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Formal Highly Enantioselective Organocatalytic Addition of Fluoromethyl Anion to α,β-Unsaturated Aldehydes

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The selective introduction of fluorine (or of fluorine-bearing building blocks) into organic molecules and polymers can dramatically alter their physical, chemical and biological properties. Thus, the unique behavior exhibited by many organofluorinated synthetic compounds has fostered their use in life and materials sciences. Therefore, extensive studies have been carried out seeking new synthetic fluorination methodologies during the past 30 years.[1] The most common strategies rely on the use of electrophilic fluorine sources, that presently allow the highly regio- and stereocontrolled introduction of a fluorine atom in a variety of organic compounds.[2] On the other hand, nucleophilic fluoroalkylation, that involves the addition of a fluorinated carbanion to an electrophile, has become one of the most important and fast-growing fields in fluorine chemistry. In 2008, Hu and co-workers successfully accomplished the nucleophilic fluoroalkylation of α,β-enones, arynes, and activated alkynes with fluorinated sulfones in racemic form.[3] It is worth noting, however, that for α,β-unsaturated aldehydes such as cinnamaldehyde, only 1,2-addition products were obtained. In the same year, Prakash and Olah reported on the phosphine- or base-catalyzed Michael addition of α-substituted fluoro(phenylsulfonyl)methane derivatives to a variety of α,β-unsaturated compounds (again with the exception of α,β-unsaturated aldehydes).[4] The same authors had previously disclosed an enantiospecific monofluoromethylation of secondary alcohols by using a fluorocarbon nucleophile in a Mitsunobu reaction.[5] There are, however, very few asymmetric nucleophilic fluorination methods reported in literature. In 2006, Shibata et al. disclosed an elegant palladium-catalyzed allylic fluoromethylation with excellent yields and enantioselectivities;[6] the same group reported in 2007 the first enantioselective monofluoromethylation of *N*-Boc imines,[7] and, more recently, the first enantioselective fluoromethylation of enones using cinchona alkaloid derivatives as organocatalysts.[8,9] An organocatalytic asymmetric difluoromethylation of aromatic aldehydes has been described by Hu[10] with moderate enantioselectivities.

Therefore, the enantioselective Michael addition of fluoroalkyl pronucleophiles to α,β-unsaturated aldehydes (**1**) appeared as a worthy synthetic objective. Based in the previous works of Shibata[6–8] and others,[3,4] we hypothesized that fluorobis(phenylsulfonyl)methane (**2**) could be an excellent nucleophile, and that the use of iminium catalysis[11] would result in the exclusive formation of 1,4-addition products.[12] Moreover, the facility of removal of the phenylsulfonyl moiety[8] makes this reactant a perfect choice in order to carry out the future conversion of the resulting compounds (**3**) into attractive and interesting products for medicinal chemistry such as fluorinated building blocks, fluoro-labeled natural products as shown in Scheme 1.

Initially, we studied the nucleophilic addition of fluorobis(phenylsulfonyl)methane (**2**) to 2-heptenal (**1d**), catalyzed by TMS-protected diphenylprolinol (**VII**). In an initial solvent screening (Table 1), we found that the reaction renders the expected addition product in good conversions and enantioselectivities when toluene or CH_2Cl_2 were used (entries 1 and 2). On the other hand, when protic solvents such as methanol or 2,2,2-trifluoroethanol were tested no reaction was observed (entries 3 and 4). Furthermore, the addition of Cs_2CO_3 as additive increased the rate of the reaction, but the enantioselectivity decreased dramatically (entries 5 and 6).

