Tetrahedron 70 (2014) 2523–2528

Contents lists available at ScienceDirect

Tetrahedron

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

Highly enantioselective direct Michael addition of 1,3-dicarbonyl compounds to β-fluoroalkyl-α-nitroalkenes

Yan Zhao [a], Xiao-Jin Wang [a], Yun Lin [b], Chen-Xin Cai [a], Jin-Tao Liu [a,*]

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[b] College of Chemistry and Environment, Nanjing Normal University, Nanjing 210097, China

ARTICLE INFO

Article history:
Received 23 October 2013
Received in revised form 12 February 2014
Accepted 24 February 2014
Available online 2 March 2014

Keywords:
Asymmetric catalysis
β-Fluoroalkyl-α-nitroalkene
1,3-Dicarbonyl compound
Michael addition reaction
Cinchona alkaloid

ABSTRACT

Cinchona alkaloid catalysts were used in the Michael addition reaction of 1,3-dicarbonyl compounds to β-fluoroalkyl-α-nitroalkenes for the first time. The catalytic system performed well over a broad scope of substrates including β-keto esters and 1,3-diketones with high diastereoselectivities and excellent enantioselectivities (up to 99% ee) under mild conditions. A wide range of useful fluorinated chiral building blocks was synthesized.

1. Introduction

The Michael addition reaction is one of the fundamental carbon–carbon bond formation reactions in organic synthesis and offers an extremely powerful tool for the synthesis of highly functionalized organic molecules.[1–3] Accordingly, the development of enantioselective catalytic protocols for this reaction has attracted considerable attention. Of particular interest is the reaction of trisubstituted carbon nucleophiles and electron-deficient olefins giving Michael adducts containing adjacent quaternary and tertiary stereocenters, which are key units in many complex natural products as well as valuable synthetic building blocks. However, this requires high efficiency catalyst to impact both high enantioselectivity and diastereoselectivity in a sterically demanding, and still remains a great challenge.

Among the Michael acceptors, nitroalkenes are very attractive because their addition reaction with nucleophiles provides a convenient access to nitroalkanes, which are versatile intermediates in organic synthesis.[2d] The nitro functionality can be easily transformed into amine,[4] nitrile oxide,[5] ketone or carboxylic acid,[6] hydrogen,[7] etc., providing a wide range of synthetically interesting compounds. However, β-fluoroalkyl-α-nitroalkenes have been so far scarcely studied and exploited in the synthesis of functionalized organofluorine molecules,[8–10] despite the fact that they constitute a very promising, highly reactive, yet easy-to-handle class of fluorinated building blocks. To our best knowledge, stereo-controlled Michael reaction of β-fluoroalkyl-α-nitroalkenes still remains a challenge for the chemists. In 2003, Zanda et al. reported the aza-Michael reaction of 3,3,3-trifluoro-1-nitropropene and α-amino esters in the synthesis of fluorinated peptidomimetics.[9] In 2006, they reported further the Michael addition of ketone-derived enamines with β-fluoroalkyl-α-nitroalkenes.[10] However, preformed enamines were required in those reactions. Additionally, in the enantioselective Michael addition reaction of carbonyl compounds catalyzed by chiral enamines, 3,3,3-trifluoro-1-nitropropene was marginally mentioned as a 'difficult' substrate featuring low yield and enantioselectivity.[11]

Recently, asymmetric organocatalysis has processed astonishingly and many kinds of catalysts, such as proline salts,[12] chiral metal complexes,[13] and organocatalysts[14] have been emerged for the Michael addition reactions. The bifunctional organocatalysts that can active both nucleophile and electrophile simultaneously have been demonstrated as efficient enantioselective organocatalysts for the asymmetric conjugate addition of nitroalkenes.[15] Therefore, readily available bifunctional catalysts based on the cinchona alkaloid scaffold were under our consideration for the asymmetric synthesis of fluorinated chiral compounds. In this paper, we report the asymmetric Michael addition of 1,3-dicarbonyl

* Corresponding author. E-mail address: jtliu@sioc.ac.cn (J.-T. Liu).

