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Organocatalytic enantioselective substitution of MBH carbonates by 2-fluoromalonates

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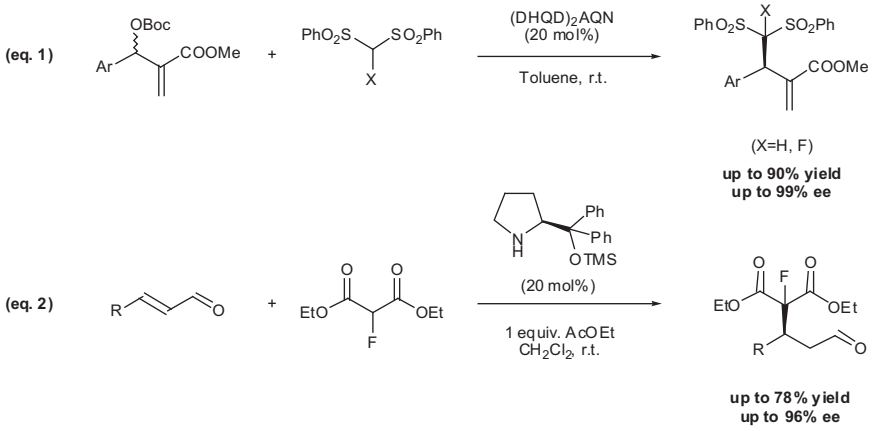
ABSTRACT

The enantioselective fluoromalonate addition to Morita–Baylis–Hillman carbonates is presented. The reaction is simply catalyzed by β-isocupreidine affording the final fluorinated products in good yields and enantioselectivities.

The asymmetric synthesis of fluorine-containing molecules[1] is one of the most important fields in organic chemistry. The unique properties of fluorinated molecules have attracted a lot of interest in the field of organic synthesis due to their wide use in both medicinal chemistry and material science.[2] Whereas organofluorinated compounds are primarily used in studies of biochemical and metabolic processes,[3] strategic fluorination is commonly employed in medicinal chemistry to improve the metabolic properties and bioavailability of drug candidates.[4]

In the realm of organocatalysis[5] several procedures have been developed for the enantioselective synthesis of fluorinated molecules starting from carbonyl compounds. These include α-fluorina-



Scheme 1. Organocatalytic methodologies developed in our research group.

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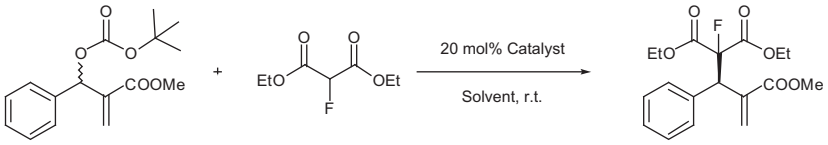
Table 1
Catalyst screening[a]

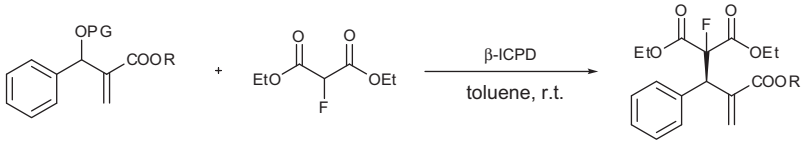


1a 2 3a

Entry	Catalyst	Solvent	Conv. (14 h)[b]	ee[c]
1	β-ICPD (I)	Toluene	80%	75%
2	Quinine (II)	Toluene	60%	77%
3	Cinchonine (III)	Toluene	Traces	80%
4	$(DHQD)_2PHAL$ (IV)	Toluene	16%	−81%
5	$(DHQ)_2PHAL$ (V)	Toluene	Traces	50%
6	$(DHQD)_2AQN$ (VI)	Toluene	31%	23%
7	$(DHQ)_2AQN$ (VII)	Toluene	23%	−9%
8	(R,R)-TUC (VIII)	Toluene	traces	ND
9	$(DHQD)_2PYR$ (IX)	Toluene	16%	49%
10	β-ICPD (I)	CF_3-Toluene	92%	77%
11	β-ICPD (I)	Xylene	85%	81%
12	β-ICPD (I)	CH_2Cl_2	Full	71%
13	β-ICPD (I)	TBME	60%	75%
14	β-ICPD (I)	AcOEt	90%	73%
15[d]	β-ICPD (I)	Toluene	95%	70%
16[e]	β-ICPD (I)	Toluene	40%	80%
17[f]	$(DHQD)_2PHAL$ (IV)	Toluene	15%	−74%

[a] Experimental conditions[15]: In a small flask, **1a** (1.2 equiv), **2** (1 equiv), and catalyst (20 mol %) were added in 0.5 mL of solvent: the reaction mixture was stirred for 14 h and then analyzed by NMR.
[b] Determined by ^1H NMR of the crude reaction.
[c] Determined by chiral HPLC.
[d] The reaction was carried out at 50 °C.
[e] The reaction was carried out at 0 °C.
[f] 1 equiv of $FeCl_2$ was used as additive.