Once we determined that toluene is a suitable solvent for the addition reaction, we screened different amines as catalysts (Table 2). The reaction is efficiently catalyzed by prolinol (**III**) or prolinamide (**IV**) (entries 3 and 4). When proline (**I**), diphenylprolinol (**II**) or cinchonidine (**VI**) were used, only traces of the product were detected after four

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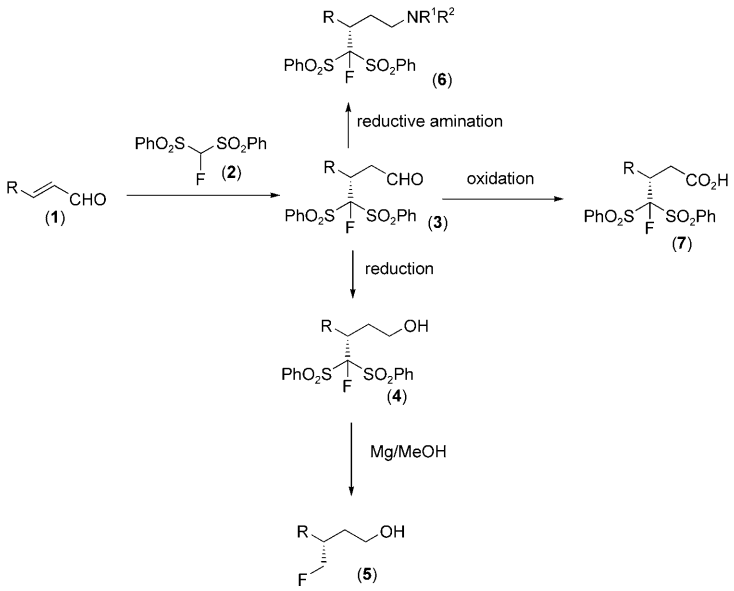
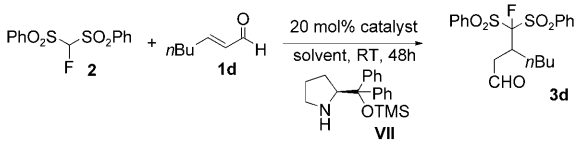


Scheme 1. Versatility of the present methodology.

Table 1. Solvent screening.[a]



Entry	Solvent	Conversion [%][b]	e.r.[c]
1	toluene	57	96:4
2	CH_2Cl_2	80	90:10
3	MeOH	traces	n.d.
4	CF_3CH_2OH	traces	n.d.
5[d]	toluene	100	57:43
6[d]	CH_2Cl_2	100	57:43

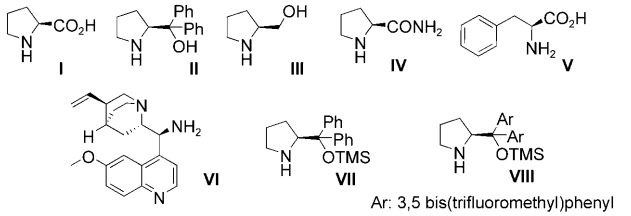
[a] In all cases, **2** (1 equiv) in solvent (1 mL) was added to a mixture of **1d** (1.5 equiv) and catalyst **VII** (0.2 equiv) at room temperature. [b] Determined by NMR. [c] Determined by chiral HPLC analysis. [d] 1 equiv of Cs_2CO_3 was added.

days (entries 1, 2 and 6, respectively). To our delight, when compounds **VII** and **VIII** were used, the reaction was efficiently catalyzed, showing high levels of enantioselectivity. Interestingly, we found a slight increase of enantioselectivities without appreciable loss of conversion at 4°C (entry 9). However, catalyst **VIII** showed very low conversion after four days. For this reason, we selected catalyst **VII** and toluene at 4°C as the best system for the monofluorination reaction.

With these optimized conditions already established, the scope of the reaction in terms of substrates was investigated next (Table 3). We found that the conditions used constitute a very general catalytic system for the asymmetric addition of fluorobis(phenylsulfonyl)methane (**2**) to a broad range of α,β-unsaturated aldehydes (**1a–j**) (Table 3).