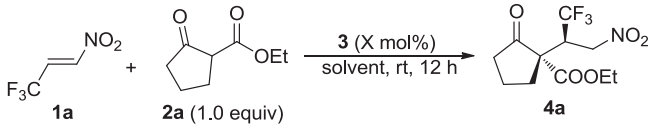
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.02.062

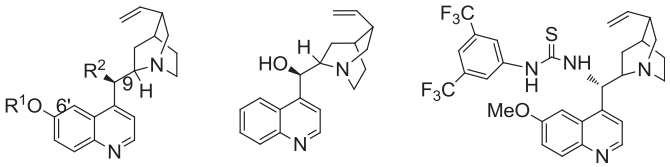
compounds to fluoroalkyl nitroolefins catalyzed by cinchona alkaloid catalysts.

2. Results and discussion

Our initial investigation involved the screening different cinchona alkaloid catalysts for the addition reaction of *trans*-3,3,3-trifluoro-1-nitropropene (**1a**) to cyclic keto ester **2a** at room temperature. As summarized in Table 1, all cinchona alkaloids **3** provided the addition product **4a** in good yields in 12 h at room temperature, although the stereoselectivity of the reaction varied from catalyst to catalyst. Using natural cinchona alkaloid **3a** as catalyst, the reaction afforded good diastereoselectivity but poor enantioselectivity in tetrahydrofuran (THF) (Table 1, entry 1). Enantioselectivity of the reaction was improved dramatically by using 9-OH protected catalyst **3b**, but the diastereoselectivity was not increased in toluene (Table 1, entry 2). In order to achieve better results in terms of both diastereoselectivity and enantioselectivity, the 6′-hydroxy cinchona alkaloids were examined as these catalysts have shown great potential as bifunctional organocatalysts for asymmetric conjugate addition reactions.[16,17] To our delight, excellent diastereoselectivity and enantioselectivity were obtained when 6′-hydroxy cinchona alkaloid **3c** or **3d** was used (Table 1, entries 3 and 4). In the case of **3e**, high diastereoselectivity and moderate enantioselectivity were afforded (Table 1, entry 5). Compound **3f**, an effective chiral catalyst in some asymmetric reactions developed recently,[18] afforded 93:7 dr and 92% ee (Table 1, entry 6). Further examination of solvent revealed that toluene was the best solvent for this reaction. Using **3c** as catalyst, 5 mol % of catalyst loading afforded the adduct with 93:7 dr and 99% ee. Lowering temperature to 0 °C gave the same result (Table 1, entries 7–13). Therefore, the optimal conditions were set as follows: carrying out the reaction in toluene at room temperature using 5 mol % **3c** as catalyst.

Table 1
Catalyst screening and reaction condition optimization





3a: R_1 = Me, R_2 = OH; **3e** **3f**
3b: R_1 = Me, R_2 = OCOPh(*p*-Cl);
3c: R_1 = H, R_2 = OCOPh;
3d: R_1 = H, R_2 = OH;

Entry[a]	3	X	Solvent	dr[c]	Yield (%)[d]	ee (%)[e]
1	**3a**	20	THF	86:14	83	4
2	**3b**	20	Toluene	85:15	84	54
3	**3c**	20	Toluene	93:7	81	96
4	**3d**	20	Toluene	>95:5	76	94
5	**3e**	20	Toluene	93:7	83	44
6	**3f**	20	Toluene	>95:5	89	92
7[b]	**3d**	20	Toluene	>95:5	87	91
8[b]	**3d**	10	Toluene	>95:5	88	91
9[b]	**3d**	5	Toluene	>95:5	83	91
10	**3c**	10	Toluene	94:6	82	99
11[b]	**3c**	10	Toluene	95:5	81	99
12	**3c**	5	Toluene	93:7	84	99
13[b]	**3c**	5	Toluene	95:5	84	99

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), **3** (X mol %), solvent, rt, 12 h.
[b] The reaction was carried out at 0 °C.
[c] Determined by ^{19}F NMR of the crude product.
[d] Isolated total yield.
[e] The ee values were determined by HPLC analysis of product **4a**.

