Tetrahedron 67 (2011) 8470–8476

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Direct aldol condensation reaction of ethyl diazoacetate with trifluoromethyl ketones

Han-Feng Cui, Lian Wang, Li-Jun Yang, Jing Nie, Yan Zheng, Jun-An Ma *

Department of Chemistry, Tianjin University, Tianjin 300072, China

ARTICLE INFO

Article history:
Received 15 June 2011
Received in revised form 25 August 2011
Accepted 6 September 2011
Available online 10 September 2011

Keywords:
Aldol condensation
Trifluoromethyl ketone
Enantioselectivity
Ethyl diazoacetate

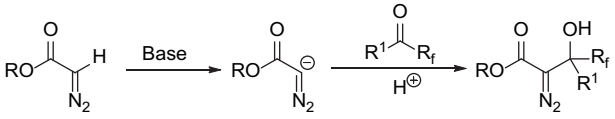
ABSTRACT

An efficient and direct aldol-type condensation of ethyl diazoacetate with trifluoromethyl ketones was developed in the presence of dialkyl zinc. A series of trifluoromethylated products were obtained in good to excellent yields (60–95%). A preliminary extension to a catalytic enantioselective aldol reaction of ethyl diazoacetate to trifluoromethyl ketones (up to 72% ee) is also described.

1. Introduction

The trifluoromethyl group is a bulky and highly electron-withdrawing group (electronegativity of 3.5 on the Pauling scale) that strongly affects the reactivity of the adjacent functional groups. Incorporation of a trifluoromethyl group into organic molecules generally increases their chemical stability owing to the high bond strength that can induce increased resistance to metabolic decomposition. Thus, over the past decades trifluoromethylated compounds have attracted considerable attention in organic synthesis, medicinal and agrochemical chemistry, and materials sciences.[1] Direct transformation of trifluoromethyl-containing building blocks is a very appealing strategy for the construction of trifluoromethylated molecules.[2] For example, 1,2-addition of various nucleophiles to trifluoromethyl ketones has been proved a particularly attractive target, due largely to (a) the ready availability and high reactivity of trifluoromethyl ketones, and (b) the high biological and medicinal utility of trifluoromethyl-substituted tertiary alcohols. However, to the best of our knowledge, no direct aldol condensation reactions of diazoacetates with trifluoromethyl ketones have been reported.[3]

α-Diazoacetates and derivatives are readily available C2 synthons in organic chemistry as a result of their diverse reactivities.[4] In addition to serving as metal–carbene precursors, α-diazoacetates and derivatives have in recent years been employed as carbon-nucleophiles in direct aldol-type condensation reactions.[5] Although much progress has been made in the development of direct aldol reactions of aldehydes and aldimines, successful aldol reactions of α-diazoacetates and derivatives with ketones are rare.[6] The direct aldol reaction between ethyl diazoacetate and trifluoromethyl ketones represents an attractive and an atom economical method toward fluorinated products (Scheme 1).



Scheme 1. Aldol reaction between diazoacetate and trifluoromethyl ketone in the presence of base.

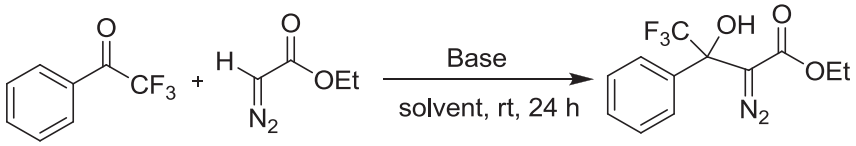
Development of new organic transformations for the synthesis of fluorine-containing functionalized compounds has been our interest and research objective.[7] As part of our ongoing studies, herein we report an efficient and direct aldol-type condensation of ethyl diazoacetate with trifluoromethyl ketones in the presence of dialkyl zinc. Such studies would be of immense benefit for expanding the scope of application of these aldol reactions in organic synthesis.

