Catalytic enantioselective conjugate addition of fluorobis(phenylsulfonyl)methane to enals: synthesis of chiral monofluoromethyl compounds†

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Received (in College Park, MD, USA) 14th April 2009, Accepted 22nd June 2009
First published as an Advance Article on the web 13th July 2009
DOI: 10.1039/b907399j

A new highly catalytic enantioselective Michael addition of fluorobis(phenylsulfonyl)methane to α,β-unsaturated aldehydes has been developed for the preparation of chiral monofluoromethyl compounds under mild reaction conditions.

Conjugate addition is one of the cornerstones of organic synthesis and is widely used in C–C bond-forming reactions.[1–4] Significant progress has been made recently in the utilization of reactive stabilized carbanions, such as nitroalkanes, malonate esters, ketoesters, 1,3-diketones, nitroesters, 1,3-dinitriles and indoles, as Michael donors in organocatalyzed asymmetric conjugate addition reactions.[2–4] In expanding the scope of this powerful process, it is imperative to explore new Michael donors and receptors, thus products with new functionalities can be introduced. It has been realized that the development of catalytic enantioselective conjugate addition processes using bis(phenylsulfonyl)-methane (BSM) and fluorobis(phenylsulfonyl) methane (FBSM)[5] as nucleophiles remains a significant challenge, despite their broad synthetic utilities. They can be readily converted into their respective methyl and fluorinated methyl groups,[6] which are important motifs found in a large collection of natural products and biologically-interesting compounds.[7] To the best of our knowledge, only a single organocatalytic study using a chiral phase transfer catalyst to promote the enantioselective conjugate addition of FBSM to enones has been reported by Shibata and co-workers.[6c,8] However, the strategy cannot be applied to enals due to the greater susceptibility of α,β-unsaturated aldehydes to undergo 1,2-addition under the strong basic reaction conditions.

In this Communication, we wish to describe an unprecedented organocatalytic enantioselective Michael addition of FBSM to α,β-unsaturated aldehydes. The process is efficiently catalyzed by a simple chiral diphenylprolinol TBS ether with high levels of enantioselectivity (86 → 99% ee) under mild reaction conditions. Furthermore, significantly, this reaction provides a uniquely valuable approach to the enantioselective synthesis of synthetically- and biologically-important chiral fluoromethyl compounds that are not accessible by existing organocatalytic asymmetric Michael reactions.[9]

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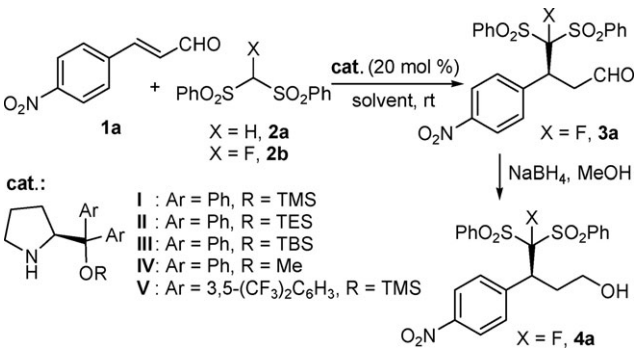
† Electronic supplementary information (ESI) available: Experimental and NMR data. CCDC 717019. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b907399j

In light of the high efficiency of diarylprolinol silyl ethers[10] in promoting Michael reactions between α,β-unsaturated aldehydes and nucleophiles without 1,2-addition side reactions, we decided to choose this class of catalysts for the conjugate addition of bis(phenylsulfonyl)methane (**2a**) and FBSM (**2b**) to α,β-unsaturated aldehydes (Table 1). In exploratory studies, a Michael reaction of 4-nitrocinnamaldehyde (**1a**) with BSM (**2a**) and FBSM (**2b**) was carried out in the presence of 20 mol% **I** at rt in CH_2Cl_2 for 24 h. No reaction occurred with **2a**, presumably due to its low reactivity (Table 1, entry 1). However, the reaction with **2b** proceeded to give the desired product, **4a**, in 53% yield, but with a low ee

Table 1 Optimization of the organocatalytic asymmetric Michael addition of **1a** to **2**[a]



Entry	Cat.	Additive	Solvent	*t*/h	Yield (%)[b]	ee (%)[c]
1[d]	**I**	None	CH_2Cl_2	24	<5	ND[e]
2	**I**	None	CH_2Cl_2	24	53	35
3	**I**	None	Et_2O	24	36	70
4	**I**	None	Toluene	24	65	81
5	**I**	None	DMSO	24	28	43
6	**II**	None	Toluene	24	44	84
7	**III**	None	Toluene	24	46	90
8[f]	**III**	$PhCO_2H$	Toluene	50	85	88
9[f]	**III**	$LiOAc·H_2O$	Toluene	52	71	91
10[f]	**III**	Na_2CO_3	Toluene	75	56	90
11[fg]	**III**	$PhCO_2H$	Toluene	72	83	99
12[fg]	**III**	$LiOAc·H_2O$	Toluene	96	40	95
13	**IV**	None	Toluene	24	40	64
14	**V**	None	Toluene	24	0	ND[e]

