MS (EI): *m/z* 267 (M⁺); HRMS calcd for C₁₄H₁₇O₅ ([M-H]) 265.1076, found 265.1042

HPLC: (CHIRALCEL OD-H, hexane/*i*PrOH = 90/10, 0.5 mL/min, 254 nm) t_R (major) = 12.0 min, t_R (minor) = 11.5 min

[α]_D²⁴ -10.01 (*c*=0.503, CHCl₃), 93% ee.

(*S*)-1-*tert*-Butyl 3-methyl-2-hydroxy-2-methylmalonate (**45c**)

The reaction of 1-*t*-Butyl 3-methyl 2-methylmalonate **3c** (40.0 mg, 0.212 mmol) with DBFOX-Ph (10.6 mg, 0.0233 mmol), Ni(ClO₄)₂·6H₂O (7.6 mg, 0.0212 mmol) and oxaziridine **44a** (50.2 mg, 0.255 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 16 h, gave **45c** (36.0 mg, 84% yield) was obtained.

Colorless oil

Molecular formula: C₉H₁₆O₅

M.W.: 204.22

R_f=0.46 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.48 (s, 9H), 1.58 (s, 3H), 3.73 (s, 1H), 3.78 (s, 3H)

¹³C NMR (50.3 MHz, CDCl₃): δ 21.7, 27.9, 53.0, 76.3, 83.4, 169.8, 171.0

IR (neat): 3505, 2983, 2955, 1736, 1671, 1453, 1371, 1291, 1249, 1154, 1121, 909, 841, 732, 649 cm⁻¹

MS (EI): *m/z* 205 (M⁺); HRMS calcd for C₉H₁₆O₅ 204.0998, found 204

GC: (HYDRODEX- β-TBDAC, 70 °C) t_R (major) = 84.7 min, t_R (minor) = 88.0 min; [α]_D²³ +6.39 (c=0.500, CHCl₃), 98% ee.

(S)-1-*tert*-Butyl 3-methyl 2-ethyl-2-hydroxymalonate (45d)

The reaction of 1-*t*-Butyl 3-methyl 2-ethylmalonate **3d** (40.0 mg, 0.198 mmol) with DBFOX-Ph (9.9 mg, 0.0217 mmol), Ni(ClO₄)₂·6H₂O (7.0 mg, 0.0198 mmol) and oxaziridine **44a** (46.8 mg, 0.237 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 36 h, gave **45d** (32.0 mg, 74% yield) was obtained.

Colorless oil

Molecular formula: C₁₀H₁₈O₅

M.W.: 218.24

R_f=0.45 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 0.90 (t, *J*=7.6 Hz, 3H), 1.48 (s, 9H), 2.02 (q, *J*=7.6 Hz, 2H), 3.74 (s, 1H), 3.78 (s, 3H)

¹³C NMR (50.3 MHz, CDCl₃): δ 7.53, 27.9, 52.9, 79.4, 83.4, 169.5, 170.6

IR (neat): 3492, 2979, 2884, 1737, 1458, 1438, 1371, 1298, 1236, 1152, 1092, 1024, 842, 806, 744, 696 cm⁻¹

MS (EI): *m/z* 219 (M⁺); HRMS calcd for C₁₀H₁₈O₅ 218.1154, found 218.1167

HPLC: (CHIRALPAK AD-H hexane/*i*PrOH = 98/2, 1.0 mL/ min, 218 nm) t_R (major) = 10.8 min, t_R (minor) = 12.6 min

[α]_D²⁵ +27.94 (c=0.503, CHCl₃), 95% ee.

(S)-1-*tert*-Butyl 3-methyl 2-butyl-2-hydroxymalonate (45e)

The reaction of 1-*t*-Butyl 3-methyl 2-butylmalonate **3e** (40.0 mg, 0.173 mmol) with DBFOX-Ph (8.6 mg, 0.0190 mmol), Ni(ClO₄)₂·6H₂O (6.2 mg, 0.0173 mmol) and oxaziridine **44a** (41.1 mg, 0.208 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 36 h, gave **45e** (34.0 mg, 80% yield) was obtained.

Colorless oil

Molecular formula: C₁₂H₂₂O₅

M.W.: 246.30

R_f=0.48 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 0.83 (t, *J*=6.8 Hz, 3H), 1.19-1.32 (m, 5H), 1.40 (s, 9H), 1.90 (t, *J*=7.6 Hz, 2H), 3.67 (s, 1H), 3.70 (s, 3H)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.0, 22.8, 25.3, 27.9, 34.3, 52.9, 79.1, 83.4, 169.5, 170.7

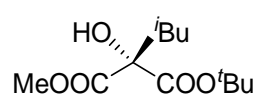
IR (neat): 3496, 2959, 2873, 1737, 1458, 1370, 1236, 1152, 746, 843 cm⁻¹

MS (EI): *m/z* 247 (M⁺); HRMS calcd for C₁₂H₂₂O₅ 246.1467, found 246.1432

HPLC: (CHIRALPAK AD-H hexane/*i*PrOH = 98/2, 1.0 mL/ min, 218 nm) *t*_R (major) = 10.8 min, *t*_R (minor) = 12.9 min

[α]_D²⁴ +23.08 (*c*=0.503, CHCl₃), 94% ee.

