Organocatalysis

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Asymmetric Allylic Monofluoromethylation and Methylation of Morita–Baylis–Hillman Carbonates with FBSM and BSM by Cooperative Cinchona Alkaloid/$FeCl_2$ Catalysis**

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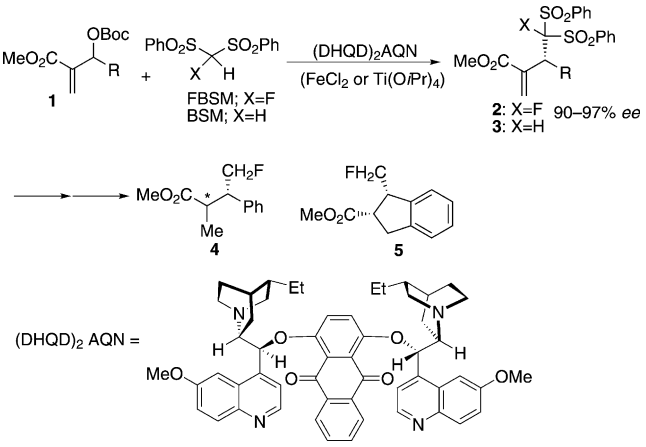
Fluorine-containing organic compounds are well recognized as potential medicinal and agrochemical candidates.[1] Incorporation of a fluorine atom into organic molecules, especially biomolecules and pharmaceuticals, can dramatically alter their lipophilicity, membrane permeability, and binding capacity to target receptors in the body.[2] Metabolic stability is also improved when a fluorine atom is introduced at a suitable position of the parent molecule. Fluorine is a close steric replacement for hydrogen, and also serves as an isosteric mimic of the hydroxy group.[3] To minimize the change in the steric bulk of the parent biomolecules, the introduction of a single fluorine atom is often strategized for the synthesis of isosteres.[4] Therefore the synthesis of monofluorinated compounds is of great importance. Among various strategies, direct monofluoromethylation with high stereoselectivity is particularly attractive as is the direct monofluorination reaction.[5] In 2006, our group[6b] and group of Hu[7a] in Shanghai independently developed fluorobis(phenylsulfonyl)methane (FBSM) as a synthetic equivalent of a monofluoromethide species for the direct construction of a C–CFH_2 bond. FBSM has now become commercially available and a number of nucleophilic monofluoromethylation reactions using FBSM have emerged, including Tsuji–Trost allylation, the Mannich reaction, conjugate addition, the Mitsunobu reaction, and the monofluoromethylation of epoxides and benzynes.[6,7] Research into FBSM has also sparked the imagination of chemists to design similar types of nucleophilic reactions using α-monofluorocarbonyl compounds as nucleophiles; these reactions afford a variety of monofluorinated compounds, represented by -CFR^1R^2 (but not CFH_2).[8] However, the introduction of an entire CFH_2 group to an asymmetric carbon center is not easy, and a limited number of successful asymmetric monofluoromethylation reactions have been published.[6b–d,7e–i] We disclose herein the first example of an organocatalyzed enantioselective allylic monofluoromethylation of Morita–Baylis–Hillman carbonates[9] **1** with FBSM using a bis(cinchona alkaloid), to provide the medicinally attractive synthons chiral α-methylene β-monofluoromethyl esters **2** with high *ee* values of 84–97% (Scheme 1). Cooperative catalysis using a bis(cinchona alkaloid) and a Lewis acid, particularly $FeCl_2$, is more effective for this transformation and using this cooperative catalysis compounds **2** are furnished with over 90% *ee* for all substrates **1**. The β-monofluoromethyl esters **2** obtained can be efficiently converted into monofluoromethylated ester **4** and interesting carbocyclic compounds **5** without any loss of enantiomeric purity. Enantioselective allylic methylation of Morita–Baylis–Hillman adducts **1** using bis(phenylsulfonyl)methane (BSM), a nonfluorinated analogue of FBSM, was also performed in the presence of a bis(cinchona alkaloid) and $FeCl_2$ (or $Ti(OiPr)_4$) to provide methylated adducts **3** in high yields with high enantioselectivities of up to 96% *ee* (Scheme 1).



Scheme 1. Enantioselective monofluoromethylation and methylation of Morita–Baylis–Hillman carbonates with FBSM and BSM catalyzed by cooperative catalysts, bis(cinchona alkaloid) and $FeCl_2$.