Under the optimal conditions, the scopes of β-fluoroalkyl-α-nitroalkenes **1** and 1,3-dicarbonyl compounds **2** were examined next. As shown in Table 2, reactions of various fluoroalkyl nitroalkenes (**1b**–**d**) with **2a** afforded the expected products (**4b**–**d**) with excellent diastereoselectivities and enantioselectivities (Table 2, entries 2–4). It should be noted that the reaction required 140 h for achieving full conversion when 3,3-difluoro-1-nitropropene **1b** was used as the substrate (entry 2). Diethyl malonate **2b** showed lower reactivity under the optimal conditions, which may be attributed to a less favored coordination. By increasing the catalyst loading to 10 mol %, the reaction of **2b** with **1a** gave the corresponding product **4e** with 99% ee (Table 2, entry 5) in 36 h. High enantioselectivities were also obtained in the reactions of ethyl acetoacetate (**2c**) and acetylacetone (**2d**) under the optimal conditions (Table 2, entries 6 and 7). In the reaction of **2c**, the enolization of adduct **4f** took place easily and decreased the diastereoselectivity. Furthermore, the reaction was applied successfully to bicyclic compound **2e** and the corresponding addition product **4h** was obtained with high stereoselectivity (89:11 dr, 99% ee). It is worth mentioning that low or moderate stereoselectivities were reported regarding the Michael addition reaction of **2e**.[15b,19] Besides ethyl esters, benzyl ester **2f** was also investigated. However, even using 10 mol % **3c** as catalyst, the reaction was very slow and a little drop in enantioselectivity was observed, partially due to the steric effect (Table 2, entry 9).

To determine the absolute configuration of chiral products **4**, we also tried the transformation of the product. To our delight, compound **4c** could be successfully reduced by zinc dust and further converted into the corresponding nitrone **5c**[20] in 36% yield with 92% ee (Scheme 1). After recrystallization, the ee value reached 96%. The absolute configuration of **5c** was unambiguously confirmed by X-ray diffraction analysis[21] (Fig. 1). Therefore, the stereochemical outcome of the corresponding Michael adduct **4** could be deduced from that of **5c** as (S_a, R_b).

Based on the above experimental results and related literature,[13a] a possible transition state was proposed for this reaction as shown in Fig. 2. As a bifunctional organocatalyst, catalyst **3c** may active keto ester and nitroolefin simultaneously in this reaction: the tertiary amine activates keto ester by stabilizing the enol intermediate through hydrogen bonding, and 6′-hydroxy of the catalyst activates nitroolefin and also orientates keto ester with the hydrogen bonding network.

3. Conclusion

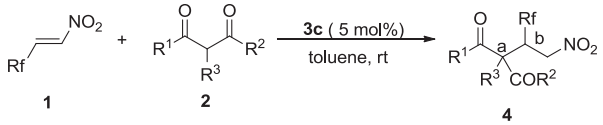
In summary, we have developed a facile method for the asymmetric Michael addition of β-fluoroalkyl-α-nitroalkenes and 1,3-dicarbonyl compounds with high efficiency and excellent stereoselectivities. Catalyzed by organocatalysts derived from cinchona alkaloid, the reaction took place under mild conditions and afforded a series of fluorinated building blocks, which might be useful in the synthesis of biologically active molecules.

4. Experimental section

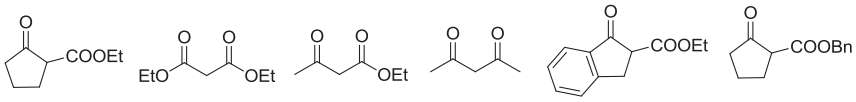
4.1. General

All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. Alkenes **1a**–**d** were prepared following literature procedures.[10] Melting points were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300

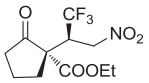
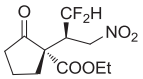
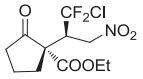
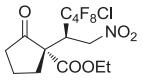
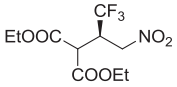
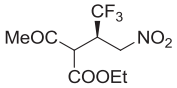
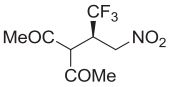
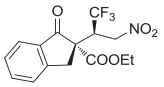
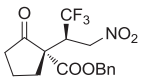
Table 2
The scope of the Michael addition reaction



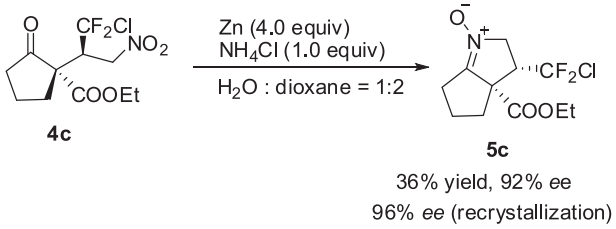
1: **a**, Rf = CF_3; **b**, Rf = HCF_2; **c**, Rf = $ClCF_2$; **d**, Rf = ClC_4F_8



