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Enantioselective Trichloromethylation of MBH-Fluorides with Chloroform Based on Silicon-assisted C–F Activation and Carbanion Exchange Induced by a Ruppert–Prakash Reagent

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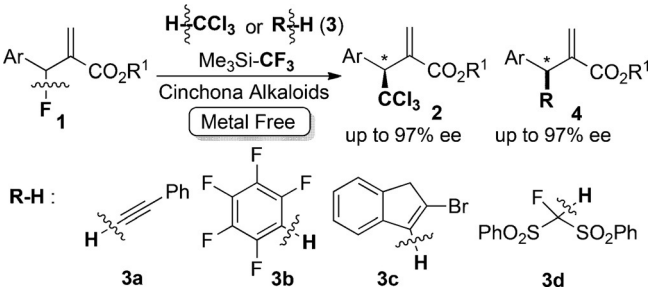
Abstract: *Enantioselective trichloromethylation of Morita–Baylis–Hillman (MBH)-type allylic fluorides with chloroform ($HCCl_3$) under organocatalysis was achieved with high to excellent enantioselectivities. Silicon-assisted C–F bond activation by a Ruppert–Prakash reagent and direct activation of $HCCl_3$ by a carbanion exchange process with trifluoromethyl (CF_3) carbanion generated in situ from the Ruppert-Prakash reagent realized the direct asymmetric trichloromethylation at a stereogenic allylic positon, without any help from transition metal catalysis, and under very mild conditions. Pre-activation of $HCCl_3$ was not required. This method was extended to the direct enantioselective introduction of other C–H compounds such as alkyne, arene, indene, and FBSM without any pre-activation under a metal-free system.*



Scheme 1. Direct enantioselective trichloromethylation of MBH-type fluorides **1** with $HCCl_3$ based on a silicon-assisted C–F bond activation and a carbanion exchange process by Me_3SiCF_3 and related asymmetric transformations.

The cleavage/activation of carbon–fluorine (C–F) bonds[1] and the direct activation of carbon–hydrogen (C–H) bonds[2] followed by sequential chemical transformations have been substantial challenges for chemists in recent decades. Many kinds of C–F and C–H bond activations have been achieved under transition metal catalysis.[1,2] In this context, we are interested in the development of methods for C–X bond activation/cleavage under mild conditions, without using transition metals. Herein, we realize this idea, including the cleavage of C–F and C–H bonds, following asymmetric C–C bond formation at a stereogenic carbon center using fluorine chemistry, exemplified by an enantioselective catalytic trichloromethylation of Morita–Baylis–Hillman (MBH)-type allylic fluorides with chloroform ($HCCl_3$). Silicon-assisted C–F bond activation of MBH-allylic fluorides **1**, followed by direct activation of the C–H bond of $HCCl_3$ (that is, a carbanion exchange process by an in situ generated trifluoromethyl (CF_3) carbanion), is key for this transformation (Scheme 1). The reaction requires neither organometallics nor strong bases, but instead relies upon catalytic amount of cinchona alkaloids and the Ruppert–Prakash reagent (trifluoromethyl)trimethylsilane (Me_3SiCF_3). A variety of allylic trichloromethylated compounds **2** were obtained in high to excellent enantioselectivities up to 97% *ee*. More importantly, this method was widely applied for the direct asymmetric introduction of other C–H compounds **3**, such as alkyne **3a**, fluorobenzene, **3b**, indene **3c**, and fluorobisphenylsulfonylmethane (**3d**, FBSM) without any pre-activation by a carbanion exchange process by CF_3 carbanion under the same reaction conditions to furnish **4** in good yields with high enantioselectivities.