The reaction takes place with excellent levels of enantioselectivity and high yields when aliphatic aldehydes are used

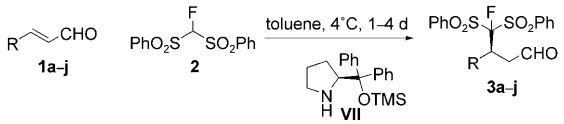
Table 2. Catalyst screening (see Table 1 for reaction scheme).[a]

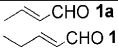
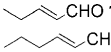
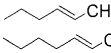
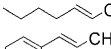
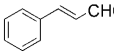
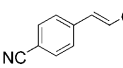
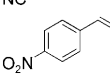
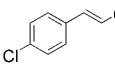
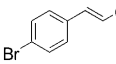
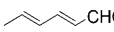


Entry	Catalyst	Conversion [%][b]	e.r.[c]
1	I	<10	51:49
2	II	traces	n.d.
3	III	83	84:16
4	IV	40	60:40
5	V	5	65:35
6	VI	traces	n.d.
7	VII	57	96:4
8	VIII	5	97:3
9[d]	VII	52	97:3

[a] In all cases, **2** (1 equiv) in toluene was added to a mixture of **1d** (1.5 equiv) and catalyst (**I–VIII**) at room temperature. [b] Determined by NMR. [c] Determined by chiral HPLC analysis. [d] Reaction run at 4°C.

Table 3. Catalyst screening.[a]



Entry	Aldehyde	Product	Yield [%][b]	e.r.[c]
1		**3a**	96	98:2
2		**3b**	87	97:3
3		**3c**	91	95:5
4		**3d**	93	96:4
5		**3e**	63	98:2
6		**3f**	77	98:2
7		**3g**	66	96:4[d]
8		**3h**	64	95:5
9		**3i**	73	95:5
10		**3j**	90	98:2

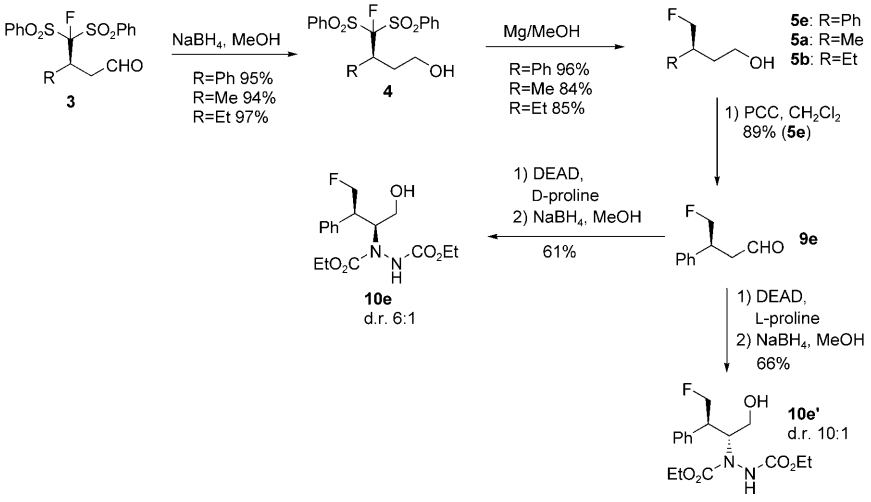
[a] In all cases, **2** (1 equiv) in toluene was added to a mixture of **1a–j** (1.5 equiv) and catalyst **VIII** (0.2 equiv) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] HPLC analysis of reduction product.