The aldol reaction of α-diazoacetates and derivatives with aldehydes has been studied extensively with a variety of bases including a number of strong bases. However, the reactions are not feasible for trifluoromethyl ketones. Efficient, clean, and direct aldol reaction using trifluoromethyl ketones is difficult in the presence of common bases, such as 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), potassium hydroxide, or sodium hydride (Table 1, entries

* Corresponding author. Tel.: +86 22 27402903; fax: +86 22 27403475; e-mail address: majun_an68@tju.edu.cn (J.-A. Ma).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.009

Table 1
Optimization of the conditions for the aldol reaction of diazoacetate with trifluoroacetophenone (**1a**)[a]



1a **2a**

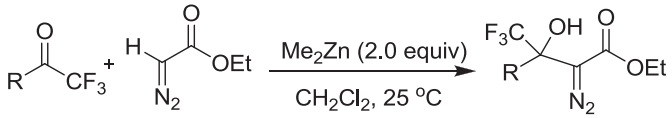
Entry	Base	Solvent	Yield[b] (%)
1	DBU	THF	0
2	KOH	THF	0
3	NaH	THF	15
4[c]	*n*-BuLi	THF	39
5[c]	LDA	THF	50
6	Et_2Zn	THF	61
7	Et_2Zn	Et_2O	56
8	Et_2Zn	CH_3CN	20
9	Et_2Zn	Toluene	80
10	Et_2Zn	CH_2Cl_2	90
11	Et_2Zn	$ClCH_2CH_2Cl$	85
12	Me_2Zn	CH_2Cl_2	95

[a] Unless otherwise noted, the reaction was carried out with diazoacetate ester (0.3 mmol) and trifluoroacetophenone (0.2 mmol) in solvent with base (0.4 mmol) for 24 h.
[b] Isolated yield (all data are the average of three experiments).
[c] Reaction temperature: −78 °C to 0 °C.

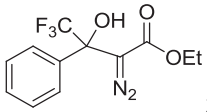
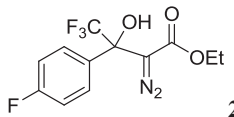
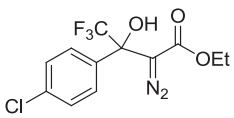
1–3). We found that the reaction of ethyl α-diazoacetate with 1,1,1-trifluoroacetophenone **1a** in tetrahydrofuran (THF) with *n*-butyl lithium or lithium diisopropylamide (LDA) as base gave the aldol product **2a** in moderate yield (entries 4 and 5). These results indicated the need of the proper base, which plays the key role for the success of the aldol reaction of fluorinated ketones. Therefore, we performed this aldol reaction by using diethyl zinc as base. The reaction is found to be clean and simple, and the aldol product **2a** was formed in 61% yield. In addition, the aldol condensation was conducted in different solvents (entries 7–11). Tetrahydrofuran, ether, and acetonitrile are not suitable for the Et_2Zn-promoted direct aldol reaction possibly due to their interaction with zinc. The use of toluene and chlorinated alkanes minimizes such interaction, resulting in enhanced yield and providing a suitable environment for the reaction. Dichloromethane was found to be the best with respect to reaction activity, and **2a** was isolated in 90% yield. A substantial change of the temperature did not have a significant effect on the reactivity. It is noteworthy that the yield was further improved to 95% in the replace of diethyl zinc with dimethyl zinc (entry 12). It is well known that dimethyl zinc is significantly less reactive than diethyl zinc in the 1,2-addition to aldehydes and ketones in the presence of the amino alcohol ligand.[8] Thus, the use of dimethyl zinc could be more favorable for the current aldol condensation.

With these optimized conditions in hand, the general scope of trifluoromethyl ketones was examined in the aldol reaction in the presence of Me_2Zn (Table 2). It was found when aromatic trifluoromethyl ketones with electron-neutral or -withdrawing groups on aromatic rings were used, the aldol reactions proceeded smoothly to give **2a**–**e** in 86–95% yield (entries 1–5). Furthermore, the aldol reactions worked well with biphenyl, 1- and 2-naphthyl trifluoromethyl ketones under our current conditions to afford

Table 2
Substrate scope for the aldol reaction[a]

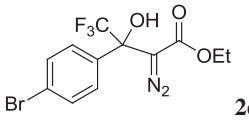
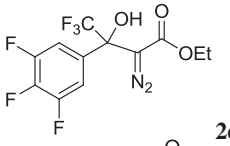
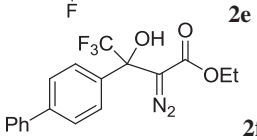
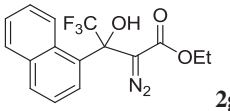
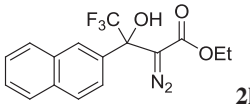
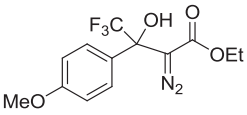
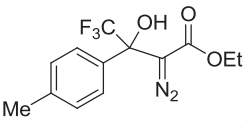
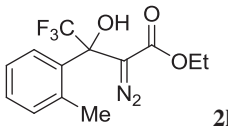
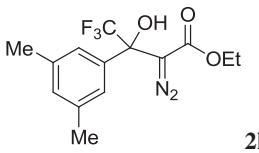
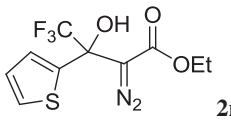
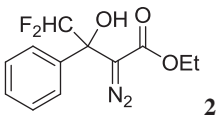
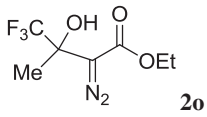


