Tetrahedron Letters 50 (2009) 4896–4898

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective conjugate addition of fluorobis(phenylsulfonyl)methane to α,β-unsaturated ketones catalyzed by chiral bifunctional organocatalysts

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ARTICLE INFO

Article history:
Received 7 May 2009
Revised 10 June 2009
Accepted 11 June 2009
Available online 14 June 2009

Keywords:
Bifunctional organocatalyst
Asymmetric catalysis
Michael reaction
Fluorobis(phenylsulfonyl)methane
Fluoromethylation

ABSTRACT

The catalytic enantioselective conjugate addition reaction of fluorobis(phenylsulfonyl)methane to α,β-unsaturated ketones promoted by chiral bifunctional organocatalysts is described. The treatment of fluorobis(phenylsulfonyl)methane to α,β-unsaturated ketones under mild reaction conditions afforded the corresponding Michael adducts with high enantioselectivity. The conjugate addition adducts are useful for the synthesis of chiral monofluoromethylated compounds.

1. Introduction

Fluorine-containing compounds are of importance in organic synthesis because of their use as medicines and agrochemicals and in fundamental studies of biochemical and metabolic processes.[1] Strategic fluorination is commonly used in medicinal chemistry to improve the metabolic property and bioavailability.[2] Enantiopure fluorine-containing organic molecules are interesting and important materials with uses in analytical, biological, and medicinal chemistry and also in the chemistry of polymers and materials.[3]

Among various strategies, electrophilic fluorination of active methines and C–C bond formation of fluorocarbon nucleophiles are two typical approaches for the construction of single fluorine-containing molecules, and their asymmetric versions are particularly attractive. Enantioselective electrophilic fluorination has been achieved with the aid of electrophilic fluorinating agents using chiral transition-metal catalysts and organocatalysts with excellent enantioselectivities.[4,5] On the other hand, the use of fluorinated active methine nucleophiles such as fluoromalonate,[6] α-fluoro-β-ketoesters,[7] and fluorobis(phenylsulfonyl)methane[8] for a catalytic asymmetric reaction has become increasingly popular. Shibata et al. have developed elegant catalytic enantioselective allylic alkylation,[8a] Mannich-type reaction of imines,[8b] and Michael addition to α,β-unsaturated ketones[8c] using nucleophilic fluorobis(phenylsulfonyl)methane (FBSM) as a synthetic equivalent of monofluoromethane. Hu's group disclosed asymmetric monofluoromethyl fluorination using chiral auxiliary.[9] Prakash et al. achieved highly stereoselective monofluoromethylation of secondary alcohols in a Mitsunobu reaction using FBSM.[10a]

The Michael addition reaction is widely recognized as one of the most general and versatile methods for the formation of C–C bonds in organic synthesis,[11] and the development of enantioselective catalytic protocols for this reaction has been the subject of intensive research.[12] Although a number of catalytic enantioselective Michael additions of active methines to α,β-unsaturated ketones have reported, up to now there is one example of these reactions with FBSM using chiral phase-transfer catalysts in the presence of inorganic base.[8c] However, an enantioselective conjugate addition of FBSM to α,β-unsaturated ketones catalyzed by chiral primary amine organocatalysts remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under mild conditions, it could provide a highly attractive, convergent approach toward optically active β-monofluoromethylated ketones. Recently, chiral primary amines have emerged as new and powerful catalysts for enantioselective organocatalytic reactions.[13]

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[14] we recently reported asymmetric conjugate addition reaction of active methines including fluoromolates and α-fluoro-β-ketoesters.[6a,7c] Herein, we wish to describe the enantioselective asymmetric conjugate addition of commercially available nucleophilic FBSM to α,β-unsaturated ketones promoted by bifunctional organocatalysts. The reaction affords the products

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doi:10.1016/j.tetlet.2009.06.056

with forming a fluorine-containing quaternary carbon center and an adjacent chiral carbon center with an excellent level of enantioselectivity and in high yields. Moreover, the products resulted from a conjugate addition reaction will generate chiral β-monofluoromethylated ketones, which can be conveniently elaborated in organic synthesis.