2a **2b** **2c** **2d** **2e** **2f**

Entry[a]	1	2	Time (h)	4	dr[b]	Yield (%)[c]	ee (%)[d]
1	**1a**	**2a**	12	 **4a**	93:7	84	99
2	**1b**	**2a**	140	 **4b**	>95:5	85	94
3	**1c**	**2a**	16	 **4c**	93:7	80	91
4	**1d**	**2a**	14	 **4d**	>95:5	90	97
5[e]	**1a**	**2b**	36	 **4e**	—	79	99
6	**1a**	**2c**	12	 **4f**	—	82	99
7	**1a**	**2d**	12	 **4g**	—	85	93
8	**1a**	**2e**	12	 **4h**	89:11	81	99
9[e]	**1a**	**2f**	120	 **4i**	94:6	77	82

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), **3c** (5 mol %), toluene, rt.
[b] Determined by ^{19}F NMR of the crude products.
[c] Isolated total yield.
[d] The ee values were determined by HPLC analysis of product **3**.
[e] 10 mol % of **3c** was used.



Scheme 1. Transformation of **4c** to **5c**.

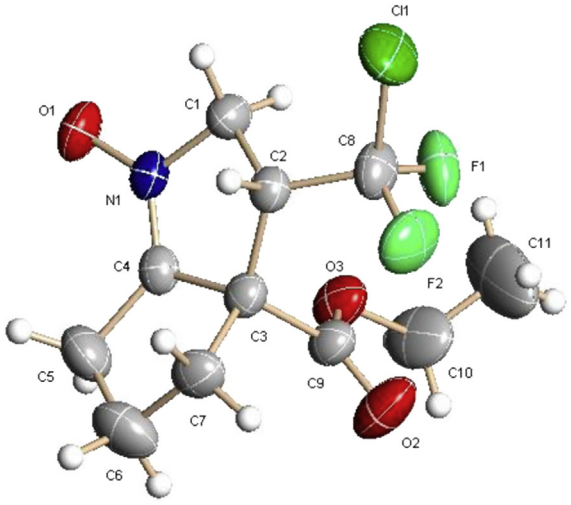


Fig. 1. The X-ray crystal structure of **5c**.

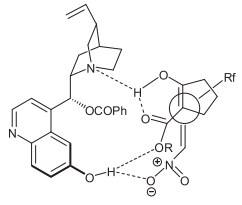


Fig. 2. Proposed transition state.

spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were obtained on a Finnigan GC–MS 4021 spectrometer. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received.

4.2. Typical procedure

To a stirred solution of nitroalkene **1a** (44 mg, 0.31 mmol) and cyclic keto ester **2a** (47 mg, 0.3 mmol) in toluene (3 mL), was added catalyst **3c** (6.2 mg, 0.015 mmol) at room temperature. The mixture was stirred for 12 h (monitored by TLC). After removal of the solvent, the residue was subjected to fast column chromatography on silica gel (petroleum ether/ethyl acetate=10:1–6:1) to give **4a**.

*4.2.1. (S)-Ethyl 2-oxo-1-((R)-1,1,1-trifluoro-3-nitropropan-2-yl)cyclopentanecarboxylate (**4a**).* Colorless oil; $[\alpha]_D^{24}$ −15.68 (*c* 1.38, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.22 (d, *J*=15.3 Hz, 1H), 4.75–4.68 (m, 1H), 4.20 (t, *J*=7.8 Hz, 2H), 3.94–3.86 (m, 1H), 2.76–2.73 (m, 1H), 2.55–2.34 (m, 2H), 2.15–2.04 (m, 3H), 1.27 (t, *J*=7.8 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −64.32 (d, *J*=7.6 Hz, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.61, 167.44, 125.69 (q, J_{C-F}=281.4 Hz), 71.10, 63.15, 58.65, 45.64 (q, J_{C-F}=26.8 Hz), 37.30, 31.64, 19.55, 13.96 ppm. IR (film) ν: 2988, 1760, 1733, 1568, 1236, 1128 cm^{-1}. MS (70 eV) *m*/*z* (%): 297 (M^+), 193 (100.00). HRMS: calcd for $C_{11}H_{14}F_3NO_5$: 297.0824, found: 297.0830. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: *n*-hexane/iso-propanol=100/1, 0.7 mL/min, retention times: t_R (minor)=20.98 min, t_R (major)=23.28 min.