More than 5000 organohalogen compounds are found in nature, and many of them show remarkable biological activities.[3] The majority of naturally occurring organohalogen compounds consists of organic chlorides, thus the development of an efficient synthetic methodology for organochlorine compounds is of great importance.[4] Among many organochlorine compounds, we are interested in the trichloromethylated compounds, since the importance of the trichloromethyl (CCl_3) group in natural products and biologically active molecules has been addressed.[5] Moreover, they have been widely used as valuable intermediates in organic synthesis.[6] Although there have been many reports on trichloromethylation reactions,[7] enantioenriched trichloromethylated compounds attract less attention than others such as racemic compounds, and the method for direct enantioselective trichloromethylation is extremely rare.[8] In recent years, we reported the enantioselective reactions of MBH-acetates,[9a] carbonates,[9b] and fluorides[9c] with fluoromethylated nucleophiles under organocatalysis providing allylic monofluoro- and trifluoromethylated compounds in high yields with high enantioselectivities.[9] During our research of the trifluoromethylation of MBH-fluorides **1** with Me_3SiCF_3, we accidently noticed that allylic trichloromethylated compounds **2** were obtained predominantly instead of trifluoromethylated ones when the reaction was carried out in chloroform, $HCCl_3$.

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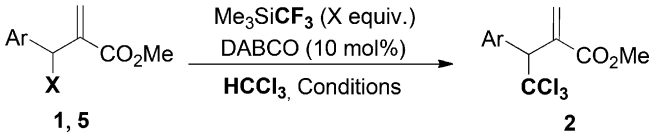
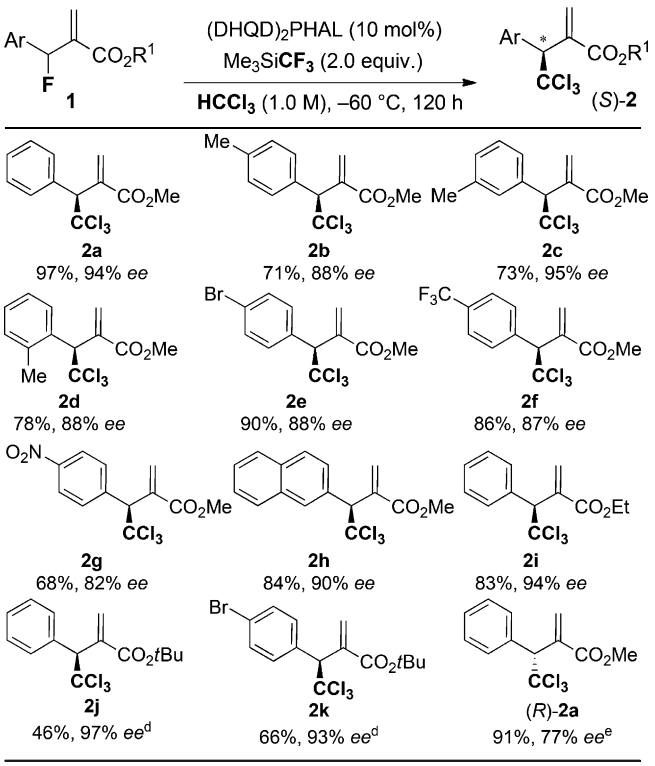
Table 1: Optimization of the reaction conditions and substrate generality for direct trichloromethylation of MBH substrates.



Run	1, 5	X, Ar	Me_3SiCF_3 (X equiv)	Conditions	Product	Yield [%][a]
1	**1a**	F, Ph	1.2	−60 °C/3 h	**2a**	65
2	**5a**	OAc, Ph	1.2	RT/24 h	**2a**	0[b]
3	**5b**	OBoc, Ph	1.2	RT/24 h	**2a**	13
4	**1a**	F, Ph	2.0	−60 °C/3 h	**2a**	77
5	**1a**	F, Ph	3.0	−60 °C/3 h	**2a**	92
6	**1a**	F, Ph	–	RT/24 h	**2a**	NR
7	**1b**	F, 4-$CH_3C_6H_4$	3.0	−60 °C/3 h	**2b**	98
8	**1e**	F, 4-BrC_6H_4	3.0	−60 °C/3 h	**2e**	88
9	**1f**	F, 4-$CF_3C_6H_4$	3.0	−60 °C/3 h	**2f**	87
10	**1h**	F, 2-Naphthyl	3.0	−60 °C/3 h	**2h**	83

[a] Isolated yield. [b] S_N2' adduct of acetate (OAc) was obtained.