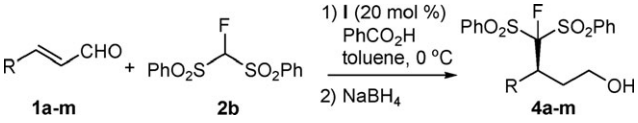
[a] Reaction conditions unless specified: a mixture of **1a** (0.10 mmol), **2b** (0.10 mmol) and catalyst (0.02 mmol) in solvent (0.8 mL) was stirred at rt for a specified time. After purification, product **3a** was reduced by $NaBH_4$ to **4a** for HPLC analysis. [b] Isolated yields based on 2 steps. [c] Determined by chiral HPLC analysis (Chiralpak OD-H). [d] **2a** was used. [e] ND = not determined. [f] 0.15 mmol of **1a** used. [g] At 0 °C.

(35%) (Table 1, entry 2). It seems that **2b** is more nucleophilic than that **2a** due to the electron-withdrawing fluorine, which renders it more prone to deprotonation under nearly neutral conditions. It is noteworthy that the reduction of aldehyde **3a** to alcohol **4a** was necessary for easy chiral HPLC analysis. An investigation of the reaction medium revealed that the polarity of the solvent had a pronounced effect on the yield and/or enantioselectivity. Highly polar solvents, such as DMSO, gave a low yield and a low ee value (Table 1, entry 5). Among the solvents probed, the best result was achieved when toluene was used (65% yield and 81% ee) (Table 1, entry 4), indicating that less polar solvents render **2b** more active due to lower levels of solvation. A survey of the catalysts revealed that ether moieties had a noticeable influence on the enantioselectivity and yield (Table 1, entries 4, 6, 7, 13 and 14). The bulky TBDMS catalyst, **III**, significantly enhanced the enantioselectivity of the reaction (90% ee), but with a low yield (46%; Table 1, entry 7). For other the catalysts probed, **IV** gave a lower ee, and no reaction occurred with **V**. Accordingly, catalyst **III** was selected for further optimization of the reaction. It was found that product **3a** had a high tendency to undergo a retro-Michael reaction. Accordingly, an excess of **1a** (1.5 equiv.) was used to significantly improve reaction yields (Table 1, entries 8–12). The effect of additives to the toluene solvent on the enantioselectivity was also probed. Both $PhCO_2H$ and $LiOAc{\cdot}2H_2O$ increased yields without sacrificing enantioselectivity (Table 1, entries 8 and 9). It is believed that the reaction rate is enhanced due to the facilitation of iminium formation from the enal by the catalyst in the presence of $PhCO_2H$. It also reasonably assumed that the rate was increased by $LiOAc{\cdot}2H_2O$ owing to either the favorable formation of the iminium ion or the speeding up of the deprotonation of FBSM. To determine its role, a stronger base, Na_2CO_3, was used (Table 1, entry 10). It was found that the reaction slowed down significantly under the same reaction conditions. These studies indicate that the formation of the iminium species is critical to the process. Finally, lowering the temperature to 0 °C led to a further increase in the enantioselectivity of the product (99% for $PhCO_2H$: Table 1, entry 11; 95% for $LiOAc{\cdot}2H_2O$: Table 1 entry 12). However, a dramatic drop in yield with $LiOAc{\cdot}2H_2O$ was seen (40%; Table 1, entry 12).

With the optimal reaction conditions in hand, we next probed the generality of this asymmetric Michael addition reaction with a wide range of α,β-unsaturated aldehydes. Again, an excess of **1** (ranging from 1.5 to 5.0 equiv.) was used in the reactions, and aldehydes **3** were reduced to alcohols **4** for convenient chiral HPLC analysis. As revealed in Table 2, the conjugate addition processes were tolerant of Michael acceptors **1** with significant structural variations. Remarkably, the aromatic moieties bearing electron-withdrawing (Table 2, entries 1–6), -neutral (Table 2, entries 7 and 8) and -donating (Table 2, entry 9) substituents on the enals could efficiently participate in the process with high efficiency. Furthermore, a similar trend was observed with heteroaromatic (Table 2, entry 10), alkenyl (Table 2, entry 11) and alkyl (Table 2, entries 12–14) enals. It was noted that when alkyl α,β-unsaturated aldehyde **1m** was investigated in the Michael reaction under the same reaction conditions in the presence of catalyst **III**, the process proceeded very slowly and gave only a 17% yield after 96 h, despite an excellent level of enantioselectivity (Table 2, entry 13). However, the change of catalyst from **III** to **I** in the absence of $PhCO_2H$ led to a significant enhancement in reactivity of the reaction with a high yield (81%) and a high enantioselectivity (92% ee) (Table 2, entries 13 *vs.* 14). The absolute stereoconfiguration of the Michael adducts was determined by single-crystal X-ray analysis based on enone **5** derived from aldehyde **3a**, through a Wittig reaction with $Ph_3P{=}CHCO_2Et$ (Fig. 1).[11]

