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Highly enantioselective fluoromalonate addition to α,β-unsaturated aldehydes

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ABSTRACT

A highly enantioselective organocatalytic fluoromalonate addition to α,β-unsaturated aldehydes is reported. The reaction is catalyzed by simple and commercially available secondary amines, affording the corresponding 1,4-adducts with high yields and enantioselectivities.

The stereoselective introduction of fluorine (or of fluorine-containing building blocks) into organic molecules and polymers can dramatically alter their physical, chemical, and biological properties. This is mainly due to the highly polarized nature of the C–F bond that usually has strong stereoelectronic interactions with neighboring bonds or with electron lone pairs of neighboring atoms.[1] Many organofluorated synthetic compounds exhibit unique physical, chemical, and biological properties that have found wide application in life sciences, in materials science, and in related disciplines. For example, fluorination is commonly used in medicinal chemistry to improve metabolic stability, bioavailability, and protein-drug interactions.[2] As a result, extensive research has been carried out seeking new synthetic fluorination methodologies during the past 30 years.[3,1] The specific incorporation of fluorine in a regio- and stereoselective fashion can be achieved both by nucleophilic and by electrophilic fluorination. Nucleophilic fluoroalkylation has become one of the most important and fast growing fields in fluorine chemistry, and most often involves the transfer of a fluorinated carbanion to an electrophile. For example, in 2008 Hu and co-workers described a convenient fluoroalkylation of α,β-enones, arynes, and activated alkynes with fluorinated sulfones in racemic form.[4] There are however few enantioselective fluorination methods reported in the literature. In 2006, Shibata and co-workers disclosed an elegant palladium-catalyzed allylic fluoromethylation that takes place with excellent yields and enantioselectivities;[5] the same author reported in 2008 the first enantioselective 1,4-fluoromethylation of enones, using *Cinchona* alkaloid derivatives as organocatalysts.[6] Sodeoka has described the direct asymmetric fluorination of oxindoles catalyzed by palladium, with excellent results.[7]

In the realm of organocatalysis, many efforts have been devoted in the past few years to the enantioselective synthesis of fluorine-containing compounds using aldehydes as the starting materials. The most common way relies on the use of electrophilic fluorine sources: for example, the asymmetric α-fluorination of aldehydes was achieved almost simultaneously by Jørgensen,[8] MacMillan,[9] and Barbas III,[10] in high yields and enantioselectivities. While Barbas III and MacMillan used imidazoline derivatives as catalysts, Jørgensen found that diphenylprolinolsilyl ether was an efficient catalyst for this transformation. However, there is only one example of asymmetric organocatalytic nucleophilic addition of fluorine-containing moieties to α,β-unsaturated aldehydes, developed in our laboratory: the enantioselective conjugate addition of fluoro bis(phenylsulfonyl)methane to α,β-unsaturated aldehydes, a reaction with excellent results.[11] In the context of an ongoing research program in our group, devoted to the development of new asymmetric methodologies based on organocatalysis,[12] we are focused in uncovering new strategies that allow us to form C–C bonds in an enantioselective fashion. Based on the previous works of Nichols on the fluoromalonate addition to nitroalkenes catalyzed by chiral magnesium salts,[13] the addition of 2-fluoromalonates to enones catalyzed by phase transfer catalysts by Kim[14] and taking into account the recent reports of Wang and Lu[15] on the addition of 2-fluoroketoesters to nitrostyrenes catalyzed by *Cinchona* alkaloids, we turned our attention to the addition of 2-fluoromalonates to α,β-unsaturated aldehydes as an easy and versatile entry to interesting products for medicinal chemistry such as building blocks for drug synthesis, and fluoro-labeled natural products (Scheme 1).

In an initial catalyst screening, we ran the addition reaction of diethyl 2-fluoromalonate (**2**) to cinnamaldehyde (**1a**) in $CHCl_3$ and we used different commercially available secondary amines as catalysts (Table 1). Simple proline was able to catalyze the reaction although with low enantioselectivities (entry 1). The proline-derived diamine **II** gave only slightly better enantioselectivity (entry 2), and MacMillan first generation catalyst **IV** (entry 4) did not catalyze the reaction. Gratifyingly, when the diphenyl prolinol derivative **III** was used, the reaction was efficiently catalyzed, achieving full conversion after 3 days and affording the conjugate

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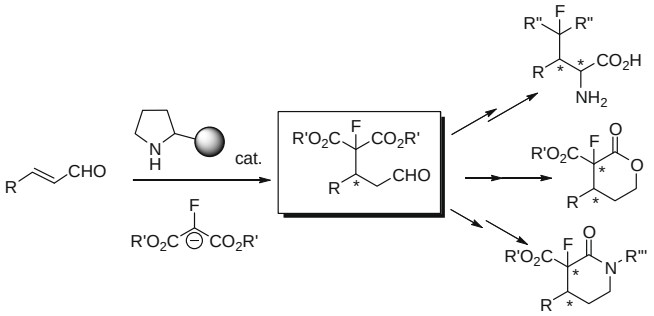
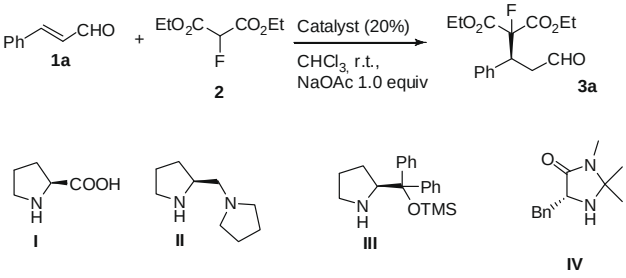


Scheme 1. Synthetic potential of the addition of 2-fluoromalonates to α,β-unsaturated aldehydes.