Table 2: Direct enantioselective trichloromethylation with $HCCl_3$ using Me_3SiCF_3.[a,b,c]

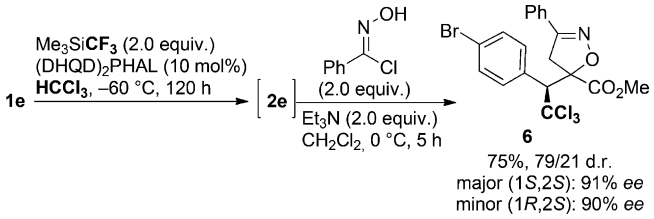


[a] Reactions were carried out using **1** (0.2 mmol), Me_3SiCF_3 (2.0 equiv) and $(DHQD)_2PHAL$ (10 mol%) in $HCCl_3$ (1.0 M) unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis. [d] $(DHQD)_2PHAL$ (20 mol%). [e] $(DHQ)_2PHAL$ was used instead of $(DHQD)_2PHAL$.

We thus started our investigation of allylic trichloromethylation of MBH-fluoride **1a** with Me_3SiCF_3 in $HCCl_3$ (Table 1). The allyl fluoride **1a** was smoothly converted into the corresponding trichloromethylated compound **2a** in $HCCl_3$ in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) at −60 °C after 3 h (65%, run 1). It was obvious that $HCCl_3$ is a source of the CCl_3 unit. We next attempted the same reaction using MBH acetate **5a**, but the acetate adduct was observed instead of **2a** (run 2). Although MBH carbonate **5b** was converted into **2a**, the yield was low (13%) at room temperature for 24 h (run 3). Using further amounts of Me_3SiCF_3 (2.0–3.0 equiv) improved the yield of **2a** to 77–92% (runs 4,5). In contrast, the reaction did not proceed in the absence of Me_3SiCF_3 (run 6). These results indicate that an in situ generated CF_3 carbanion likely acts as a base to activate the C–H of $HCCl_3$ to furnish a CCl_3 carbanion.[10] A similar C–H activation process using Me_3SiCF_3 was recently reported by two independent groups for C–H activation of CH_2Cl_2[11] and arenes;[12] however, they require a stoichiometric amount of ammonium fluorides[11] or 0.5 equivalents of metal fluorides.[12] Our process is truly an organocatalytic reaction. This allylic trichloromethylation reaction was also successfully applied to a variety of MBH fluorides **1b**,**e**,**f**, and **h**, and the desired trichloromethylated compounds **2b**,**e**,**f**, and **h** were obtained in high yields within a short period (entries 7–10).

Encouraged by these results, we advanced to the enantioselective variant of this transformation. After a brief survey of the reaction conditions, including asymmetric catalysts, temperatures, the amount of Me_3SiCF_3, and reaction concentrations, the optimal conditions were established (Supporting Information, Tables S1, S2). Thus, **1a** was treated with 2.0 equivalents of Me_3SiCF_3 in the presence of 10 mol% of $(DHQD)_2PHAL$ under a concentration of 1.0 M in $HCCl_3$, and the desired product (*S*)-**2a** was obtained in 97% yield with an excellent *ee* value of 94% after 120 h at −60 °C. The results and substrate generality are summarized in Table 2. MBH-fluorides **1** having an electron-donating methyl group at the *ortho*-, *meta*-, or *para*-position of aromatics were smoothly converted into the enantioenriched trichloromethylated compounds (*S*)-**2b**–**d** in high yields with up to 95% *ee*. Bromide, and an electron-withdrawing group, such as a CF_3 and NO_2, were also accepted as a substituent on the benzene ring to provide the corresponding CCl_3 products (*S*)-**2e**–**g** in high yields with high enantioselectivities. The sterically demanding naphthyl substrate **1h** could also be transformed into the desired CCl_3 product **2h** in 84% yield with 90% *ee*. A series of bulkier ethyl or *tert*-butyl esters of MBH-fluorides **1i**–**k** were also converted into the corresponding CCl_3 compounds (*S*)-**2i**–**k** with excellent *ee* values up to 97%, even though a higher loading of organocatalyst, 20 mol% of $(DHQD)_2PHAL$, was required to improve the reactivity of *tert*-butyl esters **1j**–**k**. The opposite enantiomer, (*R*)-**2a**, was also accessed in 91% yield with 77% *ee*, when the pseudo enantiomer of the catalyst, $(DHQ)_2PHAL$, was used instead of $(DHQD)_2PHAL$. The absolute configuration of **2e** was unambiguously *S*, assigned by X-ray crystallographic analysis of corresponding isoxazoline derivative (1*S*,2*S*)-**6** (see below, and Scheme 2); the absolute stereochemistry of the other CCl_3-products **2** was tentatively assumed to be *S* by analogy.