1 **2**

Entry	Time (h)	Product **2**	Yield[b] (%)
1	24	 **2a**	95
2	24	 **2b**	86
3	24	 **2c**	85

(*continued on next page*)

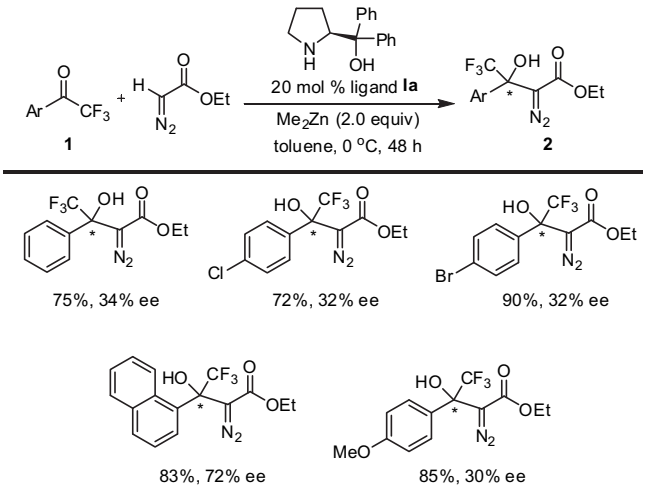
Table 2 (*continued*)

Entry	Time (h)	Product **2**	Yield[b] (%)
4	24	 **2d**	90
5	24	 **2e**	86
6	24	 **2f**	82
7	24	 **2g**	88
8	48	 **2h**	82
9	60	 **2i**	80
10	60	 **2j**	75
11	96	 **2k**	60
12	60	 **2l**	89
13	48	 **2m**	76
14	48	 **2n**	74
15[c]	48	 **2o**	88

[a] Unless otherwise noted, the reaction was carried out with diazoacetate ester (0.3 mmol) and trifluoroacetophenone (0.2 mmol) in CH_2Cl_2 with Me_2Zn (0.4 mmol).
[b] Isolated yield (all data are the average of three experiments).
[c] Reaction temperature: 0 °C.

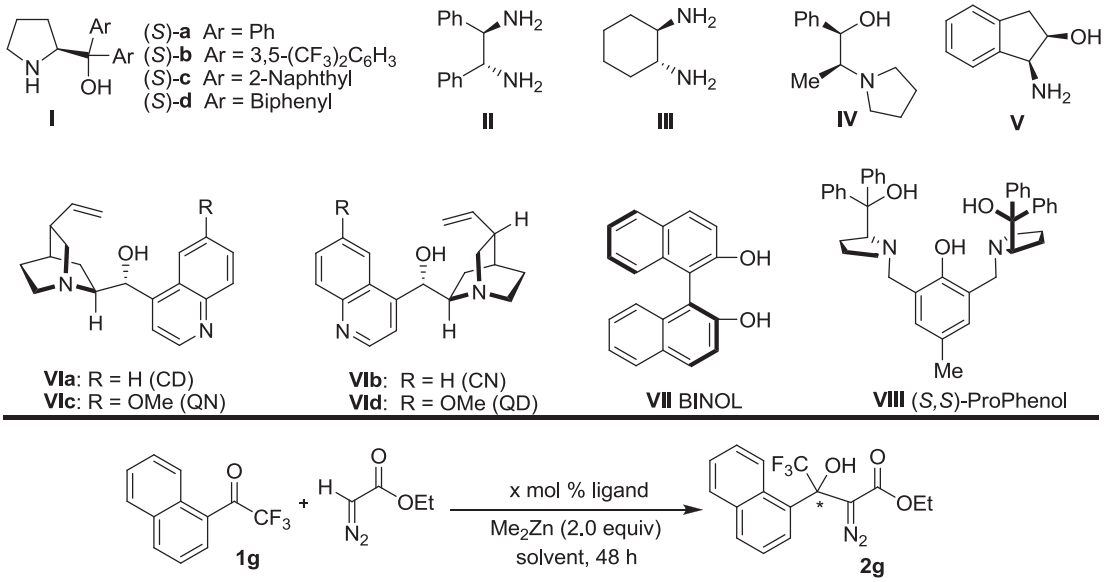
the aldol products **2f**–**h** in good yields (entries 6–8). However, the presence of electron-donating substituents on aromatic rings decreased the reaction rate, and relatively lower yields were obtained (products **2i**–**l**, entries 9–12). Both heteroaromatic trifluoromethyl ketone and 1,1-difluoroacetophenone also provide the normal adducts **2m**–**n** in good yields (entries 13 and 14). Encouraged by these results, we extended our methodology to aliphatic fluorinated ketones. We found that 1,1,1-trifluoroacetone also reacts smoothly with ethyl α-diazoacetate under mild conditions to give the corresponding fluorinated product **2o** in 88% yield (Table 2, entry 15).