*4.2.2. (S)-Ethyl 1-((R)-1,1-difluoro-3-nitropropan-2-yl)-2-oxocyclopentanecarboxylate (**4b**).* Colorless oil; $[\alpha]_D^{24}$ +4.84 (*c* 1.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.07 (td, *J*=55.8, 5.1 Hz, 1H); 5.03–4.97 (m, 1H), 4.71–4.64 (m, 1H), 4.20 (t, *J*=7.5 Hz, 2H), 3.52–3.45 (m, 1H), 2.62–2.34 (m, 3H), 2.19–2.04 (m, 3H), 1.27 (t, *J*=7.5 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −116.5 (ddd, *J*=291.0, 54.7, 18.9 Hz, 1F), −120.7 (ddd, *J*=291.0, 55.8, 18.6 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.91, 168.69, 115.16 (t, J_{C-F}=244.2 Hz), 70.36, 62.59, 58.51, 44.08 (t, J_{C-F}=20.1 Hz), 37.37, 31.90, 19.32, 13.72 ppm. IR (film) ν: 2985, 1755, 1727, 1564, 1371, 1236 cm^{-1}. MS (70 eV) *m*/*z* (%): 463 (M^+), 55 (100.00). HRMS: calcd for $C_{11}H_{15}F_2NO_5$: 279.0918, found: 279.0920. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: *n*-hexane/iso-propanol=95/5, 0.7 mL/min, retention times: t_R (minor)=15.08 min, t_R (major)=16.91 min.

*4.2.3. (S)-Ethyl 1-((R)-1-chloro-1,1-difluoro-3-nitropropan-2-yl)-2-oxocyclopentanecarboxylate (**4c**).* Colorless oil; $[\alpha]_D^{24}$ −21.7 (*c* 1.09, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.37–5.31 (m, 1H), 4.45 (dd, *J*=16.5, 6.0 Hz, 1H), 4.21–4.04 (m, 3H), 2.83–2.77 (m, 1H), 2.49–2.34 (m, 2H), 2.21–2.02 (m, 3H), 1.28 (t, *J*=6.9 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −48.3 (d, *J*=167.5 Hz, 1F), −51.3 (dd, *J*=167.5, 16.6 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.19, 167.00, 128.96 (t, J_{C-F}=295.9 Hz), 71.97, 62.92, 59.59, 51.30 (t, J_{C-F}=22.3 Hz), 37.04, 31.59, 19.30, 13.68 ppm. IR (film) ν: 2984, 1758, 1731, 1565, 1405, 1119 cm^{-1}. MS (70 eV) *m*/*z* (%): 313 (M^+), 55 (100.00). HRMS: calcd for $C_{11}H_{14}ClF_2NO_5$: 313.0529, found: 313.0521. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: *n*-hexane/iso-propanol=98/2, 0.7 mL/min, retention times: t_R (minor)=13.91 min, t_R (major)=15.25 min.

*4.2.4. (S)-Ethyl 1-((R)-6-chloro-3,3,4,4,5,5,6,6-octafluoro-1-nitrohexan-2-yl)-2-oxocyclopentanecarboxylate (**4d**).* Colorless oil; $[\alpha]_D^{24}$ +14.82 (*c* 1.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.05 (dq, *J*=15.7, 1.5 Hz, 1H), 4.74–4.68 (dd, *J*=16.8, 3.0 Hz, 1H), 4.29–4.14 (m, 3H), 2.79–2.77 (m, 1H), 2.45 (t, *J*=8.1 Hz, 2H), 2.17–2.10 (m, 3H), 1.25 (t, *J*=6.9 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −68.18 (s, 2F), −106.5 (dd, *J*=282.5, 15.8 Hz, 1F), −110.2 (dd, *J*=282.5, 6.8 Hz, 1F), −119.7–119.9 (m, 2F), −122.8–124.0 (m, 2F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.48, 167.87, 122.6 (q, J_{C-F}=276.5 Hz), 121.6 (q, J_{C-F}=278.4 Hz), 118.3 (q, J_{C-F}=276.2.4 Hz), 70.80 (t, J_{C-F}=5.2 Hz), 63.63, 62.75, 42.09 (t, J_{C-F}=19.3 Hz), 36.95, 19.18, 13.46 ppm. IR (film) ν: 2987, 1760, 1731, 1570, 1383, 1130 cm^{-1}. MS (70 eV) *m*/*z* (%): 463 (M^+), 55 (100.00). HRMS: calcd for $C_{14}H_{14}ClF_8NO_5$: 463.0433, found: 463.0434. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: *n*-hexane/iso-propanol=98/2, 0.7 mL/min, retention times: t_R (minor)=7.24 min, t_R (major)=8.22 min.

