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Communications

Asymmetric Conjugate Addition of 1-Fluoro-1-nitro(phenylsulfonyl)methane to Chalcones Catalyzed by Binaphthyl-Derived Organocatalyst

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Chiral organofluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal applications and material science.[1] Among various strategies, electrophilic fluorination[2] of active methines and C-C bond formation[3] of fluorocarbon nucleophiles are two typical approaches for the synthesis of fluorine-containing molecules. Particularly, asymmetric catalytic synthesis of chiral fluorinated compounds has received a great deal of attention in recent years. The use of fluorinated active methine nucleophiles such as fluoromalonate,[4] α-fluoro-β-ketoesters,[5] fluorobis(phenylsulfonyl)methane,[6] and 1-fluoro-1-nitro(phenylsulfonyl)methane (FNSM)[7] for a catalytic asymmetric reaction has become increasingly popular. Recently, several groups have developed elegant catalytic conjugate addition to α,β-unsaturated carbonyl compounds[7a-b] and Mannich-type reaction of imines[7c] using nucleophilic FNSM. 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 Michael-type reaction of FNSM to chalcones using cinchona-derived organocatalysts.[7a] The development of alternative reaction system for the enantioselective conjugate addition reaction of FNSM to chalcones would be highly desirable. Recently, we have introduced the binaphthyl-modified organocatalysts for the asymmetric conjugate addition and Mannich reactions of active methines.[8] We envisioned that the assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with a H-bonding motif could activate the conjugate addition of FNSM to chalcones.

As part of our continuing efforts for the enantioselective construction of stereogenic carbon centers,[9] we recently reported asymmetric conjugate addition reaction of active methines including fluoromalonates,[4] α-fluoro-β-ketoesters,[5b] and fluorobis(phenylsulfonyl)methane.[6b] Herein, we wish to describe the enantioselective asymmetric conjugate addition of FNSM to chalcones promoted by binaphthyl-modified bifunctional organocatalysts (Fig. 1).

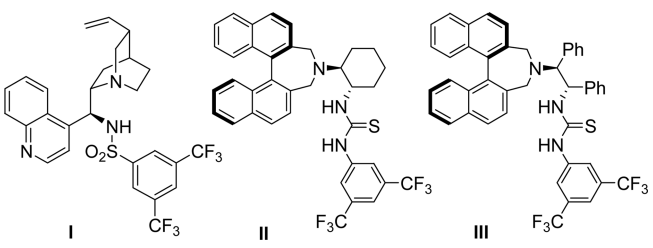
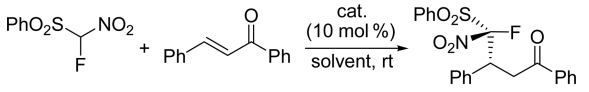


Figure 1. Structure of chiral bifunctional organocatalysts.

To determine the optimum reaction conditions, we initially investigated the reaction between FNSM (**1**) with chalcone (**2a**) in the presence of 10 mol % cinchonidine-derived bifunctional organocatalyst **I** in toluene at room temperature. This reaction exhibited good yield and low enantioselectivity (Table 1, entry 1). While binaphthyl-modified chiral bifunctional organocatalysts **II-III** bearing both central and axial chiral elements effectively promoted the addition reaction in high yield with high enantioselectivity (63-91% ee, entries 2-3). Based on the exploratory studies, we decided to select catalyst **II** for further optimization of reaction conditions. A survey of the reaction media indicated that many common solvents, such as dichloromethane, MeOH, and xylene (entries 2 and 4-6), were well tolerated in this conjugate addition reaction with good to excellent

Table 1. Optimization of the reaction conditions

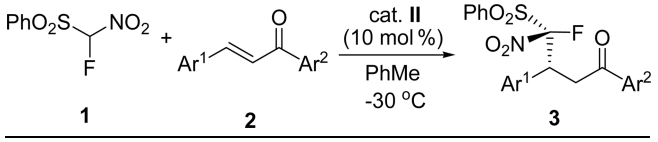


1 **2a** **3a**

Entry	Cat.	Solvent	Time (d)	Yield (%)[a]	dr (%)[b]	ee (%)[c]
1	**I**	toluene	3	90	2.3:1	45
2	**II**	toluene	3	92	3.2:1	91
3	**III**	toluene	3	63	5.2:1	63
4	**II**	CH_2Cl_2	2	82	2:1	93
5	**II**	MeOH	2	80	2:1	70
6	**II**	*p*-xylene	3	91	2:1	90
7[d]	**II**	toluene	4	92	3:1	95
8[e]	**II**	toluene	5	90	4.5:1	98

[a]Isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c]Enantiopurity of major diastereomer was determined by HPLC analysis using chiralcel OD-H column. [d]This reaction was carried out at −15 °C. [e]This reaction was carried out at −30 °C.