(entries 1, 2, 3 and 4), affording the desired adducts in up to 98:2 enantiomeric ratio. When aromatic aldehydes were used, the reaction became slower and the yields slightly decreased. When electron-withdrawing groups were placed in the aromatic ring, the reaction took place with good yields and enantioselectivities (entries 6 and 7); on the other hand, when Br or Cl where placed in the aromatic ring the yields were moderate and the enantioselectivities decreased to 95:5 e.r. (entries 8 and 9). Finally, it is noteworthy that the

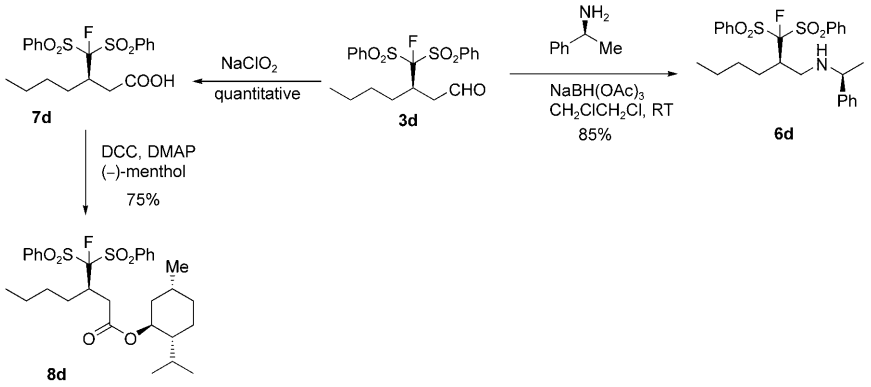
addition to dienal **1j** was completely regioselective (only β-addition product was observed), and took place with good yield and excellent enantioselectivity (entry 10).

With a range of enantiomerically enriched γ-fluoro-bisphenylsulfonyl aldehydes in hand, we were now in position to investigate the reductive desulfonylation of compounds **3** to complete the sequence of enantioselective monofluoromethylation.

In order to show the viability of this sequence, we chose compounds **3a**, **3b**, and **3e**; these compounds were reduced with sodium borohydride to afford the corresponding alcohols **4**, and then treated with Mg in methanol[6] for the removal of sulfonyl groups. We obtained compounds **5** in almost quantitative yield from the aldehydes **3** (Scheme 2).



Scheme 2. Synthesis of fluorinated alcohols.



Scheme 3. Synthetic applications of adducts **3**.

Moreover, we synthesized δ-fluoro-β-aminoalcohols in a few steps and, more important, in highly diastereo- and enantioselective fashion. Compound **5e** was oxidized by pyridinium chlorochromate in CH_2Cl_2, and the resulting aldehyde **9e** was α-aminated following the procedures described by Jorgensen[13] and List,[14] using proline and diethyl azodicarboxylate (DEAD). The resulting crude was reduced "in situ" to obtain the corresponding 4-fluoro-2-amino-1-hydroxy compounds (**10**). These compounds can be easily modified to obtain the free amino acid, or amino acid derivatives.[13,14]

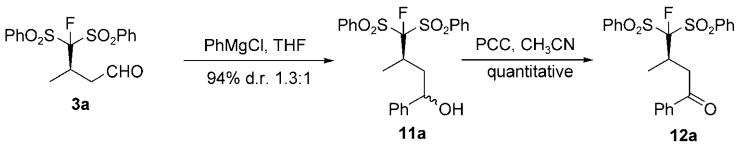
It is noteworthy that this amination methodology allows us to prepare with almost equal efficiently *anti* and *syn* amino alcohol derivatives (**10e** and **10e′**, respectively) simply by using D- or L- proline as the catalyst.

In order to expand the utility of the reaction, we decided to prepare more derivatives such as esters or amines. Compound **3d** was easily oxidized by known procedures to acid **7d** in quantitative yield; after treatment with dicyclohexylcarbodiimide (DCC) and (−)-menthol this acid afforded ester **8d** in moderate yield. Moreover, compound **3d** can be transformed to an amine derivative **6d** by reductive amination in good yield (Scheme 3).

