Synthesis of fluorinated allenes *via* palladium-catalyzed monofluoromethylation using FBSM†

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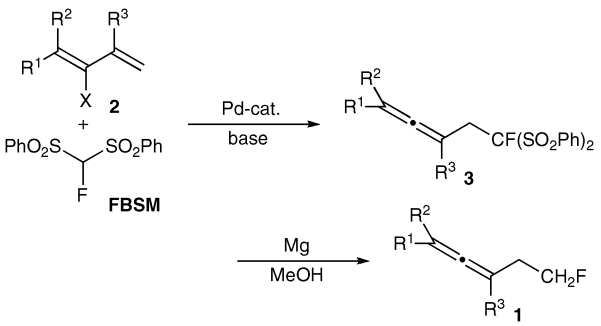
Palladium-catalyzed monofluoromethylation of substituted 2-bromo-1,3-dienes using fluorobis(phenylsulfonyl)methane (FBSM) as a pronucleophile gave previously unknown monofluoromethylated allenes in high yields, which are the isosteres of biologically attractive allenic alcohols.

Allenes have received considerable attention as unique building blocks in medicinal chemistry.[1] Due to perpendicular orientation of the two cumulated carbon–carbon double bonds in an allenic framework, allenes can be axially chiral with proper substitution, which enables the generation of stereochemical diversity in drug candidates. Although about 150 natural products comprising an allenic or a related cumulenic structure have been known, the design and synthesis of biologically active allenic compounds is a relatively undeveloped area.[2] We considered that the incorporation of a fluorine atom into allenic compounds could provide new building blocks where the unique properties of allenes and fluorine might contribute to new biological activities.[3] It is evident that fluorinated molecules play a crucial role in the pharmaceutical as well as agrochemical fields,[4] and nowadays fluorinated allenes are an emerging class of synthetic targets.[3] Among such fluorinated allenes, we became interested in monofluoromethylated allenes **1** as our synthetic targets based on the isostere design of the corresponding allenic alcohols. Allenic alcohol moiety is frequently found in allenic natural products and pharmaceuticals, such as grasshopper ketone and adenallene.[2] Recent evidence indicates that replacement of a hydroxy group by a fluorine atom is often regarded as an isosteric substitution.[5] Thus, the monofluoromethylated allenes **1** are potential mimics of the corresponding allenic alcohols and can have a significant impact on pharmacological properties. In 2006, a nucleophilic monofluoromethylation reagent, fluorobis(phenylsulfonyl)methane (FBSM), was developed as a synthetic equivalent of a fluoromethide species by Shibata's group in Nagoya.[6] This work sparked the imagination of chemists to design new nucleophilic monofluoromethylation reactions using FBSM which affords a variety of monofluoromethylated compounds.[7,8] As a part of our research program in Sapporo involving the development of a novel synthetic method for preparing a variety of functionalized allenes,[9] we report herein the efficient, simple synthesis of monofluoromethylated allenes **1** from substituted 2-bromo-1,3-dienes (or a related triflate) **2**. Our protocol comprises of two steps: after preparation of fluorobis(phenylsulfonyl)methylated allenes **3** using the palladium-catalyzed nucleophilic substitution reaction based on the FBSM chemistry, following reductive desulfonylation gives the previously unknown monofluoromethylated allenes **1** in high yields with excellent selectivity (Scheme 1).



Scheme 1 Strategy for preparing monofluoromethylated allenes.

Our initial studies were focused on the development of suitable reaction conditions including base, solvent, and palladium precursor for the Pd-catalyzed reaction of (*Z*)-^{t}BuCH=CBrCH=CH$_2$ (**2a**) and FBSM producing the allene **3a** (Table 1). Under the conditions optimized for a methylmalonate pronucleophile CHMe(CO$_2$Me)$_2$,[9a] which were with [PdCl(π-allyl)]$_2$ and NaH in THF, the reaction was very sluggish and **3a** was obtained in 24% in 12 h (entry 1). The use of KO^{t}Bu as a base in place of NaH increased the yield of **3a** to 86% (entry 2) and the yield was further improved to 90% by running the reaction in dichloromethane (entry 4). A catalyst generated from Pd(dba)$_2$ and dpbp showed the lower catalytic activity and gave only 78% of **3a** under otherwise identical reaction conditions (entry 5). Thus, a mixture of **2a** (37.8 mg, 0.20 mmol), FBSM (70 mg, 0.22 mmol), KO^{t}Bu (27 mg, 0.24 mmol), [PdCl(π-allyl)]$_2$ (1.8 mg, 5.0 μmol), and dpbp[10] (5.7 mg, 11 μmol) in CH$_2$Cl$_2$ (2 mL) was heated at 40 °C. The reaction was complete within 12 h, and 76.1 mg (90% yield based on **2a**) of **3a** was isolated as a colorless viscous liquid by silica gel chromatography.

