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Short communication

Highly enantioselective conjugate addition of fluoromalonates to nitroalkenes using bifunctional organocatalysts

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ABSTRACT

The enantioselective conjugate addition of fluoromalonates to aromatic nitroalkenes catalyzed by chiral amine-thiourea bifunctional organocatalysts generated a stereocenter at the carbon bearing the aromatic group and an adjacent prochiral center from the fluoromalonate. Treatment of fluoromalonates with aromatic nitroalkenes under mild reaction conditions afforded the corresponding 2-fluoro-2-(2-nitro-1-arylethyl)malonates with high yields (72–93%) and excellent enantioselectivities (91–98% ee).

1. Introduction

The chemistry of bioactive organofluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal application [1–4]. Introduction of fluorine atom into biologically active compounds often leads to improvement of their biological characteristics due to unique properties of the fluorine atom [5–7]. Chiral organofluorine compounds have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses [8,9]. The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C–C bonds in organic synthesis [10–12], and the development of enantioselective catalytic protocols for this reaction has been subject of intensive research [13,14]. In addition to the great success catalyzed by metal complexes, the powerful and environmentally friendly organocatalyst-mediated asymmetric Michael reaction has been explored intensively in recent years [15–21]. Michael reaction of nucleophiles to nitroalkenes represents a direct and most appealing approach to chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen, etc. [22–25]. Recently, several groups presented the catalytic asymmetric conjugate additions of active methine compounds to nitroalkenes in the presence of chiral metal complexes or organocatalysts [26–40]. To the our best knowledge, although catalytic enantioselective Michael additions of active methine compounds such as malonates [26–32], β-ketoesters [33–37], and 1,3-diketones [38–40] have reported, up to now there is one examples of these reactions with fluoromalonates using chiral Mg-box complex [42]. However, a highly enantioselective Michael addition of fluoromalonates to nitroalkenes remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under air- and moisture-tolerant conditions, it could provide a highly attractive, convergent approach toward optically active γ-nitro fluoromalonates [57].

2. Results and discussion

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers [41,43–50], we recently reported chiral amine-thiourea **I** (Fig. 1) to be a highly selective catalyst for the enantioselective amination of active methines [51,52]. We envision that the rigid binaphthyl structure can serve as an efficient stereocontrolling axial chiral element. In this communications, we wish to describe the direct asymmetric Michael reaction of fluoromalonates to nitroalkenes with catalyzed by environmentally benign bifunctional organocatalysts bearing

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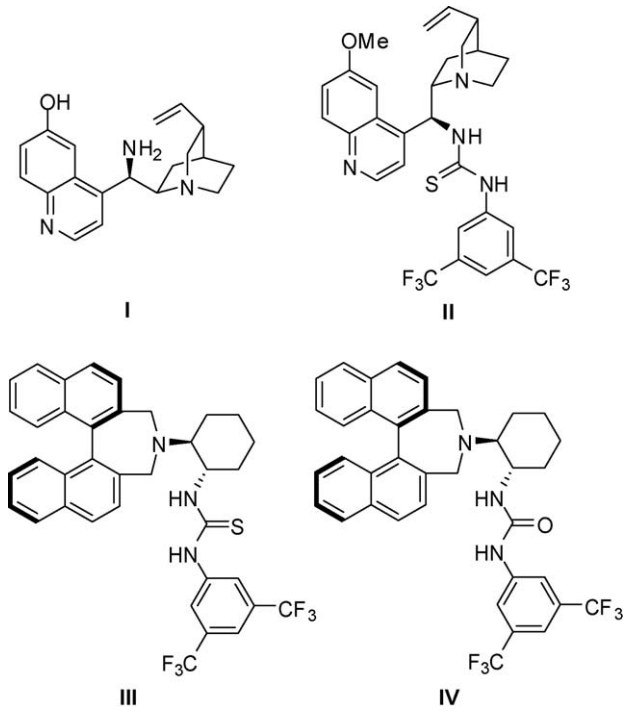
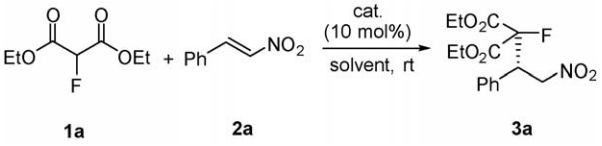