Table 2
Substrate screening[a]



1a-e 2 3a

Entry	R	PG	Solvent	Yield[b] (%)	ee[c] (%)
1	Me	Boc	Toluene	80	75
2	Et	Boc	Toluene	75	60
3	^{t}Bu	Boc	Toluene	90	90
4	Ph	Boc	Toluene	82	3
5	Me	Ac	Toluene	80	50
6	^{t}Bu	Boc	Xylene	61	87
7	Me	Boc	Xylene	85	81

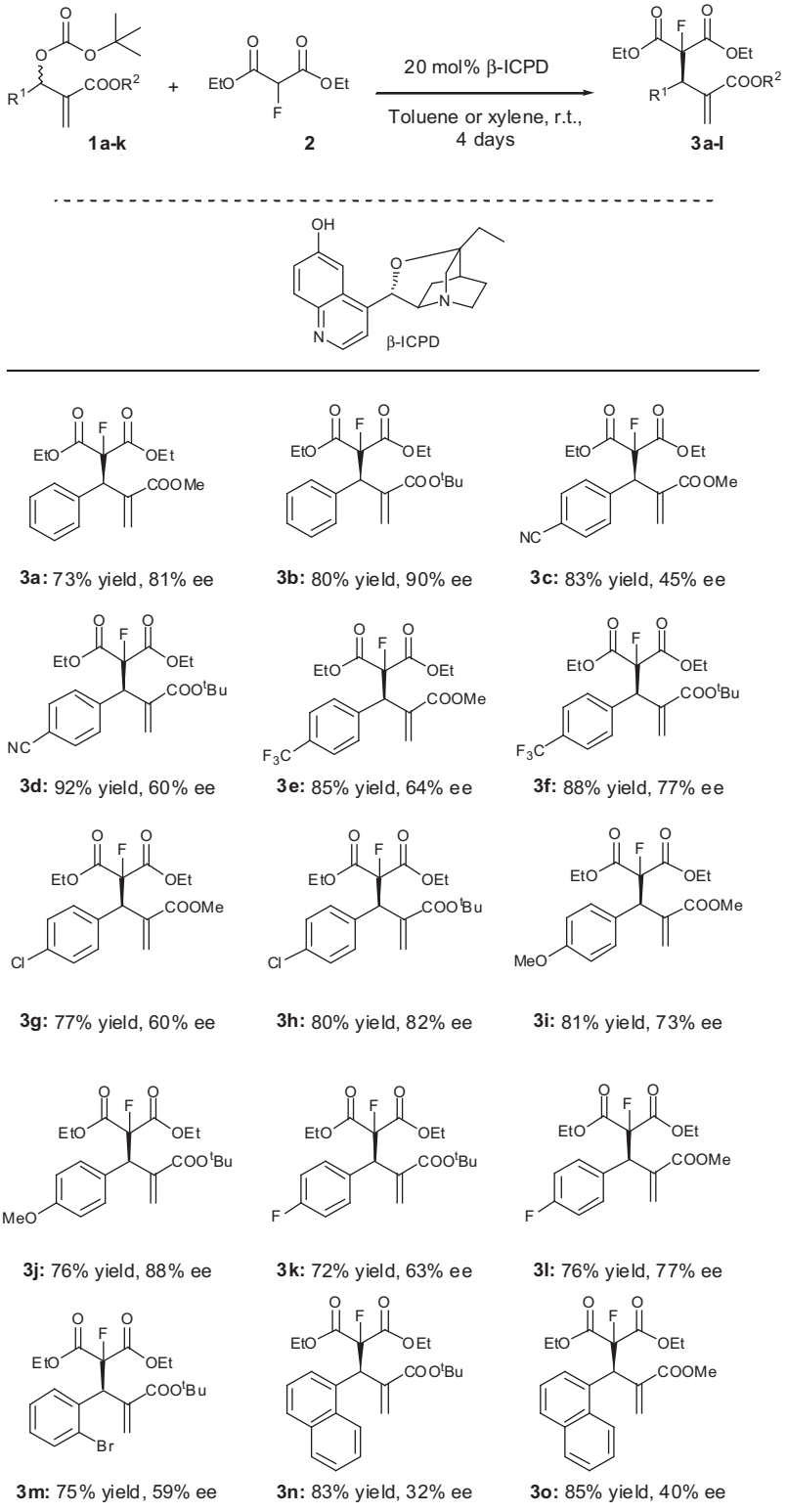
[a] Experimental conditions: In a small flask, **1a** (1.2 equiv), **2** (1 equiv), and catalyst (20 mol %) were added in 0.5 mL of solvent.
[b] Isolated yield.
[c] ee determined by chiral HPLC analysis.