As demonstrated, Michael adduct-derived alcohol **4g** can be conveniently converted into its respective monofluoromethylated compound **6** by reductive removal of the phenylsulfonyl group using activated Mg in MeOH in high yield and without racemization (Scheme 1).[6c]

Table 2 The scope of **III**-promoted Michael reactions of α,β-unsaturated aldehydes with FBSM[a]



1a-m 2b 4a-m

Entry	R	Equiv. **1**	*t*/h	Yield (%)[b]	ee (%)[c]
1	4-$NO_2C_6H_4$ (**1a**)	1.5	72	83	99
2	4-CNC_6H_4 (**1b**)	1.5	67	72	99
3	4-BrC_6H_4 (**1c**)	3.0	72	81	>99
4	4-$CF_3C_6H_4$ (**1d**)	3.0	70	80	>99
5	3-$NO_2C_6H_4$ (**1e**)	2.0	59	75	97
6	2-FC_6H_4 (**1f**)	2.4	70	74	>99
7	C_6H_5 (**1g**)	5.0	72	71	>99
8	2-Naphthyl (**1h**)	2.0	73	42	96
9[d]	4-$MeOC_6H_4$ (**1i**)	5.0	76	71	92
10	2-Furanyl(**1j**)	5.0	58	79	86
11	*trans*-PhCH=CH (**1k**)	3.0	45	77	93
12	Me (**1l**)	5.0	48	66	94
13	*n*-Pr (**1m**)	5.0	96	17	98
14[e]	*n*-Pr (**1m**)	5.0	79	81	92

[a] Reaction conditions unless specified: a mixture of **1** (0.10 mmol), **2b** (0.10 mmol) and catalyst (0.02 mmol) in solvent (0.8 mL) was stirred at rt for a specified time. After purification, product **3** was reduced by $NaBH_4$ to **4** for HPLC analysis. [b] Isolated yields based on 2 steps. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, AD or Chiralcel OD-H). [d] One equiv. of $PhCO_2H$ (0.10 mmol) and an additional 0.2 mL of hexane were employed. [e] Catalyst **I** was used and no $PhCO_2H$ was added.

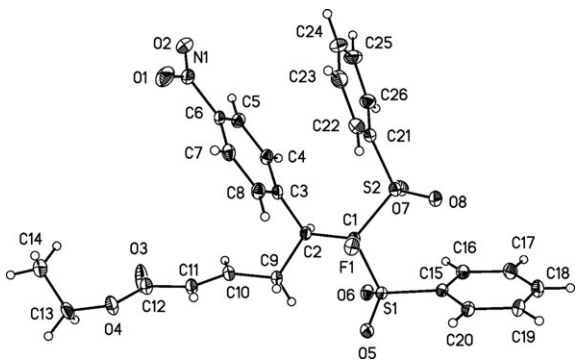
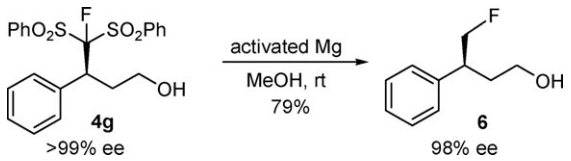


Fig. 1 The single-crystal X-ray structure of compound **5** (non-disordered view of one of two molecules; all thermal ellipsoids at a 20% probability).



Scheme 1 The transformation of **4g** into chiral monofluromethyl compound **6**.

Nowadays, the incorporation of fluorine atom(s) into bioactive molecules to improve their physiochemical and biological properties has become general practice in drug design.[12] Motivated by the broad utilities of chiral monofluoromethyl compounds in organic synthesis and medicinal chemistry, and the lack of catalytic asymmetric methods for their preparation, we have developed a novel organocatalytic asymmetric Michael addition approach to these structures that offers high enantiomeric excesses. This transformation is efficiently carried out in the presence of a simple chiral diarylprolinol TBS ether catalyst under mild reaction conditions. The significance of the methodology is highlighted by the fact that the iminium catalysis strategy employed here for enals is different from the chiral phase transfer protocol developed by Shibata co-workers, which can only be applied to enones.[6c] Furthermore, the more synthetically-versatile aldehyde adducts have more broad synthetic applications, such as oxidation to carboxylic acids, reductive aminations, aldol reactions, *etc*., than ketones, that will constitute our future endeavours.

Financial support for this work provided by the NSF (CHE-0704015) is gratefully acknowledged. Thanks are expressed to Dr Elieen N. Duesler for performing the X-ray crystallographic analysis. The Bruker X8 X-ray diffractometer was purchased *via* an NSF CRIF:MU award to the University of New Mexico, CHE-0443580.

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