Our initial investigation started by establishing a suitable catalyst for the allylic addition of FBSM to Morita–Baylis–Hillman carbonate **1a** (Table 1). Quinidine gave FBSM

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FBSM = fluorobis(phenylsulfonyl)methane, BSM = bis(phenylsulfonyl)methane.

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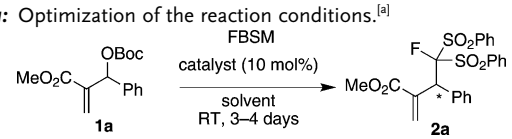
Table 1: Optimization of the reaction conditions.[a]

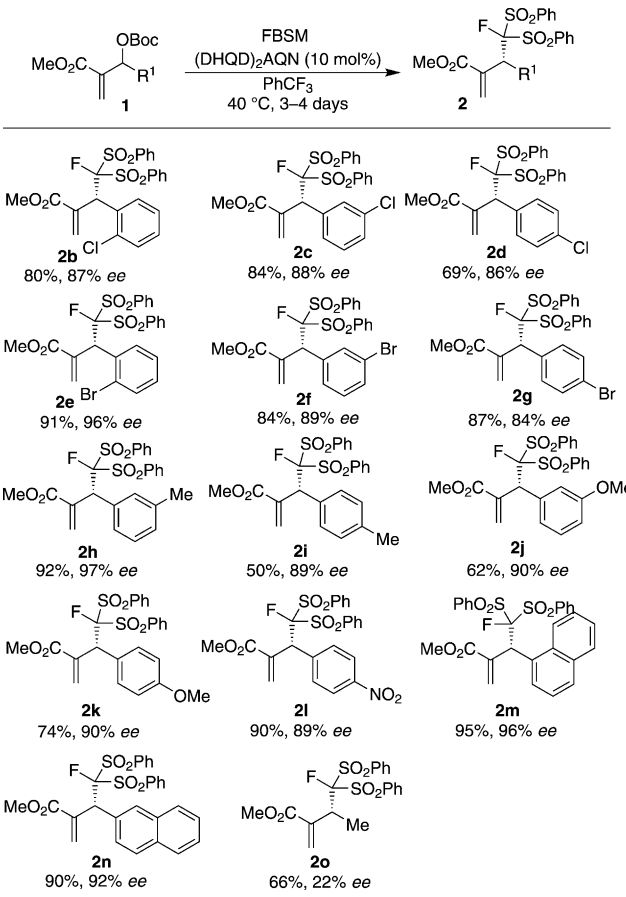


Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%]
1	Quinidine	DCE	38	9 (*S*)
2	Quinine	DCE	75	14 (*R*)
3	Cinchonine	DCE	51	18 (*S*)
4	Cinchonidine	DCE	78	65 (*R*)
5	β-ICD	DCE	31	11 (*R*)
6	$(DHQD)_2PYR$	DCE	75	75 (*R*)
7	$(DHQD)_2PHAL$	DCE	76	55 (*R*)
8	$(DHQD)_2AQN$	DCE	81	76 (*R*)
9	$(DHQ)_2PYR$	DCE	92	59 (*S*)
10	$(DHQ)_2PHAL$	DCE	81	10 (*S*)
11	$(DHQ)_2AQN$	DCE	87	15 (*S*)
12	$(DHQD)_2AQN$	CH_2Cl_2	60	85 (*R*)
13	$(DHQD)_2AQN$	THF	15	35 (*R*)
14	$(DHQD)_2AQN$	Toluene	68	95 (*R*)
15	$(DHQD)_2AQN$	$PhCF_3$	66	96 (*R*)
16[c]	$(DHQD)_2AQN$	$PhCF_3$	90	94 (*R*)
17[d]	$(DHQD)_2AQN$	$PhCF_3$	93	94 (*R*)
18[e]	$(DHQD)_2AQN$	$PhCF_3$	80	88 (*R*)
19[d]	$(DHQ)_2PYR$	$PhCF_3$	70	64 (*S*)

[a] Reactions were carried out using **1a** (1.1 equiv), FBSM (1.0 equiv), catalyst (10 mol%) in solvent at room temperature for 3–4 days unless otherwise noted. [b] Yield of the isolated product. [c] Reaction was performed at 30 °C. [d] Reaction was performed at 40 °C. [e] Reaction was performed at 50 °C. β-ICD = β-isocupreidine, DCE = 1,2-dichloroethane, $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether, $(DHQ)_2PYR$ = hydroquinine-(2,5-diphenyl-4,6-pyrimidindiyl) diether, THF = tetrahydrofuran.