tion,[6] α-trifluoromethylation,[7] and β-methylfluorination,[8] among others.

Very recently, the use of Morita–Baylis–Hillman (MBH) carbonates as electrophiles for highly enantioselective organocatalytic reactions has attracted much attention.[9] Tan and co-workers,[10] Shibata and co-workers,[11] and our research group[12] have been developing the addition of methylenesulfones or fluoromethyl(bisphenylsulfones) to MBH carbonates with excellent results (Scheme 1; Eq. 1).

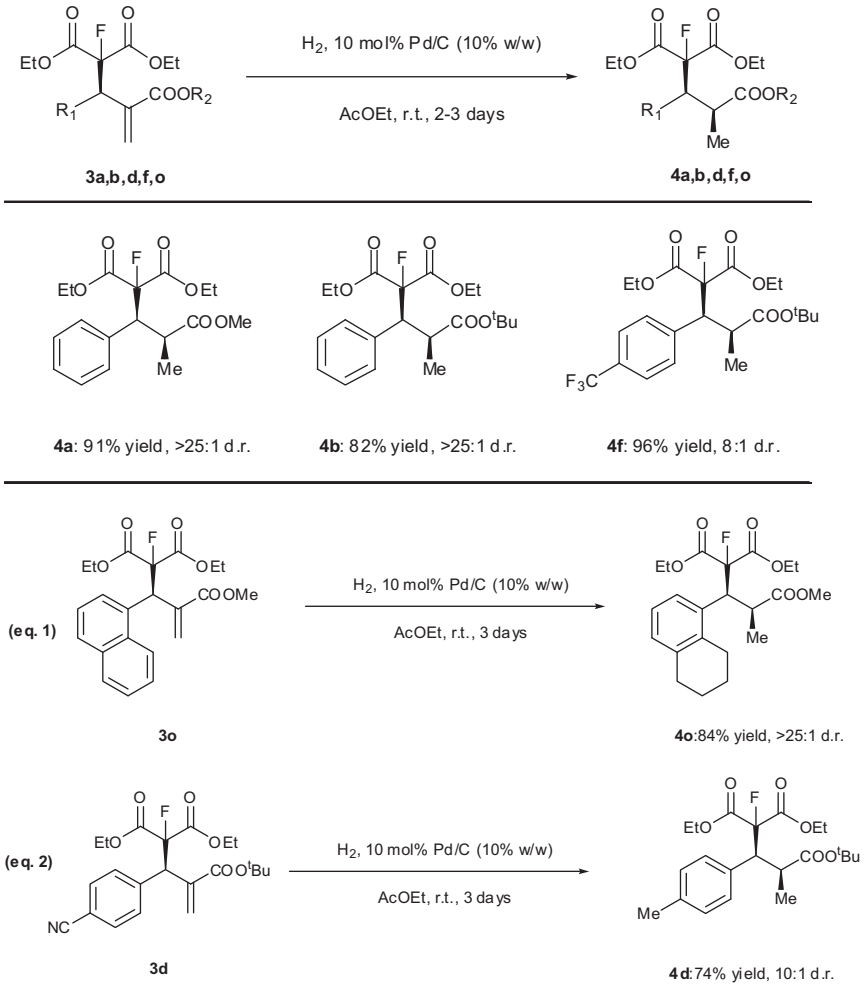
Spurred on by the excellent results obtained in the addition of fluoromalonates to enals[13] (Scheme 1; Eq. 2), and given our previous experience on organocatalysis,[14] we envisioned that the chiral tertiary amine-catalyzed reaction of racemic MBH carbonates with fluoromalonates could provide a facile stereo controlled route to chiral fluoroderivatives.