*4.2.5. (R)-Diethyl 2-(1,1,1-trifluoro-3-nitropropan-2-yl)malonate (**4e**).* Colorless oil; $[\alpha]_D^{24}$ +1.21 (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.02–4.77 (m, 2H), 4.31–4.21 (m, 4H), 4.09–4.01 (m, 1H),

3.89 (d, J=3.9 Hz, 1H), 1.30 (t, J=7.2 Hz, 6H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −69. 8 (d, J=7.2 Hz, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.31, 165.98, 126.67 (q, J_{C-F}=279.1 Hz), 70.49, 63.05, 62.62, 48.22, 41.27 (q, J_{C-F}=29.1 Hz), 13.82 ppm. IR (film) ν: 2987, 1736, 1567, 1381, 1183 cm^{-1}. ESI-MS (m/z): 319 (M^++H_2O); HRMS: calcd for $C_{10}H_{14}F_3NO_6Na$: 324.0665, found: 324.0665. The chiral HPLC analytical data: Chiralpak IC column, detected at 214 nm, eluent: n-hexane/iso-propanol=90/10, 0.7 mL/min, retention times: t_R (major)=7.30 min, t_R (minor)=13.47 min.

*4.2.6. (3R)-Ethyl 2-acetyl-4,4,4-trifluoro-3-(nitromethyl)butanoate (**4f**).* Colorless oil; $[\alpha]_D^{24}$ −8.13 (c 1.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.71 (s, 0.3H), 5.00–4.72 (m, 2H), 4.35–4.00 (m, 3.70H), 2.40 (s, 0.90H), 2.34 (s, 1.2H), 2.21 (s, 0.9H), 1.37–1.25 (m, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −68.0 (d, J=8.1 Hz, 0.9F), −69.1 (d, J=8.5 Hz, 0.9F), −69.6 (d, J=9.8 Hz, 1.2F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.30, 198.03, 180.06, 171.42, 166.50, 165.91, 125.52 (q, J_{C-F}=279.2 Hz), 125.42 (q, J_{C-F}=279.1 Hz), 125.21 (q, J_{C-F}=279.1 Hz), 72.93, 70.31, 70.26, 62.91, 62.73, 61.39, 53.32, 53.79, 41.40 (q, J_{C-F}=29.7 Hz), 41.34 (q, J_{C-F}=27.6 Hz), 40.17 (q, J_{C-F}=28.3 Hz), 31.23, 28.68, 19.74, 13.78, 13.70 ppm. IR (film) ν: 1745, 1725, 1566, 1381, 1254, 1128 cm^{-1}. MS (70 eV) m/z (%): 271 (M^+, 0.58), 43 (100.00). HRMS: calcd for $C_9H_{12}F_3NO_5$: 271.0668, found: 271.0670. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: n-hexane/iso-propanol=95/5, 0.7 mL/min, retention times: t_R (major)=6.58 min, t_R (minor)=6.88 min.

*4.2.7. (R)-3-(1,1,1-Trifluoro-3-nitropropan-2-yl)pentane-2,4-dione (**4g**).* Yellow solid; mp: 47–49 °C; $[\alpha]_D^{24}$ +39.86 (c 0.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.83 (dd, J=13.8, 1.7 Hz, 1H), 4.67 (dd, J=11.6, 7.0 Hz, 1H), 4.38 (d, J=5.7 Hz, 1H), 3.96–3.90 (m, 1H), 2.44 (s, 3H), 2.35 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −68.9 (d, J=8.7 Hz, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.86, 198.36, 125.67 (q, J_{C-F}=279.4 Hz), 70.21, 61.88, 41.43 (q, J_{C-F}=28.1 Hz), 31.98, 29.71 ppm. IR (film) ν: 2931, 1736, 1711, 1565, 1380, 1249 cm^{-1}. MS (70 eV) m/z (%): 241 (M^+), 43 (100.00). HRMS: calcd for $C_8H_{10}F_3NO_4$: 241.0562, found: 241.0564. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: n-hexane/iso-propanol=90/10, 0.7 mL/min, retention times: t_R (major)=12.68 min, t_R (minor)=13.31 min.