(*S*)-1-*tert*-Butyl 3-methyl 2-hydroxy-2-isobutylmalonate (**45f**)

 The reaction of 1-*tert*-Butyl 3-methyl 2-isobutylmalonate **3f** (20.0 mg, 0.086 mmol) with DBFOX-Ph (4.3 mg, 0.0095 mmol), Ni(ClO₄)₂·6H₂O (3.1 mg, 0.0086 mmol) and oxaziridine **44a** (20.5 mg, 0.104 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 48 h, gave **45f** (21.0 mg, 65% yield) was obtained.

Colorless oil

Molecular formula: C₁₂H₂₂O₅

M.W.: 246.30

*R*_f=0.45 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 0.92 (d, *J*=6.6 Hz, 6H), 1.49 (s, 9H), 1.71-1.84 (m, 1H), 1.90-1.99 (m, 2H), 3.71 (s, 1H), 3.76 (s, 3H)

¹³C NMR (50.3 MHz, CDCl₃): δ 27.7(d, *J*=4.0 Hz), 42.2, 52.9, 79.1, 83.5, 169.9, 171.1

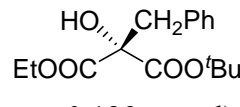
IR (neat): 3492, 2958, 1735, 1457, 1370, 12531, 1153, 1046, 912, 841, 733, cm⁻¹

MS (EI): *m/z* 247 (M⁺); HRMS calcd for C₁₂H₂₂O₅ 246.1467, found 246.1447

HPLC: (CHIRALCEL AD-H, hexane/*i*PrOH = 90/10, 0.5 mL/ min, 218 nm) *t*_R (major) = 11.8 min, *t*_R (minor) = 14.2 min

[α]_D²⁴ +14.04 (*c* =0.5, CHCl₃), 88% ee.

(*S*)-1-*tert*-Butyl 3-ethyl 2-benzyl-2-hydroxymalonate (**45g**)

 The reaction of 1-*tert*-Butyl 3-ethyl 2-benzylmalonate **3g** (30.0 mg, 0.107 mmol) with DBFOX-Ph (5.4 mg, 0.0118 mmol), Ni(ClO₄)₂·6H₂O (3.9 mg, 0.0107 mmol) and oxaziridine **44a** (25.4 mg, 0.129 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 48 h, gave **45g** (22.7 mg, 71% yield) was obtained.

Colorless oil

Molecular formula: C₁₆H₂₂O₅

M.W.: 294.34

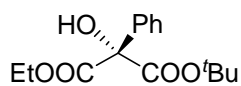
*R*_f=0.46 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.28, (t, *J*=7.0 Hz, 3H) 1.42, (s, 9H), 3.29 (s, 2H), 3.75 (s, 1H), 4.23 (q, *J*=7.4 Hz, 2H), 7.20-7.27 (m, 5H)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.3, 27.9, 40.2, 62.2, 79.2, 83.6, 126.8, 127.7, 130.2, 134.7, 168.7, 169.7

MS (EI): m/z 294 (M^+); HRMS calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1437
 IR (neat): 3489, 2980, 1734, 1496, 1455, 1370, 1298, 1237, 1155, 1120, 1054, 912, 841 cm^{-1}
 HPLC: (CHIRALCEL OJ-H, hexane/*i*PrOH = 90/ 10, 1.0 mL/ min, 254 nm) t_R (major) = 6.02 min, t_R (minor) = 7.13 min
 $[\alpha]_D^{24} +16.89$ ($c=0.5$, $CHCl_3$), 91% ee.

(S)-1-*tert*-Butyl 3-ethyl 2-hydroxy-2-phenylmalonate (45h)



The reaction of 1-*tert*-Butyl 3-ethyl 2-phenylmalonate **3h** (30.0 mg, 0.1134 mmol) with DBFOX-Ph (5.7 mg, 0.0124 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (4.1 mg, 0.0113 mmol) and oxaziridine **44a** (26.9 mg, 0.136 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) at 80 °C for 16 h, gave **45h** (23.6 mg, 74% yield) was obtained.

Colorless oil

Molecular formula: $C_{15}H_{20}O_5$

M.W.: 280.31

$R_f=0.47$ (Hexane: AcOEt=80: 20)

1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, $J=7.2$ Hz, 3H), 1.47 (s, 9H), 4.27 (q, $J=7.0$ Hz, 2H), 4.32 (s, 1H), 7.24-7.37 (m, 3H), 7.61-7.66 (m, 2H)

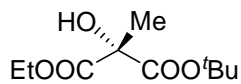
^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.2, 27.9, 62.6, 80.1, 80.2, 126.5, 127.6, 128.2, 135.9, 168.6, 170.0

MS (EI): m/z 280 (M^+); HRMS calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1280

IR (neat): 3475, 2982, 2255, 1732, 1449, 1371, 1294, 1153, 1072, 1027, 909, 838, 732 cm^{-1}

HPLC: (CHIRALCEL OD-H, hexane/*i*PrOH = 90/10, 0.5 mL/ min, 254 nm) t_R (major) = 11.06 min, t_R (minor) = 10.6 min
 $[\alpha]_D^{24} -11.28$ ($c=0.5$, $CHCl_3$), 90% ee.