adduct **2a** in low yield with low enantioselectivity (entry 1). The use of quinine and cinchonine slightly improved the yields and enantioselectivities of **2a** (entries 2 and 3, respectively). When cinchonidine was used, the enantioselectivity was improved to 65% *ee* (entry 4). In contrast, β-ICD was found to be ineffective (entry 5). We next attempted to use bis(cinchona alkaloids), such as $(DHQD)_2PYR$, $(DHQD)_2PHAL$, $(DHQD)_2AQN$, $(DHQ)_2PYR$, $(DHQ)_2$-PHAL, and $(DHQ)_2AQN$ (entries 6–11). High enantioselectivities of **2a** (up to 76% *ee*) were observed in the presence of $(DHQD)_2PYR$ and $(DHQD)_2AQN$ (entries 6 and 8, respectively). The effect of the solvent was next surveyed (entries 12–15); toluene and 1,1,1-trifluorotoluene were found to be equally suitable for this reaction with a catalytic amount of $(DHQD)_2AQN$ (entries 14 and 15, respectively). The reaction temperature was studied and the yield of **2a** was improved at a slightly higher reaction temperature (entries 16–18). Thus, the best result ((*R*)-**2a**, 93% yield with 94% *ee*) was obtained at 40 °C (entry 17). It should be mentioned that the *ee* value of the other enantiomer of **2a** ((*S*)-**2a**) was also improved to an acceptable value under the best temperature and solvent conditions in the presence of $(DHQ)_2PYR$ (entries 9–11 and 19).

With the optimized reaction conditions established, the scope of substrates **1** for the enantioselective allylic monofluoromethylation reaction using FBSM was investigated (Scheme 2). Compounds **2** were obtained with high yields and high enantioselectivities and these results were almost

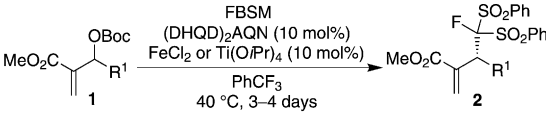


Scheme 2. Enantioselective monofluoromethylation of Morita–Baylis–Hillman carbonates with FBSM catalyzed by cinchona alkaloids.

independent of the nature (halides, electron-donating, and electron-withdrawing groups) and position (*ortho*, *meta*, and *para* positions) of the substituent on the aromatic ring of the Morita–Baylis–Hillman carbonates. Functional groups, such as chloro (**1b–d**), bromo (**1e–g**), methyl (**1h–i**), methoxy (**1j–k**), and nitro (**1l**) groups, were well tolerated under the reaction conditions and the corresponding allylic FBSM adducts **2b–l** were obtained with up to 97% *ee*. Sterically demanding 1-naphthyl and 2-naphthyl Morita–Baylis–Hillman carbonates **1m** and **1n** were also nicely converted into the desired adducts **2m** and **2n** in high yields and with high *ee* values of 96% (**2m**) and 92% (**2n**). However, the nonaromatic Morita–Baylis–Hillman carbonate **1o** failed to undergo the FBSM addition reaction with high enantiocontrol, thus giving **2o** with 22% *ee* (Scheme 2). This lack of enantiocontrol for nonaromatic substrates is a limitation of the present method.[10] The absolute stereochemistry of **2** was confirmed by X-ray crystallographic analysis of the derivative (1*S*,2*S*)-**7** (see Scheme 5 and Figure S1 in the Supporting Information).

This procedure works particularly well with the aromatic Morita–Baylis–Hillman carbonates **1a–n** as substrates and

gives high levels of enantioselectivity[10] (14 examples, up to 97% *ee*), although half of the products did not have fully satisfactory *ee* values, that is they had values of less than 90% *ee* (7 examples: **2b**, **2c**, **2d**, **2f**, **2g**, **2i** and **2l**; 84–89% *ee*). To improve the enantioselectivity of the corresponding substrates to over 90% *ee* we next examined the effect of the Lewis acid on the reaction outcome. After considerable investigation using a variety of Lewis acids, including $FeCl_3$, $FeBr_2$, $Ti(OiPr)_4$, $AlCl_3$, and $Y(OTf)_3$ (see Table S1 in the Supporting Information for details), both $FeCl_2$ and $Ti(OiPr)_4$ were found to be equally effective cooperative catalysts with $(DHQD)_2AQN$ for this transformation, and over 90% *ee* was achieved for all the substrates **1** (Scheme 3; $FeCl_2$ gave slightly better results