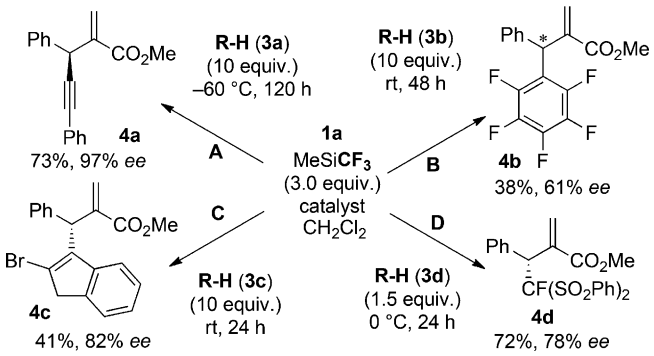
We next applied a one-pot synthesis of the biologically attractive chiral trichloromethylated spiro-isoxazoline[13] **6** from *p*-bromo substituted MBH fluoride **1e** (Scheme 2). Namely, treatment of **1e** with Me_3SiCF_3 in $HCCl_3$ under the conditions mentioned above for 120 h provided **2e**, which was



Scheme 2. One-pot synthesis of trichloromethylated spiro-isoxazoline **6** from **1e**.

directly reacted with *N*-hydroxybenzimidoyl chloride without purification in a 1,3-dipolar cycloaddition reaction to furnish chiral trichloromethylated isoxazoline **6** in 75% overall yield with 79:21 d.r. The enantiopurities of both isomers **6** were retained with or above >90% *ee*. X-ray crystallographic analysis of the major isomer of **6** revealed that the absolute stereochemistry is (1*S*,2*S*)-**6**.[19]

We finally assessed the potential of this silicon-assisted direct enantioselective allylic substitution reaction of MBH fluorides **1** with other non-pre-activated C–H compounds such as H–C(sp) (alkyne **3a**), H–C(sp^2) (arene **3b** and indene **3c**), and H–C(sp^3) (FBSM **3d**). After brief optimization of the reaction conditions, we succeeded in obtaining the desired allylic substitution products **4a–d** in moderate to good yields with high enantioselectivities under a non-metallic system (Scheme 3). The stereochemistries of **4** were determined by



Scheme 3. Direct enantioselective allylic substitution reactions with R–H compounds using Me_3SiCF_3. A) $(DHQD)_2$ PHAL (20 mol%) in CH_2Cl_2 (1.0 M); B) $(DHQD)_2$PHAL (10 mol%) in CH_2Cl_2 (0.5 M); C) $(DHQD)_2$AQN (10 mol%) in CH_2Cl_2 (0.5 M); D) $(DHQD)_2$AQN (10 mol%) in CH_2Cl_2 (0.5 M).

comparisons with reported data.[9,14] Although the corresponding expected trifluoromethylated product **7a**[9] was also obtained as a by-product, greater optimization of the reaction conditions is required to achieve higher conversion.