In our preliminary experiments, we investigated the reaction of MBH carbonate **1a** with 2-fluorodiethylmalonate **2** in the presence of different chiral organic Lewis bases. As depicted in Table 1, β-isocupreidine (**I**) (β–ICPD, Table 1; entry 1) was found to be the most active catalyst in toluene solution, giving 80% conversion to the expected product within 14 h and with good enantioselectivity. Quinine (**II**) demonstrated similar results in terms of enantioselectivity but with lower conversion (entry 2; Table 1). Cinchonine (**III**), $(DHQD)_2PHAL$ (**IV**), $(DHQ)_2PHAL$ (**V**), $(DHQD)_2AQN$



Scheme 2. Reaction scope (Experimental conditions: In a small flask, **1** (1.2 equiv), **2a** (1 equiv), and B-ICPD (20 mol %) were added in 0.5 mL of toluene (methyl acrylate derivatives) or xylene (*tert*-butyl acrylate derivatives).[15] Isolated yields after flash chromatography. ee determined by chiral HPLC analysis).

(**VI**), $(DHQ)_2AQN$ (**VII**), $(DHQD)_2PYR$ (**IX**), and Takemoto catalysts (TUC) (**VIII**) gave both low conversions and enantioselectivities (entries 3–9; Table 1). Further optimization of the reaction conditions with regard to the solvent showed that xylenes (isomer mixture) afforded the best enantioselectivity while maintaining a good conversion (entry 11; Table 1). Trifluoromethyl benzene, CH_2Cl_2, and AcOEt all gave excellent conversions but with slightly lower enantioselectivities than xylene (entries 10, 12 and 14; Table 1). TBME resulted in both low conversion and enantioselectivity (entry 13; Table 1). Raising the temperature increased conversion



Scheme 3. Catalytic hydrogenation of **3**.

but diminished its enantioselectivity. On the other hand, at 0 °C, the reaction renders the final product in low conversion but reasonable ee (entry 16; Table 1). The addition of a mild Lewis acid such as $FeCl_2$ did not improve the outcome of the reaction (entry 17; Table 1).

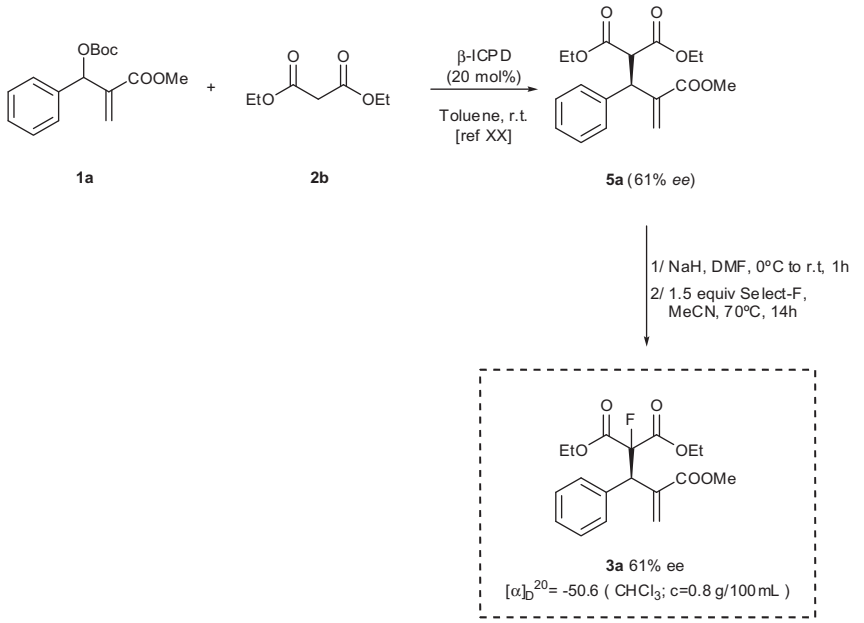
Based on these results, we found that the optimal conditions for this reaction are to use xylene as the solvent at room temperature with β-ICPD as the catalyst.

After determining the optimum conditions, we proceeded to study the scope of the reaction in terms of the ester moiety of the MBH carbonate. As shown in Table 2, the ee was strongly influenced by the nature of the ester. When we used ethyl acrylate derivative (**1b**) the ee decreased to 60%. The best result was achieved when using *tert*-butyl acrylate derivative (**1c)** in toluene, achieving 90% yield and 90% ee (entry 3; Table 2). However, when phenyl acrylate derivative **1d** was used, the product obtained was almost racemic (entry 4; Table 2). Finally, we studied the reaction using an alternative leaving group such as acetyl. Unfortunately, this reaction afforded **3a** in good yield but with low enantioselectivity (entry 5; Table 2).