Validation of the feasibility of the proposed Michael addition process started by evaluating a model reaction between FBSM (**2**) with (*E*)-4-phenylbut-3-en-2-one (**1a**) in the presence of 10 mol % bifunctional catalysts (Fig. 1) in co-solvent of dichloromethane/MeOH (9:1) at room temperature. As shown in Table 1, while chiral primary amine organocatalyst **I** bearing both central and axial chiral elements effectively promoted the addition in high yield but with no enantioselectivity (entry 1), 9-amino-9-deoxy-epicinchona alkaloids (**III**–**VIII**) gave enhanced ee values (entries 3–8). The best result has been obtained with 9-amino-9-deoxyepiquinine (**IV**). Based on the exploratory studies, we decided to select catalyst **IV** for further optimization of reaction conditions. A survey of the reaction media indicated that many common solvents, such as dichloromethane/MeOH (9:1) (entry 4), DMSO, DMF, dichloroethane, 1,4-dioxane, MTBE, and diethyl ether (entries 9–14), were well tolerated in this conjugate addition reaction with good to excellent enantioselectivities. Among the solvents probed, the best results (87% yield and 91% ee) were achieved when the reaction was conducted in MTBE (entry 13). We examined our investigations by examining the reactivity and selectivity with organocatalyst **IV** in the presence of different acids and bases as additives (entries 15–20). In the presence of base, the reaction yield was improved but selectivity was decreased slightly, presumably because base may enhance the nucleophilicity of deprotonated FBSM.

With optimal reaction conditions in hand, we then carried on evaluating the generality of this protocol. The results of a representative selection of α,β-unsaturated ketones for the conjugate addition reaction are summarized in Table 2. As demonstrated, organocatalyst **IV** catalyzed Michael addition of FBSM (**2**) to α,β-unsaturated ketones **1** proved to be a general approach for the synthesis of versatile chiral monofluorinated ketones **3** with structural variation of the α,β-unsaturated ketones.[15] Notably, good to high enantiomeric excess was obtained (80–93% ee). The α,β-unsaturated ketones bearing substituted aryl, naphthyl, and alkyl group in β-position could effectively participate in the process (entries 1–6). Furthermore, cyclic systems were also effective substrates for the process (entries 7 and 8). Unfortunately, the reaction of FBSM to chalcone was not preceded in these reaction conditions.

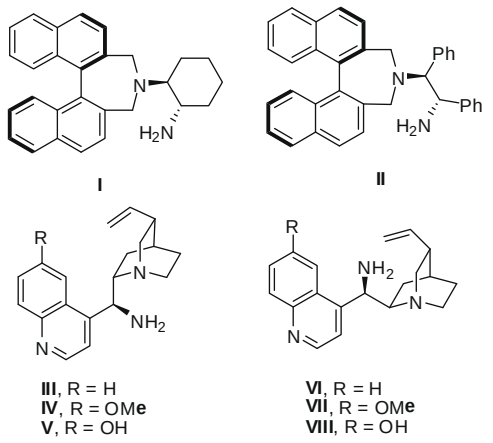
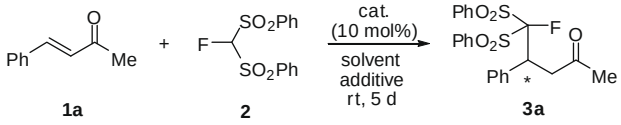


Figure 1. Structure of chiral primary amine catalysts.

Table 1
Optimization of the reaction conditions

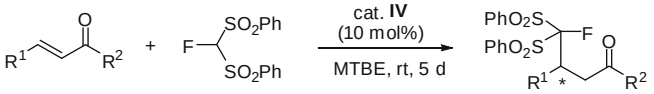


1a **2** **3a**

Entry	Cat.	Additive	Solvent	Yield[a] (%)	ee[b] (%)
1	**I**	—	CH_2Cl_2/MeOH (9:1)	82	9
2	**II**	—	CH_2Cl_2/MeOH (9:1)	79	5
3	**III**	—	CH_2Cl_2/MeOH (9:1)	90	78
4	**IV**	—	CH_2Cl_2/MeOH (9:1)	92	84
5	**V**	—	CH_2Cl_2/MeOH (9:1)	85	84
6	**VI**	—	CH_2Cl_2/MeOH (9:1)	80	−65
7	**VII**	—	CH_2Cl_2/MeOH (9:1)	80	−70
8	**VIII**	—	CH_2Cl_2/MeOH (9:1)	86	−63
9	**IV**	—	DMSO	93	87
10	**IV**	—	DMF	93	79
11	**IV**	—	$Cl(CH_2)_2Cl$	87	90
12	**IV**	—	1,4-Dioxane	90	80
13	**IV**	—	MTBE	87	91
14	**IV**	—	Et_2O	87	90
15[c]	**IV**	$C_6H_5CO_2H$	CH_2Cl_2	70	88
16[c]	**IV**	4-NO_2–$C_6H_4CO_2H$	CH_2Cl_2	72	85
17[c]	**IV**	HCO_2H	CH_2Cl_2	65	23
18[d]	**IV**	NaOAc	CH_2Cl_2/MeOH (9:1)	92	84
19[d]	**IV**	$C_6H_5CO_2Na$	CH_2Cl_2/MeOH (9:1)	92	60
20[d]	**IV**	LiOAc	CH_2Cl_2/MeOH (9:1)	94	62

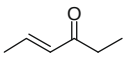
[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using a Chiralpak AS column.
[c] 20 mol % of additive was used.
[d] 10 mol % of additive was used.