Table 1
Catalyst screening[a]



Entry	Catalyst	Time (d)	Conversion[b] (%)	ee[c] (%)
1	I	7	64	15
2	II	7	53	32
3	III	3	100	92
4	IV	7	Traces	n.d.

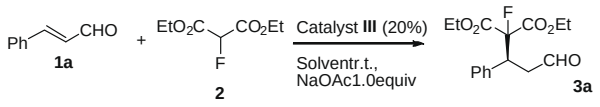
[a] Experimental conditions: a mixture of **1a–g** (0.5 mmol), catalyst III (20%), and **2a** (0.25 mmol) in $CHCl_3$ (1 mL) was stirred at rt for the time shown in the Table. After full conversion the crude product was purified by column chromatography.
[b] Isolated yield.
[c] Ee determined by chiral HPLC analysis.

addition product with a 92% ee. However, the reaction did not work without using stoichiometric amounts of a basic additive. Further optimization of the reaction conditions showed that the role of the base is crucial: 1 equiv of NaOAc produced the best results, while KOAc, Et_3N, or $NaHCO_3$ gave inferior conversions and/or enantioselectivities. When the amount of catalyst was decreased the reaction became extremely slow. We proceeded next to the optimization of the solvent, taking again the addition of diethyl 2-fluoromalonate (**2**) to cinnamaldehyde (**1a**) (Table 2) as a benchmark reaction.

Diphenylprolinol derivative **III** afforded the best results when the reaction was run in dichloromethane, achieving full conversion after 3 days and with 96% enantiomeric excess (entry 2). It should be noticed that the reaction works well in other solvents such as acetonitrile (entry 4), or methanol (entry 5). The use of dimethylformamide (entry 3) or of toluene (entry 6) led to a substantial lowering of the reaction rate.

Once we uncovered suitable reaction conditions for the enantioselective addition of diethyl 2-fluoromalonate to cinnamic aldehyde, we studied the scope of the process with different unsaturated aldehydes. The reaction did not work when aliphatic unsaturated aldehydes were used, probably due to their instability in the reaction conditions, but cinnamaldehyde derivatives gave excellent results as shown in Table 3.

Table 2
Conditions screening[a]

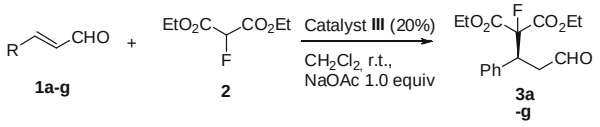


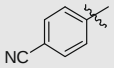
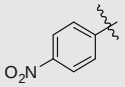
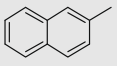
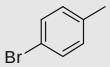
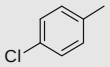
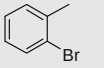
Entry	Solvent	Time (d)	Conversion[b] (%)	ee[c] (%)
1	$CHCl_3$	3	100	92
2	CH_2Cl_2	1	100	96
3	DMF	7	26	90
4	ACN	7	71	90
5	MeOH	7	58	88
6	Toluene	2	31	n.d.

[a] Experimental conditions: a mixture of **1a–g** (0.5 mmol), catalyst III (20%), and **2a** (0.25 mmol) in the selected solvent (1 mL) was stirred at rt for the time shown in the Table. After full conversion the crude product was purified by column chromatography.
[b] Isolated yield.
[c] Ee determined by chiral HPLC analysis.

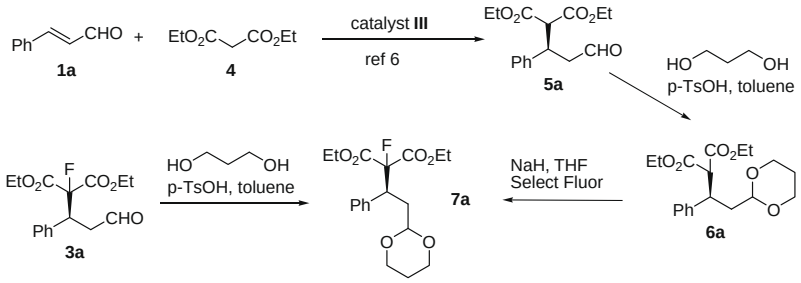
Gratifyingly, in all cases the 2-fluoromalonate addition took place with moderate to good yields and with high enantioselectivities. For example, when *para*-nitro cinnamaldehyde was used, the addition product was obtained with 69% yield and with 94% ee (entry 3). The reaction works well with cyanide (entry 2) or halogen substituents in the *para* position of the aromatic ring (entries 5 and 6). It is noteworthy that the reaction performs well when *ortho*-bromo cinnamaldehyde was used, affording the malonate