Under these optimized conditions, the Pd-catalyzed reactions took place very cleanly for a wide range of dienyl substrates **2** to give the allenic compounds **3** in high yields.

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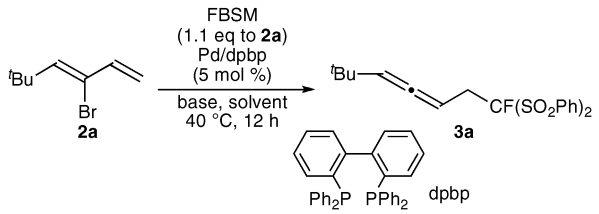
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. See DOI: 10.1039/b912531k

Table 1 Optimization of palladium-catalyzed reaction of **2a** with FBSM



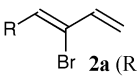
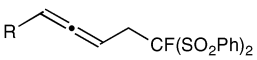
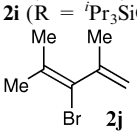
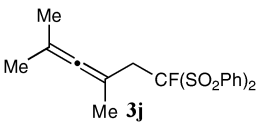
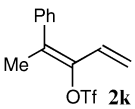
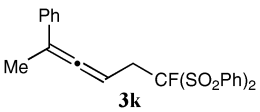
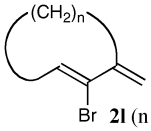
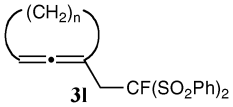
Entry	Base	Solvent	Pd-precursor	Yield (%)[a]
1	NaH	THF	$[PdCl(\pi\text{-allyl})]_2$	24
2	KO^{t}Bu	THF	$[PdCl(\pi\text{-allyl})]_2$	86
3	Cs_2CO_3	THF	$[PdCl(\pi\text{-allyl})]_2$	72
4	KO^{t}Bu	CH_2Cl_2	$[PdCl(\pi\text{-allyl})]_2$	90
5	KO^{t}Bu	CH_2Cl_2	$Pd(dba)_2$	78

[a] Isolated yield by silica gel chromatography.

The results of the Pd-catalyzed reaction are summarized in Table 2. Bromodienes with a sterically diverse alkyl substituent afforded the corresponding allenes in excellent yields (89–93%; entries 1–3). Arylallenes **3d–f** were obtained as well in 81–83% yields by the present reaction (entries 4–6), however, the aryldiene bearing an electron withdrawing trifluoromethyl substituent **2g** gave **3g** in as low as 42% (entry 7). Whereas all the substrate **2g** was consumed during the reaction, the low yield of **3g** could be ascribed to oligomerization/polymerization of the dienyl substrate **2g** and/or the allenic product **3g**. Indeed, poorly characterized gummy material was observed in the reaction mixture. Similarly, the reactions of silylmethyl-substituted dienes **2h** and **2i** yielded the corresponding homoallenylsilanes **3h** and **3i**, respectively, in good yields (entries 8 and 9). The present Pd-catalyzed reaction was applicable to preparation of multisubstituted FBSM-allenes (entries 10–13). The reaction of **2j** provided a persubstituted allene **3j** in 82% (entry 10). A dienyl triflate was equally reactive as the bromodienes: the triflate **2k** furnished the trisubstituted allene **3k** in 86% yield under identical conditions (entry 11). Cyclic dienylbromides **2l** and **2m** also underwent the Pd-catalyzed reaction to give the corresponding endocyclic allenes **3l** and **3m** in 82% and 87% yields, respectively (entries 12 and 13).

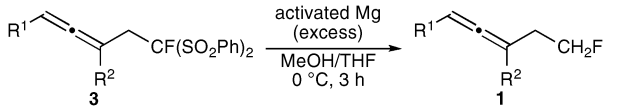
With various fluorobis(phenylsulfonyl)methylallenes **3** in our hands, reductive desulfonylation of **3**, which should lead to the envisaged monofluoromethylallenes **1**, was examined. Whereas a significant decrease of molecular weight (*i.e.*, increase of volatility) was expected upon the transformation, the desulfonylation was performed on the selected FBSM-allenes of relatively larger molecular weight. The short list of the FBSM-allenes for the desulfonylation, however, was carefully chosen to demonstrate sufficient diversity of the present chemistry, which included disubstituted allenes with an alkyl (**3b**), an aryl (**3f**), or a silylmethyl (**3i**) group and a trisubstituted endocyclic allene (**3m**). Desulfonylation of **3** was carried out according to the Carpino's procedure[11] with slight modifications. Due to low solubility of the FBSM-allenes in methanol, a MeOH–THF mixture was used as a solvent.