Table 2
Enantioselective conjugate addition of FBSM to α,β-unsaturated ketones

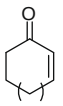


1 **2** **3**

1a, R^1 = Ph, R^2 = Me
1b, R^1 = *p*-Me-C_6H_4, R^2 = Me
1c, R^1 = *p*-MeO-C_6H_4, R^2 = Me
1d, R^1 = *p*-F-C_6H_4, R^2 = Me
1e, R^1 = 1-naphthyl, R^2 = Me



1f

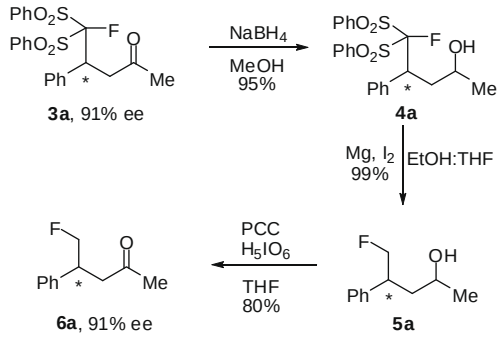


1g, n=1
1h, n=0

Entry	1	Yield[a] (%)	ee[b] (%)
1	**1a**	**3a**, 87	91
2	**1b**	**3b**, 90	90
3	**1c**	**3c**, 92	93
4	**1d**	**3d**, 90	86
5	**1e**	**3e**, 85	86
6	**1f**	**3f**, 85	80
7	**1g**	**3g**, 93	89
8	**1h**	**3h**, 87	86

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using chiral columns (Chiralpak AS for **3a**, AD-H for **3b–c, 3e–f**, and Chiralcel OD-H for **3d** and **3g–h**).

The conjugate addition adduct **3a** can be readily converted into the corresponding monofluoromethylated ketone **6a** by a sequence of steps (reduction of the carbonyl group, reductive desulfonation, and oxidation of the hydroxyl group) without racemization (Scheme 1).



Scheme 1. Conversion of 1,4-addition adduct **3a** into monofluoromethylated ketone **6a**.

In conclusion, we have developed organocatalytic enantioselective conjugate addition reaction of FBSM (**2**) to α,β-unsaturated ketones **1** to afford synthetically useful chiral monofluoromethylated ketones. The process is efficiently catalyzed by a simple cinchona alkaloid derivative. The significance of the approach is highlighted by its capability to introduce a monofluorine-containing quaternary carbon center and an adjacent chiral carbon center with high enantioselectivity and yields under mild reaction conditions. In principle, the strategy we have described can be extended to other fluorinated stabilized carbanions as well. Further details and application of this asymmetric Michael addition of fluorocarbon nucleophiles will be presented in due course.

Acknowledgment

This research was supported by Korea Research Foundation Grant founded by the Korean Government (MEST, Basic Research Promotion Fund) (KRF-2009-0071779).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.056.

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15. General procedure for asymmetric conjugate addition of FBSM (**2**) to α,β-unsaturated ketones **1**: To a stirred mixture of FBSM (**2**, 113.1 mg, 0.36 mmol) and 9-amino-9-deoxyepiquinine (**IV**, 9.7 mg, 0.03 mmol) in MTBE (0.6 mL) were added α,β-unsaturated ketones **1** (0.3 mmol) at room temperature. After being stirred for 5 d, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford desired product **3**.Compound **3a**: $[\alpha]_D^{25} = -130.1$ (*c* 0.25, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ = 2.20 (s, 3H), 3.88–3.93 (m, 2H), 4.52–4.60 (m, 1H), 7.00–7.05 (m, 2H), 7.14–7.18 (m, 3H), 7.42–7.50 (m, 2H), 7.57–7.69 (m, 3H), 7.75–7.82 (m, 3H), 7.88–7.93 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 30.4, 42.1, 43.0 (d, *J* = 19.3 Hz), 115.0 (d, *J* = 264.5 Hz), 127.9, 128.0, 128.4, 129.2, 130.5, 131.1, 131.3, 133.6 (d, *J* = 4.6 Hz), 134.0, 134.9, 135.4, 136.3, 208.0; ESI-HRMS: *m/z* calcd for $C_{23}H_{22}FO_5S_2$ $[M+H]^+$: 461.0893; found: 461.0889; Chiralpak AS, *n*-hexane/2-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm, t_R = 21.6 min (minor), t_R = 24.1 min (major), 91% ee.