Next, we studied the scope of the reaction using different substituents on the aryl ring of the MBH carbonate. As shown in Scheme 2, the reaction gave good yields for all of the substituents tested, but the enantioselectivity of the reaction is strongly dependent of the nature of the substituent. When electron withdrawing groups such as 4-CN or 4-CF_3 (**3c–f**) was used, the ee decreased substantially. Electron-donating groups such as 4-OMe, 4-Cl, or 4-F gave yields similar to those obtained with the unsubstituted phenyl **3a**, albeit with slightly lower enantioselectivities (**3g–l**). Finally, when bulky aryl substituents such as 2-bromophenyl or 1-naphthyl were used, the enantioselectivities of the resulting compounds (**3m–o**) dropped dramatically.

We then decided to further extend the applicability of the reaction by derivatization of compounds **3**. The reduction of the double bond was achieved by treatment of compounds **4** with Pd over H_2, affording the hydrogenated products in excellent yields and moderate to excellent (>25:1 dr) diastereoselectivities (Scheme 3). Remarkably, when compounds **3o** and **3d** were treated in the reaction conditions the over-reduced products **4o** and **4d** were obtained in excellent yields and diastereoselectivities (Scheme 3).

The absolute configuration of adducts was ascertained by chemical correlation (Scheme 4). Following the procedure developed by Hiemstra,[16] we prepared the enantioenriched compound **5a**, with an (*R*) absolute configuration. After fluorination of the malonate moiety by sequential treatment with sodium hydride and Selectfluor® we obtained compound **3a**, .that exhibited an optical rotation ($[\alpha]_D^{25}$ −50.6 (*c* = 0.8 g/100 mL, $CHCl_3$, 61% ee) of the same sign than that of compound **3a**, obtained by our methodology with β-ICPD as the catalyst ($[\alpha]_D^{25}$ −65.6 (*c* = 0.8 g/100 mL, $CHCl_3$ 81% ee). This indicates that the absolute configuration of this compound is also (*R*) (Scheme 4).



Scheme 4. Determination of the absolute configuration of **3a.**

To summarize, we have described a practical, inexpensive, and powerful organocatalytic alternative to organometallic allylic substitution. We have achieved asymmetric fluoromalonate addition to MBH carbonates with excellent yields and good enantioselectivities. Moreover, we have demonstrated the broad applicability of this method. Mechanistic studies and synthetic applications of this new methodology, as well as the discovery of new reactions based on this concept are currently ongoing in our laboratories.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.121.

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15. *General Procedure*: In a small vial, MBH carbonate **1a–e** (0.25 mmol, 1 equiv), 2-fluoromalonate **2**, (67 mg, 0.375 mmol, 1.5 equiv), and catalyst **I** (8 mg, 0.025 mmol, 10 mol %) in 1 mL of toluene were stirred at room temperature overnight. The crude mixture was monitored by ^{1}H NMR and after completion the crude was purified by column chromatography, affording compound **3**. *1,1-diethyl 3-methyl 1-fluoro-2-phenylbut-3-ene-1,1,3-tricarboxylate (**3a**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28(m, 2H), 7.24–7.20(m, 2H), 6.37–6.37(m, 1H),

6.17(m, 1H), 5.08 (d, J_{H-F} = 35.2 Hz, 1H), 4.24–4.22 (m, 2H), 4.03–4.02(m, 2H), 3.63(s, 3H), 1.24–1.22(t, J = 7.1 Hz, 3H), 1.03–1.02(t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.2, 164.9, 164.8, 164.5, 138.1, 138.1, 134.9, 129.8, 129.8, 128.2, 127.8, 127.02, 126.9, 98.0, 95.9, 62.9, 62.7, 52.2, 49.0, 48.8, 13.8, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −174.1 (d, J = 35.4 Hz). HRMS (ESI) calcd. for $C_{18}H_{25}FNO_6$ $(M+NH_4)^+$, 370.1666 found 370.1665. Enantiomeric excess: 81%, $[\alpha]_D^{20}$ −65.6 ($CHCl_3$; c = 0.8 g/100 mL) determined by HPLC (Daicel Chiralpak IA, *i*-PrOH/Hexane = 5/95), UV 254 nm, flow rate 0.8 mL/min, major 9.7 min, minor 10.9 min.

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