(S)-1-*tert*-Butyl 3-ethyl 2-hydroxy-2-methylmalonate (45i)



The reaction of 1-*tert*-Butyl 3-ethyl 2-methylmalonate **3i** (35.4 mg, 0.175 mmol) with DBFOX-Ph (8.8 mg, 0.0193 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (6.4 mg, 0.0175 mmol) and oxaziridine **44a** (41.4 mg, 0.210 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) at 80 °C for 14 h, gave **45i** (27.5 mg, 72% yield) was obtained.

Colorless oil

Molecular formula: $C_{10}H_{18}O_5$

M.W.: 218.24

$R_f=0.46$ (Hexane: AcOEt=80: 20)

^1H NMR (200 MHz, CDCl_3): δ 1.32 (t, $J=7.2$ Hz, 3H), 1.48 (s, 9H), 1.58 (s, 3H), 3.74 (s, 1H), 4.24 (q, $J=7.2$ Hz, 2H)

^{13}C NMR (50.3 MHz, CDCl_3): δ 14.3, 21.6, 27.9, 62.1, 76.2, 83.3, 169.9, 170.6

IR (neat): 3491, 2981, 2939, 1737, 1450, 1371, 1286, 1244, 1155, 1119, 959, 844 cm^{-1}

MS (APCI (-)): m/z 218 (M^+), 161 ($\text{M}^+ - t\text{Bu}$); HRMS calcd for $\text{C}_{10}\text{H}_{18}\text{O}_5$ 218.1154, found 218.1167

HPLC: (CHIRALPAK AD-H, hexane/*i*PrOH = 98/2, 1.0 mL/min, 218 nm) t_R (major) = 11.9 min, t_R (minor) = 12.6 min

$[\alpha]_D^{25} +5.30$ ($c=0.916$, CHCl_3), 94% ee.

(*S*)-1-*tert*-Butyl 3-ethyl 2-ethyl-2-hydroxymalonate (45j)

The reaction of 1-*tert*-Butyl 3-ethyl 2-ethylmalonate **3j** (30.0 mg, 0.1387 mmol) with DBFOX-Ph (6.9 mg, 0.0152 mmol), $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (4.9 mg, 0.0138 mmol) and oxaziridine **44a** (32.9 mg, 0.166 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1.0 mL) at 80 °C for 62 h, gave **45j** (17.0 mg, 52% yield) was obtained.

Colorless oil

Molecular formula: $\text{C}_{11}\text{H}_{20}\text{O}_5$

M.W.: 232.27

$R_f=0.46$ (Hexane: AcOEt=80: 20)

^1H NMR (200 MHz, CDCl_3): δ 0.90 (t, $J=7.4$ Hz, 3H), 1.28 (t, $J=7.0$ Hz, 3H), 1.47, (s, 9H), 2.01 (q, $J=7.2$ Hz, 2H), 3.72 (s, 1H), 4.24 (q, $J=7.2$ Hz, 2H)

^{13}C NMR (50.3 MHz, CDCl_3): δ 15.8, 21.7, 33.6, 33.7, 63.7, 79.1, 82.5, 158.5, 159.1

IR (neat): 3495, 2980, 1735, 1459, 1370, 1231, 1153, 1028, 843, cm^{-1}

MS (EI): m/z 232 (M^+); HRMS calcd for $\text{C}_{11}\text{H}_{19}\text{O}_5$ ($[\text{M}-\text{H}]$) 231.1232, found 231.1181

HPLC: (CHIRALCEL AD-H, hexane/*i*PrOH = 90/10, 0.5 mL/min, 218 nm) t_R (major) = 12.8 min, t_R (minor) = 14.1 min

$[\alpha]_D^{24} +17.73$ ($c=0.5$, CHCl_3), 90% ee.

(*S*)-1-*tert*-Butyl 3-propyl 2-benzyl-2-hydroxymalonate (45k)

The reaction of 1-*tert*-Butyl 3-propyl 2-benzylmalonate **3k** (30.0 mg, 0.102 mmol) with DBFOX-Ph (5.2 mg, 0.0112 mmol), $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (3.7 mg, 0.0102 mmol) and oxaziridine **44a** (24.3 mg, 0.123 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1.0 mL) at 80 °C for 48 h, gave **45k** (19.1 mg, 63% yield) was obtained.