Fig. 1. Structures of various chiral organocatalysts.

both central and axial chiral elements. A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic asymmetric Michael addition of ethyl fluoromalonate (**1a**) with β-nitrostyrene (**2a**). When the reaction was performed in toluene at room temperature in the presence of 10 mol% catalyst **I**, product **3a** was isolated in high yield with 43% ee (Table 1, entry 1). We first examined the impact of the structure of catalysts **I**–**IV** on enantioselectivities (Table 1, 43–85% ee, entries 1–4). The best results have been obtained with catalyst **IV**. Concerning the solvents (entries 4–9), the use of halogenated solvents gave the good results in the yield and the enantiomeric

Table 1
Optimazation of the reaction conditions



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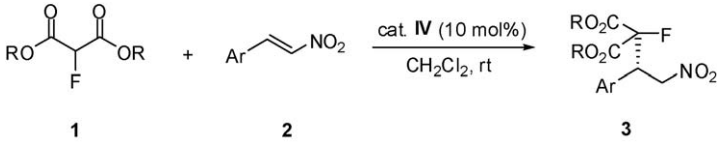
Entry	Cat.	Solvent	Time (day)	Yield[a] (%)	ee[b] (%)
1	**I**	Toluene	5	80	43
2	**II**	Toluene	5	81	65
3	**III**	Toluene	5	83	79
4	**IV**	Toluene	5	91	85
5	**IV**	THF	7	80	85
6	**IV**	CH_3CN	7	85	67
7	**IV**	CH_2Cl_2	2	93	96
8	**IV**	DCE	3	91	95
9	**IV**	CH_2Br_2	3	93	93
10[c]	**IV**	CH_2Cl_2	6	73	96
11[d]	**IV**	CH_2Cl_2	10	75	94
12[e]	**IV**	CH_2Cl_2	15 h	97	87

[a] Isolated yield.
[b] Enantiopurity was determined by HPLC analysis using with a Chiralpak AD-H column.
[c] This reaction was carried out at −25 °C.
[d] This reaction was carried out at −40 °C.
[e] This reaction was carried out at 40 °C.

excess (93–96% ee, entries 7–9). Temperature effect was also significant, with a slightly lower enantioselectivity being given at temperatures either lower or higher than room temperature (entries 10–12). However, the yield was higher if the reaction proceeded at higher temperature (entry 12). To examine the generality of the catalytic asymmetric Michael reaction of fluoromalonates **1** by using new bifunctional organocatalyst **IV**, we studied the addition of fluoromalonates **1** to wide range of para-substituted aromatic and heteroaromatic nitroalkenes **2**. As it can be seen by the results summarized in Table 2, the corresponding products **3a**–**k** were obtained in high to excellent yields with excellent enantioselectivities (91–98% ee). The absolute configuration of **3** was determined by comparing chiral HPLC data and specific rotation with authentic samples [57].

Table 2
Catalytic enantioselective Michael reaction of fluoromalonates



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Entry	**1**, R	**2**, Ar	Time (d)	Yield[a] (%)	ee[b] (%)
1	Et	Ph	2	**3a**, 93	96
2	Et	4-F-Ph	5	**3b**, 80	98
3[c]	Et	2-F-Ph	4	**3c**, 75	93
4	Et	4-Cl-Ph	5	**3d**, 80	97
5[c]	Et	4-Br-Ph	3	**3e**, 78	95
6[c]	Et	4-Me-Ph	4	**3f**, 72	95
7[d]	Et	4-OMe-Ph	6	**3g**, 78	97
8[c]	Et	2-furyl	4	**3h**, 80	97
9	Me	2-NO_2-Ph	5	**3i**, 85	97
10[c]	Me	2-thienyl	4	**3j**, 77	98
11[c]	Me	1-naphthyl	5	**3k**, 75	91

[a] Isolated yield.
[b] Enantiopurities were determined by HPLC analysis using with chiral columns (Chiralcel OD-H for **3g**, Chiralpak AD-H for **3a–f** and **3h–k**).
[c] This reaction was carried out at −25 °C.
[d] This reaction was carried out using a catalyst **III**.