A plausible reaction mechanism for the asymmetric allylic substitution reaction of MBH fluorides **1** mediated by Me_3SiCF_3 is shown in Figure 1. This transformation starts with the activation of the strongest C–F bond of allyl fluoride **1** by the silicon atom of Me_3SiCF_3.[9,15] An ion pair of cationic intermediate **I** and a CF_3 carbanion should be generated by an S_N2' addition of the chiral tertiary amine catalyst at the terminal alkenyl position of **1** with the release of stable F–

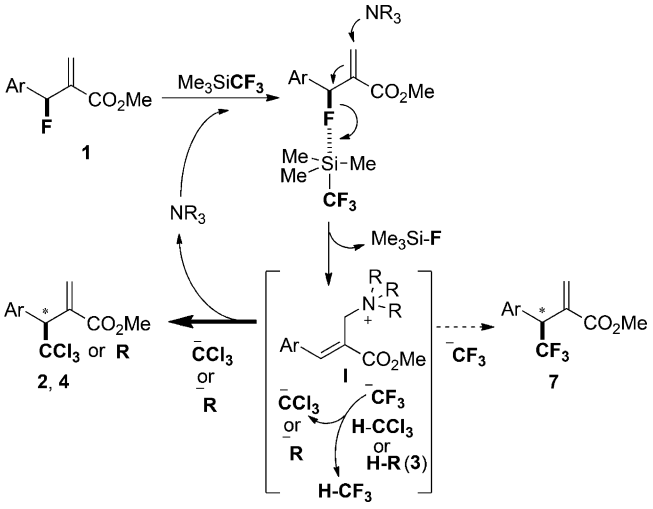


Figure 1. A proposed reaction mechanism consisting of three important steps: i) C–F bond activation, ii) carbanion exchange of CF_3 to CCl_3, and iii) enantioselective SN_2' addition.

$SiMe_3$. It should be noted that the CF_3 carbanion rapidly abstracts H^+ from the surrounding chloroform, H–CCl_3,[11,16] rather than its direct nucleophilic attack on the alkene moiety of ammonium salts **I**, resulting in a new ion pair of CCl_3 carbanion and cationic intermediates **I**, with the release of stable fluoroform, HCF_3. The enantioselective nucleophilic trichloromethylation by CCl_3 carbanion to the ammonium salts **I** by a secondary S_N2' process proceeds to give the enantioenriched CCl_3-products **2**. A similar reaction mechanism could be considered for the direct activation of other C–H compounds **3**,[12,17] although the competitive trifluoromethylation to **7** was observed in this case.

In summary, we have developed an efficient protocol for the enantioselective allylic trichloromethylation reaction of MBH-type fluorides[18] by metal-free, silicon-assisted C–F bond activation and direct C–H activation of chloroform, $HCCl_3$ by a carbanion exchange process with CF_3 carbanion, using the Ruppert–Prakash reagent, Me_3SiCF_3. This transformation affords a wide range of chiral trichloromethylated compounds in high yields with high enantioselectivities. Direct enantioselective trichloromethylation is rare, and to our knowledge, this is the first example of the use of chloroform for an enantioselective trichloromethylation reaction. The direct asymmetric introduction of other C–H compounds such as alkyne, arene, indene, and FBSM without pre-activation was also achieved under the same reaction conditions.

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Keywords: C-F activation · fluorine · organocatalysis · silicon · trichloromethylation

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[18] The use of MBH-type chlorides and bromides instead of MBH-fluorides **1** failed because MBH-type chlorides are too unstable to be prepared, and MBH-type bromides are isomerized to internal alkenes or react by an SN_2' reaction to provide internal alkenes. These facts clearly show the advantage of MBH-fluorides. See; M. Y. Shandala, S. M. Kalil, M. S. Al-Dabbagh, *Tetrahedron* **1984**, *40*, 1195 – 1198; K. H. Kim, S. Lee, J. Lee, M. J. Go, J. N. Kim, *Tetrahedron Lett.* **2013**, *54*, 5739 – 5743; M.-L. Yao, G. W. Kabalka, D. W. Blevins, M. S. Reddy, L. Yong, *Tetrahedron* **2012**, *68*, 3738 – 3743.

[19] CCDC 1419720 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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