Colorless oil

Molecular formula: $\text{C}_{17}\text{H}_{24}\text{O}_5$

M.W.: 308.36

$R_f=0.44$ (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 0.95, (t, *J*=7.4 Hz, 3H), 1.42, (s, 9H), 1.63-1.73 (m, 2H), 3.30 (s, 2H), 3.76 (s, 1H), 4.12 (t, *J*=6.8 Hz, 2H), 7.20-7.27 (m, 5H)

¹³C NMR (50.3 MHz, CDCl₃): δ 10.54, 22.08, 27.9, 40.3, 67.7, 79.3, 83.6, 126.8, 127.8, 130.2, 134.7, 168.7, 169.8

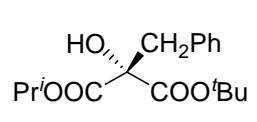
IR (neat): 3489, 2975, 1735, 1496, 1455, 1370, 1294, 1232, 1155, 1120, 1057, 913, 842, 745, 701 cm⁻¹

MS (EI): *m/z* 308 (M⁺); HRMS calcd for C₁₇H₂₂O₄ (M-H₂O) 290.1518, found 290.1524

HPLC: (CHIRALCEL OJ-H, hexane/*i*PrOH = 90/10, 0.5 mL/min, 254 nm) *t*_R (major) = 12.3 min, *t*_R (minor) = 14.6 min

[α]_D²⁴ +13.54 (*c* = 0.5, CHCl₃), 90% ee.

(*S*)-1-*tert*-Butyl 3-isopropyl 2-benzyl-2-hydroxymalonate (**45l**)

 The reaction of 1-*tert*-Butyl 3-isopropyl 2-benzylmalonate **3l** (30.0 mg, 0.102 mmol) with DBFOX-Ph (5.2 mg, 0.0112 mmol), Ni(ClO₄)₂·6H₂O (3.7 mg, 0.0102 mmol) and oxaziridine **44a** (24.3 mg, 0.123 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 62 h, gave **45l** (15.1 mg, 48% yield) was obtained.

Colorless oil

Molecular formula: C₁₇H₂₄O₅

M.W.: 308.36

*R*_f=0.44 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.26 (d, *J*=6.2 Hz, 6H), 1.43 (s, 9H), 3.28 (s, 2H), 3.73 (s, 1H), 5.02-5.08 (m, 1H), 7.19-7.27 (m, 5H)

¹³C NMR (50.3 MHz, CDCl₃): δ 21.7 (d, *J*=2.7 Hz), 27.9, 40.1, 70.1, 79.1, 83.4, 126.7, 127.7, 128.2, 130.2, 134.9, 168.7, 169.2

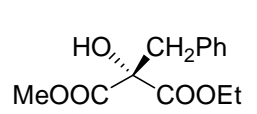
MS (EI): *m/z* 308 (M⁺); HRMS calcd for C₁₇H₂₂O₄ (M-H₂O) 290.1518, found 290.1524

IR (neat): 3489, 2980, 1734, 1455, 1435, 1371, 1294, 1240, 1156, 1105, 912, 841, 747, 701 cm⁻¹

HPLC: (CHIRALCEL AD-H, hexane/*i*PrOH = 90/10, 0.5 mL/min, 254 nm) *t*_R (major) = 16.8 min, *t*_R (minor) = 20.3 min

[α]_D²⁴ +7.08 (*c* = 0.5, CHCl₃), 82% ee.

(*S*)-1-ethyl 3-methyl 2-benzyl-2-hydroxymalonate (**45m**)

 The reaction of 1-ethyl 3-methyl 2-benzylmalonate **3m** (30.0 mg, 0.1269 mmol) with DBFOX-Ph (6.3 mg, 0.0139 mmol), Ni(ClO₄)₂·6H₂O (4.6 mg, 0.0126 mmol) and oxaziridine **44a** (30.1 mg, 0.1522 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 14 h, gave **45m** (31.5 mg, 98% yield) was obtained.

Colorless oil

Molecular formula: C₁₃H₁₆O₅

M.W.: 252.26

*R*_f=0.36 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.27, (t, *J*=7.2 Hz, 3H), 3.44 (s, 2H), 3.72 (s, 1H), 3.78 (s, 3H), 4.23 (q, *J*=7.2 Hz, 2H), 7.23-7.24 (m, 5H)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.2, 40.8, 53.3, 62.7, 79.3, 126.9, 127.9, 130.1, 134.3, 169.5, 169.5

IR (neat): 3489, 2983, 1740, 1496, 1437, 1279, 1233, 1120, 1034, 839, 749, 701 cm⁻¹

MS (EI): *m/z* 252 (M⁺); HRMS calcd for C₁₃H₁₄O₄ (M-H₂O) 234.0892, found 234.0915

HPLC: (CHIRALCEL AD-H, hexane/*i*PrOH = 90/10, 1.0 mL/min, 254 nm) *t*_R (major) = 10.0 min, *t*_R (minor) = 11.0 min

[α]_D²⁴ +1.90 (*c* = 1.0, CHCl₃), 12% ee.

(*S*)-1- Ethyl 3-phenyl 2-hydroxy-2-methylmalonate (**45n**)

The reaction of 1- Ethyl 3-phenyl 2-methylmalonate **3n** (30.0 mg, 0.135 mmol) with DBFOX-Ph (6.8 mg, 0.0149 mmol), Ni(ClO₄)₂·6H₂O (4.9 mg, 0.0135 mmol) and oxaziridine **44a** (31.9 mg, 0.162 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 3 h, gave **45n** (25.6 mg, 80% yield) was obtained.