3. Conclusions

In conclusion, we have developed a highly efficient catalytic asymmetric Michael reaction of fluoromalonates **1** to nitroalkenes **2** using bifunctional organocatalyst **IV** [57]. The desired γ-nitro-α-fluoro carbonyl compounds **3** were obtained in good to high yields and excellent enantioselectivities (91–98% ee) were observed. We believe that this method provides an efficient route for the preparation of chiral γ-nitro-α-fluorocarboxylic acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further details and application of this Michael addition of fluoromalonates will be presented in due course.

4. Experimental

4.1. General information

All reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring and monitored by analytical thin layer chromatography using Merck pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm), I_2, *p*-anisaldehyde, ninhydrin, and phosphomolybdic acid, solution as an indicator. Purification of reaction products was carried out by flash chromatography using E. Merck silica gel 60 (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C). Mass spectra were measured on Sciex API-2000 and Jeol HX110/110A using electrospray ionization technique. Optical rotations were measured on a JASCO-DIP-1000 digital polarimeter with a sodium lamp. The enantiomeric excesses (ee's) were determined by HPLC using the indicated chiral columns. Fluoromalonates **1** [53] and bifunctional organocatalysts **I** [54], **II** [55], and **III** [51,52] were prepared by previous reports.

4.2. Synthesis of bifunctional organocatalyst IV

Under a nitrogen atmosphere, to a solution of 3,5-bis(trifluoromethyl)phenylisocyanate (133 mg, 0.525 mmol) in dry THF (4.5 mL) was added *N*-(1*S*, 2*S*)-2-{(*R*)-3,5dihydro-4*H*-dinaphth[2,1-c:1′,2′-e]azepin-4yl}-cyclohexaneamine (196 mg, 0.5 mmol) [56]. After the reaction mixture was stirred for 14 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the product **IV** (83%, 268 mg). $[\alpha]_D^{28} = -132.8$ (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, DMSO-d_6) 9.57 (s, 1H), 8.12–7.90 (m, 6H), 7.90–7.75 (m, 2H), 7.53–7.35 (m, 3H), 7.30–7.09 (m, 4H), 6.59 (s, 1H), 4.19–3.78 (m, 1H), 3.98 (d, J = 12.2 Hz, 2H), 3.50 (d, J = 12.2 Hz, 2H), 2.98–2.68 (m, 1H), 2.35–2.12 (m, 1H), 1.82–1.57 (m, 3H), 1.57–1.10 (m, 4H); ^{13}C NMR (50 MHz, DMSO-d_6) 154.7, 142.6, 134.5, 133.9, 132.4, 130.5 (q, J_{C-F} = 32.1 Hz), 130.5, 128.2, 126.5, 126.0, 125.7, 125.4, 123.3 (q, J_{C-F} = 270.8 Hz), 116.9, 113.1, 66.8, 51.2, 50.7, 33.1, 26.8, 25.3, 24.3; ESI-MS m/z 647.9 $[M+H]^+$.

4.3. General procedure for asymmetric conjugate addition of fluoromalonates 1 to nitroalkenes 2

To a stirred solution of fluoromalonate **1** (0.2 mmol) and catalyst **IV** (6.5 mg, 0.01 mmol) in dichloromethane (0.5 mL) was added nitroalkene **2** (0.1 mmol) at room temperature. After being stirred for 2–6 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 **3.3a**: $[\alpha]_D^{20} = 14.9$ (c = 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 1.01 (t, J = 6.9 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H), 3.93–4.18 (m, 2H), 4.32–4.42 (m, 2H), 4.57 (ddd, J = 30.3, 9.5, 4.8 Hz, 1H), 4.81 (dd, J = 13.4, 9.5 Hz, 1H), 4.93 (dd, J = 13.4, 4.8 Hz, 1H), 7.29–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 13.6, 13.9, 47.3 (d, J = 18.3 Hz), 62.9, 63.6, 75.5 (d, J = 5.8 Hz), 94.5 (d, J = 200.2 Hz), 128.8, 129.0, 129.2, 132.9, 163.6 (d, J = 26.1 Hz), 164.6 (d, J = 25.5 Hz); R_t HPLC (80:20, *n*-hexane: *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 5.4 min (minor), 6.1 min (major). 96% ee.

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