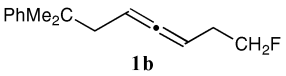
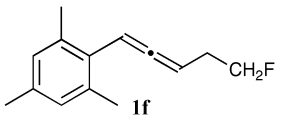
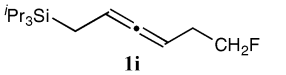
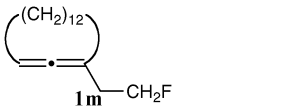
Table 2 Palladium-catalyzed reaction of **2** with FBSM giving allene **3**[a]

Entry	Substrate **2**	FBSM-allene **3**	Yield (%)[b]
1	 **2a** (R = ^{t}Bu)		90
2	**2b** (R = $PhCMe_2CH_2$)	**3b**	89
3	**2c** (R = $^nC_8H_{17}$)	**3c**	93
4	**2d** (R = Ph)	**3d**	83
5	**2e** (R = *p*-$MeOC_6H_4$)	**3e**	81
6	**2f** (R = 2,4,6-$Me_3C_6H_2$)	**3f**	82
7	**2g** (R = *p*-$CF_3C_6H_4$)	**3g**	42
8	**2h** (R = Me_3SiCH_2)	**3h**	85
9	**2i** (R = $^iPr_3SiCH_2$)	**3i**	85
10	 **2j**	 **3j**	82
11	 **2k**	 **3k**	86
12	 **2l** (n = 9)	 **3l**	82
13	**2m** (*n* = 12)	**3m**	87

[a] Reaction was carried out with **2** (0.20 mmol), FBSM (0.22 mmol), and KO^{t}Bu (0.22 mmol) in CH_2Cl_2 at 40 °C for 12 h in the presence of the catalyst (5 mol%) generated from $[PdCl(\pi\text{-allyl})]_2$ and dpbp. [b] Isolated yield by silica gel chromatography.

Table 3 Desulfonylation of **3** giving CH_2F-allene **1**[a]



Entry	FBSM-allene **3**	CH_2F-allene **1**	Yield (%)[b]
1	**3b**	 **1b**	59 (>95)
2	**3f**	 **1f**	52 (>95)
3	**3i**	 **1i**	70 (>95)
4	**3m**	 **1m**	65 (>95)

[a] Reaction was carried out with **3** (0.30 mmol) and activated Mg turnings (*ca.* 30 equiv. to **3**) in MeOH–THF (1/3) at 0 °C for 3 h. [b] Isolated yield by silica gel chromatography. GC yield in parentheses.

Magnesium turnings, which were activated with $BrCH_2CH_2Br$ in THF, were extremely effective in the reductive desulfonylation and the reaction completed within 3 h even at 0 °C. The results of the desulfonylation are listed in Table 3. In all cases, the reactions were very clean under these conditions. GC and NMR analyses of the crude reaction mixtures showed exclusive formation of **1** in nearly quantitative yields (>95%). The isolated yields of the desulfonylated products **1**, however, were relatively poor, which could be ascribed to handling loss of the products due to their high volatility. It should be noted that the allenic frameworks in **3** were completely retained in **1** during the reductive desulfonylation and isomerization into conjugated dienes and/or alkynes (propargyls) were not detected at all.

In summary, we have developed a novel protocol for preparing a series of monofluorinated allenic compounds. The palladium-catalyzed nucleophilic substitution of 2-bromo-1,3-dienes **2** with FBSM affords the desired fluorobis(phenylsulfonyl)methylated allenes **3** in high yields. The two phenylsulfonyl moieties in **3** can be easily and cleanly removed by a treatment with Mg in MeOH–THF to provide the previously unknown monofluoromethylated allenes exclusively, which are non-polar isosteres of allenic alcohols. The use of a chiral Pd-catalyst in this protocol is presently under investigation to develop an enantioselective synthesis of axially chiral monofluoromethylated allenes. The design and synthesis of biologically attractive fluoromethylated compounds is also in progress and will be reported in due course.

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