Colorless oil

Molecular formula: C₁₂H₁₄O₅

M.W.: 238.23

*R*_f=0.47 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.35 (t, *J*=7.0 Hz, 3H), 1.77 (s, 3H), 3.86 (s, 1H), 4.34 (q, *J*=7.0 Hz, 2H), 7.07 (d, *J*=7.4 Hz, 2H), 7.25 (t, *J*=7.4 Hz, 1H), 7.39 (t, *J*=7.2 Hz, 2H)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.3, 21.8, 62.9, 76.3, 120.8, 126.2, 129.4, 150.1, 169.0, 170.4

IR (neat): 3493, 2987, 2941, 1746, 1590, 1493, 1376, 1267, 1222, 1191, 1162, 1101, 1017, 744, 689 cm⁻¹

MS (EI): *m/z* 210 (M⁺-Et); HRMS calcd for C₁₂H₂₄O₅ 238.0841, found 238.0817

HPLC: (CHIRALCEL OJ-H, hexane/*i*PrOH = 90/10, 1.0 mL/min, 254 nm) *t*_R (major) = 23.4 min, *t*_R (minor) = 26.7 min; 66% ee [81% ee was obtained by using (+)-3c reagent]

[α]_D²⁵ -2.99 (*c* = 0.813, CHCl₃), [lit.⁸⁶ [α]_D -0.45 (*c* = 2.1, CHCl₃)].

(*S*)-1- Ethyl 3-(2-fluorophenyl) 2-hydroxy-2-methylmalonate (**45o**)

The reaction of 1- Ethyl 3-(2-fluorophenyl) 2-methylmalonate **3o** (40.0 mg, 0.166 mmol) with DBFOX-Ph (8.4 mg, 0.018 mmol), Ni(ClO₄)₂·6H₂O (6.0 mg, 0.016 mmol) and oxaziridine **44a** (36.2 mg, 0.183 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 2 h, gave **45o** (39.1 mg, 91% yield) was obtained.

Colorless oil

Molecular formula: C₁₂H₁₃FO₅

M.W.: 256.22

*R*_f=0.46 (Hexane: AcOEt=80: 20)

⁸⁶ G. Guanti, L. Banfi, K. Powels, M. Rasparini, C. Scolastico, N. Fossati, *Tetrahedron: Asymmetry* **2001**, *12*, 271-277

¹H NMR (200 MHz, CDCl₃): δ 1.34 (t, *J*=7.2 Hz, 3H), 1.79 (s, 3H), 3.88 (s, 1H), 4.35 (q, *J*=7.2 Hz, 2H), 7.07 (d, *J*=7.4 Hz, 2H), 7.20-7.27 (m, 5H)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.1, 21.8, 63.0, 116.6 (d, *J*=17.9 Hz), 124.3 (d, *J*=3.9 Hz), 127.4 (d, *J*=7.1 Hz), 150.9, 155.9, 167.9, 170.2

¹⁹F-NMR (CDCl₃, 188 MHz): -128.18- -128.24 (m, 1F)

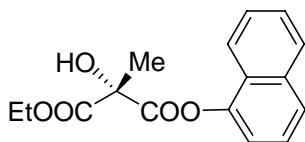
IR (neat): 3482, 2987, 2257, 1746, 1602, 1500, 1459, 1377, 1259, 1102, 1017, 912, 854, 733 cm⁻¹

MS (EI): *m/z* 256; HRMS calcd for C₁₂H₂₂FO₅ ([M-H]) 255.0669, found 255.0716

HPLC: (CHIRALCEL OJ-H, hexane/*i*PrOH = 90/10, 1.0 mL/min, 254 nm) *t_R* (major) = 17.2 min, *t_R* (minor) = 15.5 min

[α]_D²⁵ -5.44 (*c* = 1.0, CHCl₃), 88% ee.

(S)-1- Ethyl 3-naphthalen-1-yl 2-hydroxy-2-methylmalonate (45p)



The reaction of 1- Ethyl 3-naphthalen-1-yl 2-methylmalonate **3p** (40.0 mg, 0.146 mmol) with DBFOX-Ph (7.4 mg, 0.016 mmol), Ni(ClO₄)₂·6H₂O (5.4 mg, 0.014 mmol) and oxaziridine **44a** (31.9 mg, 0.161 mmol) in ClCH₂CH₂Cl (1.0 mL) at 80 °C for 2 h, gave **45p** (40.0 mg, 93% yield) was obtained.

Colorless oil

Molecular formula: C₁₆H₁₆O₅

M.W.: 288.29

R_f = 0.47 (Hexane: AcOEt = 80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.39 (t, *J*=7.2 Hz, 3H), 1.88 (s, 3H), 4.00 (s, 1H), 4.41 (q, *J*=7.2 Hz, 2H), 7.24 (dd, *J*=7.6 Hz, 1H), 7.54-7.41 (m, 3H), 7.88-7.73 (m, 3H)

¹³C NMR (50.3 MHz, CDCl₃): δ 14.3, 22.0, 63.1, 117.3, 120.6, 125.0, 126.4 (d, *J*=17.4 Hz), 127.8, 134.4, 145.8, 168.9, 170.6

IR (neat): 3504, 2986, 2255, 1746, 1599, 1508, 1447, 1390, 1260, 1220, 1158, 1105, 1013, 910, 791, 744, 648 cm⁻¹

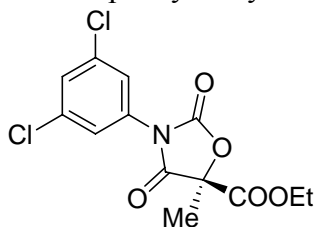
MS (EI): *m/z* 288; HRMS calcd for C₁₆H₁₆O₅ 288.0998, found 288.1006

HPLC: (CHIRALCEL OJ-H, hexane/*i*PrOH = 90/10, 1.0 mL/min, 254 nm) *t_R* (major) = 24.8 min, *t_R* (minor) = 18.5 min

[α]_D²⁵ -6.3 (*c* = 1.0, CHCl₃), 90% ee.