*4.2.8. (S)-Ethyl 1-oxo-2-((R)-1,1,1-trifluoro-3-nitropropan-2-yl)-2,3-dihydro-1H-indene-2-carboxylate (**4h**).* Yellow oil; $[\alpha]_D^{24}$ +87.77 (c 0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.80–7.67 (m, 2H), 7.56–7.42 (m, 2H), 5.33 (dd, J=15.9, 1.2 Hz, 1H), 4.95–4.87 (m, 1H), 4.28–4.11 (m, 3H), 3.90 (d, J=17.1 Hz, 1H), 3.35 (d, J=17.1 Hz, 1H), 1.27–1.15 (m, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −63.9 (d, J=5.92 Hz, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.78, 167.57, 152.47, 136.38, 133.33, 128.33, 126.25, 125.53 (q, J_{C-F}=281.1 Hz), 125.43, 71.14, 63.14, 59.18, 45.58 (q, J_{C-F}=26.8 Hz), 34.96, 13.65 ppm. IR (film) ν: 2987, 1743, 1722, 1568, 1243 cm^{-1}. MS (70 eV) m/z (%): 345 (M^+), 205 (100.00). HRMS: calcd for $C_{15}H_{14}F_3NO_5$: 345.0824, found: 345.0815. The chiral HPLC analytical data: Chiralpak AS-H column, detected at 214 nm, eluent: n-hexane/iso-propanol=95/5, 0.7 mL/min, retention times: t_R (minor)=23.38 min, t_R (major)=28.45 min.

*4.2.9. (S)-Benzyl 2-oxo-1-((R)-1,1,1-trifluoro-3-nitropropan-2-yl)cyclopentanecarboxylate (**4i**).* White solid, mp: 68–70 °C; $[\alpha]_D^{24}$ −15.74 (c 1.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32–7.18 (m, 5H), 5.07–5.00 (m, 3H), 4.61–4.50 (m, 1H), 3.87–3.78 (m, 1H), 2.70–2.64 (m, 1H), 2.40–2.24 (m, 2H), 2.10–1.93 (m, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −64.2 (d, J=7.6 Hz, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.05, 166.08, 133.27, 127.88, 127.78, 124.39 (q, J_{C-F}=281.5 Hz), 69.76, 67.51, 57.48, 44.42 (q, J_{C-F}=26.9 Hz), 36.03, 30.34, 18.30 ppm. IR (film) ν: 2966, 1758, 1732, 1564, 1380, 1172 cm^{-1}. ESI-MS (m/z): 377 (M^++H_2O). HRMS: calcd for $C_{16}H_{16}F_3NO_5Na$: 382.0868, found: 382.0872. The chiral HPLC analytical data: Chiralpak AD-H column, detected at 214 nm, eluent: n-hexane/iso-propanol=90/10, 0.7 mL/min, retention times: t_R (minor)=10.42 min, t_R (major)=11.88 min.

*4.2.10. The preparation of **5c**.* Compound **4c** (157 mg, 0.5 mmol) and NH_4Cl (27 mg, 0.5 mmol) were dissolved in H_2O/dioxane (1:2, 3.0 mL) and the mixture was cooled to 5 °C. Under vigorous stirring, Zn powder (130 mg, 2.0 mmol) was added. After stirring for 30 min, the mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The resulted mixture was filtered and the solid was washed with MeOH (10 mL). The liquid phase was evaporated to its half volume and extracted with $CHCl_3$ (3×5 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash column chromatography (ethyl acetate/EtOH=5:1) to give **5c**.

*4.2.11. (3R,3aS)-3-(Chlorodifluoromethyl)-3a-(ethoxycarbonyl)-2,3,3a,4,5,6-hexahydrocyclopenta[b]pyrrole 1-oxide (**5c**).* White solid, mp: 142–144 °C; $[\alpha]_D^{24}$ −104.3 (c 0.97, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.85 (t, J=12.0 Hz, 1H), 4.32–4.17 (m, 3H), 3.39–3.10 (m, 1H), 2.80–2.73 (m, 1H), 2.67–2.56 (m, 1H), 2.46–2.36 (m, 1H), 2.29–2.01 (m, 2H), 1.64–1.53 (m, 1H), 1.31 (t, J=6.9 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −67.3 (d, J=8.1 Hz, 2F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.28, 153.40, 125.70 (t, J_{C-F}=293.1 Hz), 67.16, 63.01, 62.77, 56.50 (t, J_{C-F}=25.0 Hz), 34.77, 26.49, 21.81, 13.88 ppm. IR (film) ν: 2947, 1733, 1644, 1238 cm^{-1}. EI (m/z): 281 (M^+). HRMS: calcd for $C_{11}H_{14}ClF_2NO_3$: 281.0630, found: 281.0631. The chiral HPLC analytical data: Chiralpak IC column, detected at 214 nm, eluent: n-hexane/iso-propanol=70/30, 0.7 mL/min, retention times: t_R (minor)=19.31 min, t_R (major)=22.36 min.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 21172243) and the Natural Science Foundation of the Education Commission of Jiangsu Province (Grant No. 07KJB150059) is gratefully acknowledged.