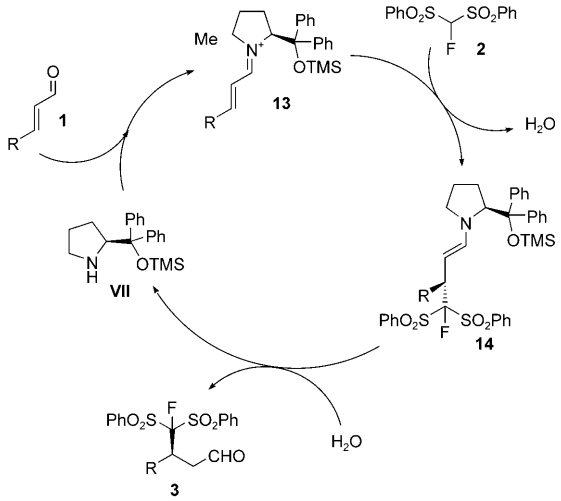
The absolute configuration of adducts was ascertained by chemical correlation. Thus, addition of phenylmagnesium chloride to aldehyde **3a** and subsequent oxidation gave compound **12a** as shown in Scheme 4. Comparison with the literature data[8] revealed that the absolute configuration of the known ketone **12a** is (2*R*) ($[\alpha]_D^{25} = +30.4$ (c = 1.2, $CHCl_3$), lit. (ref. [6]) ($[\alpha]_D^{25} = +24.1$ (c = 1.0, $CHCl_3$)).

The stereochemical outcome can be rationalized by the mechanistic proposal outlined in Scheme 5. Thus, efficient shielding of the *Re* face of the chiral iminium intermediate **13** by the bulky aryl groups of **VII** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon of **13**. This mechanism is in accordance with those proposed for other amine-catalyzed reactions between nucleophiles and enals.[15]

In conclusion, we have described the first organocatalytic enantioselective fluoro(bisphenylsulfonyl)methylation of α,β-unsaturated aldehydes in high yields and enantioselectivities. The resulting compounds were converted into a wide range of derivatives to show the applicability of this new methodology. Moreover, we synthesized valuable 4-fluoro-2-amino-1-alkanols that can be easily transformed to fluoroaminoacids or fluoroaminoalcohols by known procedures. Mechanistic studies, synthetic applications of this transformation as well as develop-



Scheme 4. Determination of absolute configuration.



Scheme 5. Proposed mechanism.

ment of fluorine-containing molecules synthesis based on this new methodology are ongoing in our laboratories and will be reported in due course.

Experimental Section

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **VII** (16 mg, 0.05 mmol) and toluene. Then, the solution was cooled to 4 °C and the α,β-unsaturated aldehyde **1a–j** (0.375 mmol) and fluorobis(phenylsulfonyl)methane (**2**; 78 mg, 0.25 mmol) were added. The stirring was maintained at 4 °C for 1–4 d until completion of the reaction (monitored by ^{1}H NMR) and then directly purified by flash chromatography to afford the products **3a–j**.

Compound 3a: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ = 1.52 (dd, J = 6.9, J' = 1.7 Hz, 3H), 3.19 (dd, J = 19.1, J' = 9.6 Hz, 1H), 3.44–3.37 (m, 1H), 3.73 (dd, J = 19.1, J' = 2.1 Hz, 1H), 7.73–7.66 (m, 6H), 8.00–7.98 (m, 2H), 8.09–8.05 (m, 2H), 9.88 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (d, J = 8.4 Hz), 31.4 (d, J = 18.7 Hz), 45.3 (d, J = 5.7 Hz), 116.0 (d, J = 256 Hz), 128.9, 129.0, 131.0, 135.2, 135.3,198.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −134.7 ppm; HRMS: m/z: calcd for $[C_{17}H_{17}FO_5S_2Na]^+$: 407.0394; found: 407.0391; $[\alpha]_D^{25} = -65$ (c = 0.5, $CHCl_3$, 96% *ee*); HPLC: Chiralpack IA hexane/isopropanol 90:10, 1 mL min^{-1}, t_R = 42 and 45 min.

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Keywords: enantioselectivity · fluorine · organocatalysis · nucleophilic addition · stereoselectivity

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