(R)-Ethyl 3-(3,5-dichlorophenyl)-5-methyl-2,4-dioxoxazolidine-5-carboxylate ((R)-chlozoline) (46)

A solution of malonic ester **45p** (40.0 mg, 0.156 mmol) in dry *n*-hexane (6.0 mL) was treated, under N₂, with triethylamine⁸⁷ (21.7 μ L, 0.156 mmol) and 3,5-dichlorophenylisocyanate (44.1 mg, 0.234 mmol). After stirring at rt for 30 min, the reaction mixture was refluxed for overnight (15h). After cooling, the suspension was filtered and the filtrate evaporated to dryness, the crude materials were purified by column chromatography using (hexane/AcOEt = 9/1) to afford chlozoline **46** in 78% yield.



White solid

Molecular formula: C₁₃H₁₁Cl₂NO₅

M.W.: 332.13

R_f=0.66 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.34 (t, *J*=7.2 Hz, 3H), 1.90 (s, 3H), 4.34 (q, *J*=7.2 Hz, 2H), 7.24 (s, 1H), 7.43 (s, 2H)

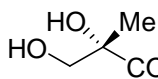
¹³C NMR (50.3 MHz, CDCl₃): δ 14.1, 18.9, 63.9, 83.8, 123.5, 129.0, 129.2, 132.0, 135.4, 151.6, 163.6, 167.9

IR (KBr): 3335, 3277, 3088, 2925, 2854, 1827, 1756, 1715, 1587, 1458, 1222, 1171, 804, 671 cm⁻¹

MS (EI): *m/z* 331 (M⁺)

[α]_D²⁴ -15.81 (*c* =0.5, CHCl₃) [lit.³[α]_D -16.79.9 (*c* =2.0, CHCl₃).

(S)-tert-Butyl 2-hydroxy-2-(hydroxymethyl)propanoate (47)



To a solution of (*S*)-1-*tert*-Butyl 3-methyl-2-hydroxy-2-methylmalonate **45c** (157 mg, 0.770 mmol) in dry THF (5.0 mL) was added a solution of LiAl(O^{*t*}Bu)₃H (1.0 M in THF, 3.8 mL, 3.85 mmol) at -78 °C by syringe over 15 min. The solution was allowed to warm to room temperature, then raised the temperature up to 60°C, stirred for 4 h and cooled 0°C, after addition of a saturated solution of potassium sodium tartrate, the organic materials were extracted with ethyl acetate three times and the combined organic phase was washed with brine three times and dried over Na₂SO₄, and concentrated, the crude materials were purified by column chromatography using (hexane/AcOEt = 1:1) to afford alcohol **47** in 66% yield.

Colorless oil

Molecular formula: C₈H₁₆O₄

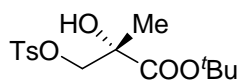
M.W.: 176.21

R_f=0.36 (Hexane: AcOEt=60: 40)

⁸⁷ G. Guanti, L. Banfi, K. Powles, M. Rasparini, C. Scolastico, N. Fossati, *Tetrahedron: Asymmetry* **2001**, *12*, 271-277.

^1H NMR (200 MHz, CDCl_3): δ 1.31 (s, 3H), 1.50 (s, 9H), 2.33 (dd, $J=9.3, 4.2$ Hz, 1H), 3.53 (dd, $J=11.2, 4.0$ Hz, 1H), 3.64 (s, 1H), 3.74 (dd, $J=11.0, 9.4$ Hz, 1H)
 ^{13}C NMR (50.3 MHz, CDCl_3): δ 22.2, 28.1, 68.4, 75.3, 82.9, 174.6
 IR (neat): 3455, 2979, 2935, 2876, 1727, 1459, 1370, 1283, 1236, 1139, 1056, 842 cm^{-1}
 MS (APCI (-)): m/z 177 (M^+)
 $[\alpha]_{\text{D}}^{25} -9.58$ ($c=0.416$, CHCl_3).

(S)-2-(tert-Butoxycarbonyl)-2-hydroxypropyl 4-methylbenzenesulfonate (48)



To a solution of alcohol (*S*)-*tert*-Butyl 2-hydroxy-2-(hydroxymethyl)propanoate **47** (89.7 mg 0.509 mmol) in dry CHCl_3 (1.5 mL) and pyridine (1.5 mL) was added. The solution was cooled to 0 °C, and *p*-tosyl chloride⁸⁸ (145 mg, 0.764 mmol) was added directly. After stirring for 10 min at 0 °C, the cooling bath was removed, and the solution was stirred at room temperature for 17 h. 1N HCl was added, and the product was extracted three times with CH_2Cl_2 , the combined organic layers were washed with water and brine. The organic solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuum. The product was purified by column chromatography on silica gel (hexane/AcOEt = 7/3) to give a white color solid **7** in 49% yield.