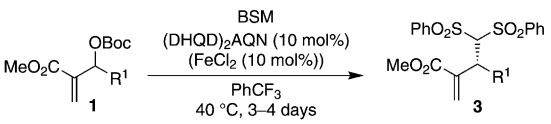


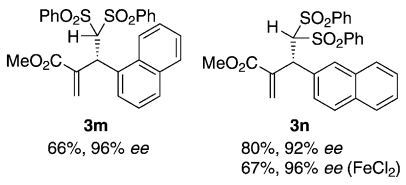
2b 80%, 95% *ee* ($FeCl_2$); 91%, 91% *ee* ($Ti(OiPr)_4$)
2c 95%, 97% *ee* ($FeCl_2$); 96%, 92% *ee* ($Ti(OiPr)_4$)
2d 85%, 93% *ee* ($FeCl_2$); 93%, 92% *ee* ($Ti(OiPr)_4$)
2f 91%, 92% *ee* ($FeCl_2$); 91%, 92% *ee* ($Ti(OiPr)_4$)
2g 81%, 94% *ee* ($FeCl_2$); 99%, 91% *ee* ($Ti(OiPr)_4$)
2i 91%, 97% *ee* ($FeCl_2$); 89%, 95% *ee* ($Ti(OiPr)_4$)
2j 43%, 92% *ee* ($FeCl_2$)
2l 80%, 92% *ee* ($FeCl_2$); 99%, 90% *ee* ($Ti(OiPr)_4$)
2n 93%, 96% *ee* ($FeCl_2$)

Scheme 3. Improvement of enantioselectivity by up to 10% *ee* was observed by cooperative catalysts, cinchona alkaloid and $FeCl_2$ or $Ti(OiPr)_4$.

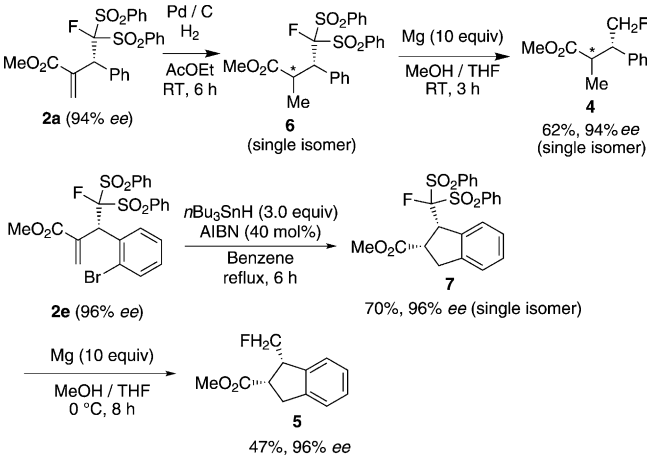
than $Ti(OiPr)_4$). The enantioselectivity was improved by as much as 10% (**2g**). It should be noted that the method was also found to be applicable for the enantioselective methylation of aromatic Morita–Baylis–Hillman carbonates **1m** and **1n** using BSM,[11] the nonfluorinated analogue of FBSM, to furnish the corresponding methylated products **3m** and **3n** in 96% *ee* and 92% *ee*, respectively. The slightly lower *ee* value for **3n** was improved to 96% *ee* by using the cooperative catalyst, $FeCl_2$ (Scheme 4).

The FBSM adducts **2** were smoothly transformed into pure monofluoromethylated compounds. Two examples were carried out (Scheme 5): 1) Reduction of **2a** using H_2 over Pd/C followed by reductive desulfonylation with Mg/MeOH furnished monofluoromethylated ester **4**[12] diastereoselec-





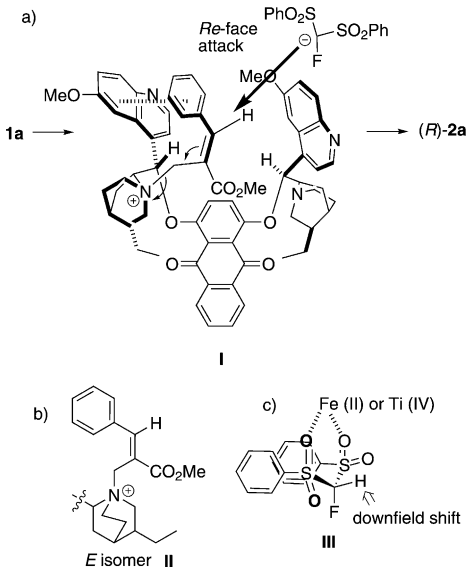
Scheme 4. Enantioselective methylation of Morita–Baylis–Hillman carbonates with BSM, a nonfluorinated analogue of FBSM.