Table 3
Aldehyde scope[a]



Entry	Product	R	Time (d)	Yield[b] (%)	ee[c] (%)
1	**3a**		1	66	96
2	**3b**		3	68	93
3	**3c**		3	69	94
4	**3d**		4	39	94
5	**3e**		3	75	95
6	**3f**		3	73	94
7	**3g**		2	78	96

[a] Experimental conditions: A mixture of **1a–g** (0.5 mmol), catalyst III (20%), and 2a (0.25 mmol) in CH_2Cl_2(1 mL) was stirred at −40 °C for the time shown in the Table. After full conversion the crude product was purified by column chromatography.
[b] Isolated yield.
[c] Ee determined by chiral HPLC analysis.



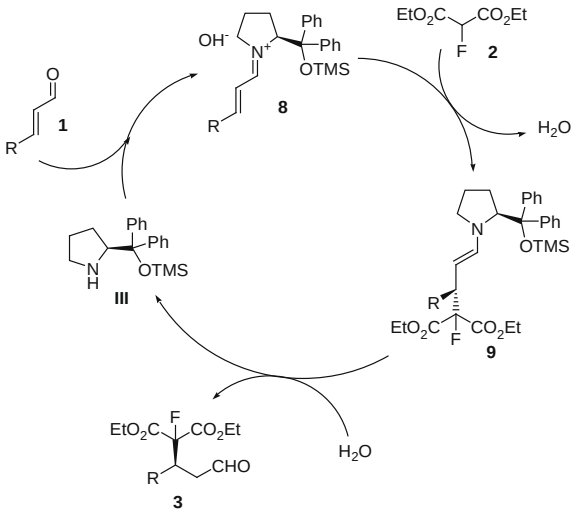
Scheme 2. Determination of absolute configuration.

product in 78% yield and 96% ee (entry 7). On the other hand, when the β-naphthyl derivative **3d** was used the yield of the reaction dropped dramatically probably due to steric interactions (entry 4).

The absolute configuration of adducts was ascertained by chemical correlation (Scheme 2). Following the procedure developed by Jørgensen and co-workers,[16] we prepared the highly enantiopure compound **5a**, with an (*R*) absolute configuration. After protection of the aldehyde in acetal form and fluorination by of the malonate moiety by treatment with sequential sodium hydride and Selectfluor® we obtained compound **7a** that exhibited essentially the same optical rotation ($[\alpha]_D^{25}$ +8.1 (*c* 1.0, $CHCl_3$) when compared to the cyclic acetal derived from **3a** ($[\alpha]_D^{25}$ +7.3 (*c* 1.2, $CHCl_3$). This indicates that the absolute configuration of this compound is also (*S*).

This stereochemical outcome is in accordance with the mechanism described for other organocatalytic Michael additions catalyzed by diphenylprolinol derivatives reported in the literature.[17] Thus, efficient shielding of the *si*-face of the chiral iminium intermediate **4** by the bulky aryl groups of chiral pyrrolidine **III** leads to stereoselective *re*-facial nucleophilic conjugate addition by 2-fluoromalonate, as shown in Scheme 3.

In summary, we have reported a highly enantioselective 2-fluoromalonate addition to aromatic α,β-unsaturated aldehydes.[18] The reaction is efficiently catalyzed by commercially available chiral pyrrolidine derivatives and gives the corresponding adducts with moderate to good yields and with excellent enantioselectivities. 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.



Scheme 3. Proposed mechanism and stereochemical outcome.

Acknowledgments

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18. Compound **3a**: Colorless oil. ^{1}H NMR (400 MHz. $CDCl_3$): δ (ppm) 9.56 (q, J = 1.5 Hz, 1H), 7.38–7.23 (m, 5H), 4.40–4.24 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.06–3.94 (m, 2H), 3.05 (ddd, J^1 = 1.5 Hz, J^2 = 9.9 Hz, J^3 = 17.2 Hz, 1H), 2.96 (ddd, J^1 = 1.5 Hz, J^2 = 5.2 Hz, J^3 = 17.2 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz. $CDCl_3$): δ (ppm) = 198.8, 165.5, 165.1, 164.8, 164.5, 136.4, 129.3, 129.3, 128.6, 128.1, 98.1, 95.4, 63.2, 62.5, 44.4, 43.7, 43.5, 36.9, 36.8, 13.9, 13.7.^{19}F NMR (282 MHz, CDCl3): δ (ppm) −174.2 (d, J = 5.2 Hz) $[\alpha]_D^{25}$ +14.7 (c 1.0, $CHCl_3$, 99% ee). HRMS (ESI): Calcd for $[C_{16}H_{19}FNaO_5]^+$: 333.1109; found: 333.1113. HPLC (Chiralpak® IC, 1 mL min^{-1}, hexanes:IPA 80:50, 220 nm): t_R = 5.9 min (minor), 7.1 min (major).