White solid

Molecular formula: $\text{C}_{15}\text{H}_{22}\text{O}_6\text{S}$

M.W.: 330.39

$R_f=0.29$ (Hexane: AcOEt=80: 20)

^1H NMR (200 MHz, CDCl_3): δ 1.31 (s, 3H), 1.47 (s, 9H), 2.44 (s, 3H), 3.41 (s, 1H), 3.92 (d, $J=9.6$ Hz, 1H), 4.21 (d, $J=7.6$ Hz, 1H), 7.32 (d, $J=8.6$ Hz, 2H), 7.76 (d, $J=8.6$ Hz, 2H)

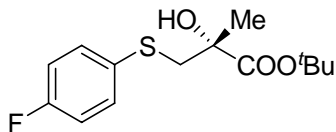
^{13}C NMR (50.3 MHz, CDCl_3): δ 21.8, 22.2, 27.9, 73.3, 74.3, 83.7, 127.8, 129.6, 132.6, 144.7, 172.2

IR (KBr): 3498, 2984, 2939, 1727, 1597, 1359, 1251, 1177, 1139, 987, 940, 834, 818, 670 cm^{-1}

MS (APCI (-)): m/z 330 (M^+)

$[\alpha]_{\text{D}}^{26} +2.15$ ($c=0.330$, CHCl_3).

(R)-tert-Butyl 3-(4-fluorophenylthio)-2-hydroxy-2-methylpropanoate (49)



Sodium hydride (30.1 mg, 0.753 mmol) was placed into a 30 mL flask and added dry hexane (2.0 mL), stirred for 10 min, then hexane was removed by syringe under nitrogen condition, then THF (3.0 mL) was added. The solution was cooled to 0 °C, 4-fluorobenzenethiol (80.4 μL , 0.753 mmol) was added drop wise with syringe at 0 °C, which was stirred for 1 h at that temperature, then (*S*)-2-(*tert*-Butoxycarbonyl)-2-hydroxypropyl 4-methylbenzenesulfonate **48** (82.9 mg, 0.251 mmol)

⁸⁸ P. Schwerdtfeger, G. A. Heath, M. Dolg, M. A. Bennett, *J. Am. Chem. Soc.* **1992**, 118, 7517-7528.

in THF (2.0 mL) was added to the above mixture, warmed to rt, and stirred for 3 h. Added water and ethyl acetate, extracted organic layer, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (hexane/AcOEt = 9/1) compound **49** in 88% yield.

Colorless oil

Molecular formula: C₁₂H₁₃FO₅

M.W.: 256.22

R_f=0.46 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.41 (s, 3H), 1.45 (s, 9H), 3.22 (dd, *J*=25.8, 13.4 Hz, 2H), 3.51 (s, 1H), 6.91-6.99 (m, 2H), 7.37-7.44 (m, 2H)

¹⁹F NMR (188 MHz, CDCl₃): δ -114.9 to -115.1 (m)

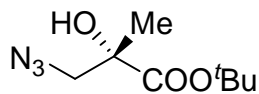
¹³C NMR (50.3 MHz, CDCl₃): δ 25.9, 28.0, 45.6, 75.0, 82.9, 115.7 (d, *J*=21.6 Hz), 131.5 (d, *J*=3.2 Hz), 132.4 (d, *J*=7.9 Hz), 161.5 (d, *J*=245 Hz), 173.9

IR (neat): 3505, 2979, 2933, 1727, 1590, 1491, 1370, 1283, 1221, 1156, 1090, 828 cm⁻¹

MS (EI): *m/z* 286 (M⁺)

[α]_D²⁵ -6.80 (*c* =0.463, CHCl₃).

(*S*)-*tert*-Butyl 3-azido-2-methyl-2-hydroxy propionate (**51**)



To a solution of (*S*)-2-(*tert*-Butoxycarbonyl)-2-hydroxypropyl 4-methylbenzenesulfonate **48** (75.0 mg, 0.226 mmol) in DMF (2.0 mL) was added NaN₃ (44.2 mg, 0.684 mmol) and resulting mixture was stirred at 80 °C for 9 h. The reaction mixture was diluted with CH₂Cl₂, washed with water, brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. The purified by column chromatography on silica gel eluting with hexane/AcOEt = 90/10 to give **51** in 92% yield.

Colorless oil

Molecular formula: C₈H₁₅N₃O₃

M.W.: 201.22

R_f=0.49 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.36 (s, 3H), 1.50 (s, 9H), 3.38 (s, 2H), 3.55 (s, 1H)

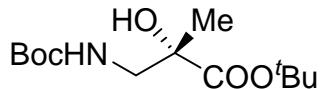
¹³C NMR (50.3 MHz, CDCl₃): δ 23.6, 28.0, 58.6, 75.1, 83.3, 173.5

IR (neat): 3504, 2981, 2935, 2103, 1725, 1457, 1395, 1371, 1267, 1139, 955, 913, 841, 828, 734 cm⁻¹

MS (EI): *m/z* 201 (M⁺)

[α]_D²⁵ -76.28 (*c* =0.5, CHCl₃).