Scheme 5. Conversion of chiral α-methylene β-monofluoromethylated esters **2a** and **2e** into monofluoromethylated compounds **4** and **5**.

tively in good yield without any loss of enantiopurity. 2) Intramolecular radical cyclization of **2e** was carried out in the presence of nBu_3SnH and AIBN to afford dihydroindene derivative **7** in 70% yield with diastereoselectively. The stereochemistry of **7** was assigned a *cis* configuration by X-ray analysis (see Figure S1 in the Supporting Information).[13] The dihydroindene **7** was converted into 1-monofluoromethylindene **5** (47% yield)[14] by reductive desulfonylation mediated by Mg in MeOH without any loss of enantiopurity of the starting substrate **2e** (Scheme 5).

Although the number of possible conformations of the cinchona alkaloids in solution make it difficult to analyze the transition-state structure of the substrate/catalyst complexes, the reaction intermediate for the *R*-selective formation of **2** catalyzed by $(DHQD)_2AQN$ is presumably in the open conformation, similar to the conformation reported for the reaction intermediates of the osmium-catalyzed asymmetric dihydroxylation[15] and the asymmetric direct aldol reaction[16] (Scheme 6a). With $(DHQD)_2AQN$ in the open conformation, the quinuclidine nitrogen atom of $(DHQD)_2AQN$ could attack the MBH carbonate **2a** in a S_N2' manner to afford the cationic intermediate **I**. The $(DHQD)_2AQN$–MBH adduct would be preferentially formed as the *E* isomer **II**, in accordance to the conformational analysis of quinuclidine-MBH ester adducts by Mayr and co-workers (Scheme 6b).[9o] The MBH moiety (from **1a**) in **I** might be in part stabilized through the π–π stacking in the U-shape cleft of $(DHQD)_2AQN$. The *Si* face of adduct is blocked by the left half of the quinidine moiety, which is bonded to the MBH moiety by a N–C covalent bond. Thus, the FBSM anion would presumably approach the *Re* face in the preferable S_N2'/*anti*-elimination manner (Scheme 6a). The low enantioselectivity of the nonaromatic MBH carbonate **1o** could be explained by the lack of corresponding π–π stacking interactions in the transition state. The addition of a Lewis acid, either $FeCl_2$ or $Ti(OiPr)_4$, improves the enantioselectivity of **2**, but the effect is not so striking (maximum 10% *ee* increase). This could be explained by bidentate chelation[17] of FBSM with the Lewis acid, thus locking the FBSM conformation so as to favor a closed conformation (**III**; Scheme 6c), although the closed



Scheme 6. a) A proposed transition-state model from **1a** to (*R*)-**2a**; b) the proposed geometry of the $(DHQD)_2AQN$/MBH adduct; c) the proposed coordinated structure of FBSM with a Lewis acid.

conformation is an inherent preference of a FBSM carbanion even in the absence of Lewis acid.[19] A ^1H NMR investigation of 1:1 mixture of FBSM and $Ti(OiPr)_4$ in $[D_6]$benzene strongly supports this hypothesis, since the methine proton of FBSM gives a signal that is $\delta = 0.036$ ppm downfield relative to the signal in the original spectrum of FBSM (see Figure S2 and S3 in the Supporting Information). In the locked closed conformation **III**, FBSM would easily approach the reaction center and avoid steric interactions in the transition state **I**, although this outcome is dependent on the substate structure (Scheme 6a).[19,20]

In summary, the organocatalyzed enantioselective allylic monofluoromethylation of Morita–Baylis–Hillman carbonates using FBSM was achieved in high yields with high *ee* values for the first time.[19b] Cooperative catalysis with bis(cinchona alkaloid) and $FeCl_2$ was found to be most suitable for this transformation. Addition of $Ti(OiPr)_4$ instead of $FeCl_2$ also improves the enantioselectivity. This should be a powerful protocol to access enantiomeric α-methylene β-monofluoromethyl esters, which are useful synthetic building blocks for further transformations. Enantioselective allylic methylation was also achieved using BSM instead of FBSM under identical catalytic conditions.

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[20] Discussion of the optimized geometries of the catalyst/substrate complex using DFT calculations for the reaction of Morita–Baylis–Hillman carbonates with FBSM without cooperative catalysis appeared during the reviewing process of this manuscript, see reference [19b].