Table 2. Enantioselective conjugate addition of FNSM (**1**) to chalcones **2**



1 **2** **3**

Entry	**2**, Ar^1, Ar^2	**3**, Yield (%)[a]	dr (%)[b]	ee (%)[c]
1	Ph, Ph	**3a**, 90	4.5:1	98
2	Ph, *p*-$MeOC_6H_4$	**3b**, 89	2.5:1	91
3	Ph, *p*-$CF_3C_6H_4$	**3c**, 94	3:1	98
4	Ph, *p*-$NO_2C_6H_4$	**3d**, 98	3.2:1	87
5	*p*-$MeOC_6H_4$, Ph	**3e**, 89	4.5:1	90
6	*p*-ClC_6H_4, Ph	**3f**, 84	6:1	92
7	*p*-$NO_2C_6H_4$, Ph	**3g**, 81	7:1	93

[a]Isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c]Enantiopurity of major diastereomer was determined by HPLC analysis using chiralcel OD-H (for **3a**, **3c**, **3d**, and **3f**), chiralpak AD-H (for **3b**, **3e**, and **3g**) columns.

enantioselectivities. Among the solvents probed, the best results (91% ee) were achieved when the reaction was conducted in toluene (entry 2). Lowering the temperature to −30 °C with catalyst **II** led to improve the enantioselectivity (98% ee, entry 8). The absolute configuration of Michael adduct **3a** has been determined by comparison of the chiral HPLC properties with literature values.[7a]

With optimal reaction conditions in hand, we evaluated the generality of this protocol. As demonstrated in Table 2, organocatalyst **II** catalyzed Michael addition of FNSM (**1**) to chalcone derivatives **2** proved to be a general approach for the synthesis of versatile chiral monofluorinated ketones **3** with structural variation of the substituents of aryl group of chalcone derivatives.[10] Notably, high to excellent enantiomeric excess was obtained (87-98% ee).

We suppose that a carbonyl group of the chalcone (**2a**) is activated by the thiourea moiety of catalyst through hydrogen bonding, and the FNSM (**1**) is activated by the basic nitrogen atom in tertiary amine (Fig. 2). These interactions control the stereochemical outcome of the reaction and increase the reaction rate.

In conclusion, we have developed a highly enantioselective catalytic conjugate addition reaction of FNSM (**1**) to chalcone derivatives **2** using a binaphthyl-derived tertiary amine-thiourea organocatalyst. Further details and application of this asymmetric Michael addition of fluorocarbon nucleophiles will be presented in due course.

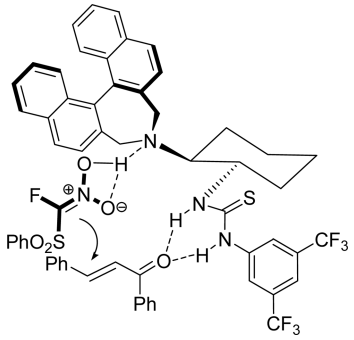


Figure 2. Proposed stereochemical model.

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10. **General procedure:** To a stirred mixture of chalcone **2** (0.2 mmol) and catalyst **II** (13.2 mg, 0.02 mmol) in toluene 0.8 mL was added FNSM (**1**, 87.6 mg, 0.4 mmol) at −30 °C. The reaction mixture was stirred for 5 d at −30 °C and concentrated. The residue was purified by column chromatography on silica gel to give the Michael adduct **3**. **(3*R*,4*R*) 4-Fluoro-4-nitro-1,3-diphenyl-4-(phenylsulfonyl)butan-1-one** (**3a**): Major diastereoisomer. $[\alpha]_D^{24}$ = 21.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84-7.79 (m, 2H), 7.67-7.59 (m, 1H), 7.55-7.51 (m, 3H), 7.43-7.36 (m, 4H), 7.31-7.25 (m, 2H), 7.24-7.13 (m, 3H), 5.10 (ddd, *J* = 26.7, 10.5, 2.7 Hz , 1H), 3.80 (dd, *J* = 17.5, 10.5 Hz, 1H), 3.37 (dd, *J* = 17.5, 2.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.0, 135.8, 135.4, 133.6, 132.6, 132.5, 130.5, 130.2, 129.1, 128.6, 127.9, 125.3 (*J* = 290.0 Hz), 43.8 (*J* = 16.8 Hz), 39.3; HRMS (ESI) calcd $C_{22}H_{19}FN_5S$ $[M+H]^+$: 428.0968; found 428.0965; HPLC (98:2 = *n*-hexane:*i*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OD-H column, t_R = 44.6 min (major), t_R = 38.4 (minor), 98% ee.