***tert*-Butyl (*S*)-2-(*tert*-butoxycarbonyl)- 2-methyl- 2-hydroxypropylcarbamate (**52**)**



To a solution of (*S*)-*t*-Butyl 3-azido-2-benzyl-2-fluoropropionate **51** (30.0 mg, 0.149 mmol) in ethyl acetate (2.0 mL), (Boc)₂O (51.0 μ L, 0.223 mmol), Pd-C (5.0 mg) were added and resulting mixture was stirred under hydrogen atmosphere for 4 h at room temperature. This reaction mixture was filtered through celite to remove Pd-C. After removal of the solvent, the crude product was purified by column chromatography on silica gel eluting with hexane/AcOEt = 85/15 to give **52** (97% yield).

Colorless oil

Molecular formula: C₁₃H₂₅NO₅

M.W.: 275.34

R_f=0.23 (Hexane: AcOEt=80: 20)

¹H NMR (200 MHz, CDCl₃): δ 1.34 (s, 3H), 1.42 (s, 9H), 1.47 (s, 9H), 3.10 (d, *J*=4.4 Hz, 1H), 3.17 (d, *J*=4.2 Hz, 1H), 3.59 (t, *J*= 6.0 Hz, 1H), 3.65 (s, 1H), 4.92 (s, 1H)

¹³C NMR (100.6 MHz, CDCl₃): δ 23.5, 27.9, 28.4, 48.1, 74.5, 79.2, 82.9, 155.3, 174.5

IR (neat): 3404, 2979, 2934, 2250, 1722, 1512, 1456, 1393, 1368, 1250, 1164, 1042, 1018, 968, 909, 847, 776, 733 cm⁻¹

MS (EI): *m/z* 275 (M⁺)

[α]_D²⁵ +23.89 (*c* =0.5, CHCl₃).

Publication list

1. **“Desymmetrization-like Catalytic Enantioselective Fluorination of Malonates and Its Application to Pharmaceutically Attractive Molecules”**

Dhande Sudhakar Reddy, Norio Shibata, Jun Nagai, Shuichi Nakamura, Takeshi Toru and Shuji Kanemasa.

Angew. Chem. Int. Ed. **2008**, 47, 164-168. (VIP)

2. **“DBFOX-Ph/metal complexes: Evaluation as catalysts for enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones”**

Takehisa Ishimaru, Norio Shibata, Dhande Sudhakar Reddy, Takao Horikawa, Shuichi Nakamura and Takeshi Toru.

Beilstein J. Org. Chem. **2008**, 4, No. 16.

3. **“Dynamic Kinetic Asymmetric Transformation in the α -Hydroxylation of Racemic Malonates and its Application to Biologically Active Molecules”**

Dhande Sudhakar Reddy, Norio Shibata, Jun Nagai, Shuichi Nakamura and Takeshi Toru.

Angew. Chem. Int. Ed. **2008**, In press (early view).

Oral presentations:

- 1) ○ Dhanda Sudhakar Reddy, Jun Nagai, Shuichi Nakamura, Norio Shibata, Takeshi Toru
[Desymmetrization-like Catalytic Enantioselective Fluorination of Malonates]
88th Japan Chemical Society Annual Meeting, Tokyo, Japan, March, **2008**, 1 J2-50
- 2) ○ Dhanda Sudhakar Reddy, Takehisa Ishimaru, Jun Nagai, Takao Horikawa, Shuichi Nakamura, Norio Shibata, Takeshi Toru
[Catalytic Enantioselective Fluorination Reactions of Malonates and α -Aryl Acetates by DBFOX-Ph/Lewis acid Complexes]
39th Annual Meeting of Union of Chemistry-Related Societies in Chubu Area, Japan, November, **2008**, 1N10.
- 3) ○ Dhanda Sudhakar Reddy, Jun Nagai, Shuichi Nakamura, Norio Shibata, Takeshi Toru
[Enantioselective Fluorination of Malonates by DBFOX-Ph/Lewis acid Complexes]
32th Fluorine Conference of Japan, Nagoya, November, **2008**, O14.
- 4) ○ Dhanda Sudhakar Reddy, Takehisa Ishimaru, Jun Nagai, Takao Horikawa, Shuichi Nakamura, Norio Shibata, Takeshi Toru
[Catalytic Asymmetric Fluorination of Malonates and α -Aryl Acetates by DBFOX-Ph/Lewis acid Complexes]
The 35th Symposium on Main Group Element Chemistry Tokyo, December, **2008**, 52A.

Poster presentations:

- 1) Takao Horikawa, Ishimaru Takehisa, Dhanda Sudhakar Reddy, Jun Nagai, Shuichi Nakamura, Norio Shibata, Takeshi Toru
[Enantioselective Fluorination of α -Arylacetates by DBFOX-Ph/Lewis acid Complexes]
32th Fluorine Conference of Japan, Nagoya, November, **2008**, P-43.

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