Supplementary data

Copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HPLC spectra for the products are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.062.

References and notes

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1992.
2. For recent reviews of asymmetric Michael addition reactions, see: (a) Tomioka, K.; Nagaoka, Y.; Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, NY, 1999; (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171; (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877; (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688; (e) Sibi, M.; Manyem, S. *Tetrahedron* **2001**, *56*, 8033.
3. For recent reviews of organocatalytic asymmetric Michael addition, see: (a) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299; (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
4. (a) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897; (b) Maeri, R. E.; Heinzer, J.; Seebach, D. *Liebigs Ann.* **1995**, 1193; (c) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356; (d) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733; (e) Lloyd, D. H.; Nichols, D. E. *J. Org. Chem.* **1986**, *51*, 4294.
5. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
6. Pinnick, H. W. *Org. React.* **1990**, *38*, 655.
7. Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. *Tetrahedron* **1985**, *41*, 4013.

8. (a) Schechter, H.; Ley, D. E.; Roberson, E. B., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4984; (b) For a review see: Zanda, M. *New J. Chem.* **2004**, *28*, 1401.
9. Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887.
10. Molteni, M.; Consonni, R.; Giovenzana, T.; Malpezzi, L.; Zanda, M. *J. Fluorine Chem.* **2006**, *127*, 901.
11. Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.
12. (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176; (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.
13. For some selected references in this area, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194; (b) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem.—Eur. J.* **1998**, *4*, 818; (c) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506; (d) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430.
14. (a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661; (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652; (c) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66; (d) Wascholowski, V.; Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem.—Eur. J.* **2008**, *14*, 6155; (e) Jiang, Z.; Ye, W.; Yang, Y.; Tan, C. H. *Adv. Synth. Catal.* **2008**, *350*, 2345.
15. (a) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481; (d) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713; (e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367; (f) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; (g) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (h) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416; (i) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437; (j) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195.
16. For selected examples on the application of 6′-OH Cinchona alkaloid organocatalysts for asymmetric Michael addition to nitroalkenes see: (a) Chauhan, P.; Chimni, S. S. *Adv. Synth. Catal.* **2011**, *353*, 3203; (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 2047; (c) Xuan, Y.; Nie, S.; Dong, L.; Zhang, J.; Yan, M. *Org. Lett.* **2009**, *11*, 1583; (d) Li, H.; Zhang, S.; Yu, C.; Song, X.; Wang, W. *Chem. Commun.* **2009**, 2136; (e) Raimondi, W.; Lettieri, G.; Dulcere, J. P.; Bonne, D.; Rodriguez, J. *Chem. Commun.* **2010**, 7247; (f) He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 936.
17. For selected examples showing application of 6′-OH Cinchona alkaloids as bifunctional organocatalysts for asymmetric Michael addition to other electrophiles see: (a) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948; (b) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem.* **2006**, *118*, 4407; *Angew. Chem., Int. Ed.* **2006**, *45*, 4301; (c) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C. G.; Broker, G. A.; Tiekink, E. R. T. *Adv. Synth. Catal.* **2008**, *350*, 537; (d) Lu, J.; Zhou, W.; Liu, F.; Loh, T. *Adv. Synth. Catal.* **2008**, *350*, 1796.
18. (a) Connon, S. J. *Chem. Commun.* **2008**, 2499; (b) Donyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
19. Luo, J.; Xu, L. W.; Hay, R. A. S.; Lu, Y. X. *Org. Lett.* **2009**, *11*, 3887.
20. Compound **5c** is sensitive to sunlight, see Ref.: Zeng, Y.; Smith, B. T.; Hershberger, J.; Aubé, J. *J. Org. Chem.* **2003**, *68*, 8065.
21. CCDC 752000 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.