As a successive study, the enantioselective version of the described aldol condensation reaction using chiral ligands was also disclosed. In order to obtain good ees, it is suitable to use a high loading amount of the chiral ligand (20 mol %). Systemic optimization on the other reaction conditions (including chiral ligands **I**–**VIII**, solvent, and temperature, Table 3) led to the discovery that the best results were obtained when toluene was used as the solvent and the reactions run at 0 °C in the presence of (*S*)-diphenylprolinol **Ia** (83% yield, 72% ee, entry 20). Several aldol products were obtained in respectable yields with moderate to good enantioselectivities (Scheme 2). It should be noted that even increasing



Scheme 2. The catalytic enantioselective aldol reaction of ethyl diazoacetate with trifluoromethyl ketones.

Table 3
Optimization of the conditions for the enantioselective aldol reaction of diazoacetate with the substrate **1g**

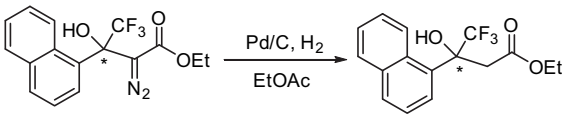


Entry	Ligand (mol %)	Solvent	Temperature (°C)	Yield (%)[a]	ee[b] (%)
1	**Ia** (20)	CH_2Cl_2	25	85	59
2	**Ib** (20)	CH_2Cl_2	25	90	6
3	**Ic** (20)	CH_2Cl_2	25	85	54
4	**Id** (20)	CH_2Cl_2	25	96	56
5	**II** (20)	CH_2Cl_2	25	85	23 (—)
6	**III** (20)	CH_2Cl_2	25	88	0
7	**IV** (20)	CH_2Cl_2	25	92	0
8	**V** (20)	CH_2Cl_2	25	55	50 (—)
9	**VIa** (20)	CH_2Cl_2	25	80	13 (—)
10	**VIb** (20)	CH_2Cl_2	25	65	7
11	**VIc** (20)	CH_2Cl_2	25	40	14 (—)
12	**VId** (20)	CH_2Cl_2	25	38	9
13	**VII** (20)	CH_2Cl_2	25	75	0
14	**VIII** (20)	CH_2Cl_2	25	90	7
15	**Ia** (30)	CH_2Cl_2	25	90	65
16	**Ia** (20)	CH_2Cl_2	0	85	70
17	**Ia** (20)	CH_2Cl_2	−20	59	62
18	**Ia** (20)	$ClCH_2CH_2Cl$	0	95	57
19	**Ia** (20)	Et_2O	0	47	52
20	**Ia** (20)	Toluene	0	83	72

[a] Isolated yield.
[b] ee was determined by HPLC analysis on a chiral stationary phase.

of the amount of chiral ligand or lowering of the temperature did not improve the enantioselectivity of the products.

These aldol products **2** are versatile synthetic intermediates and can be readily transformed into trifluoromethylated tertiary alcohols. For example, direct hydrogenation of **2g** in the presence of Pd/C catalyst gave rise to **3** in good yield. Furthermore, hydrogenation of the optically active compound **2g** provided the corresponding product **3** without detectable loss of enantioselectivity (Scheme 3).



2g 72% ee

3 74% yield, 71% ee

Scheme 3. Synthetic transformation of **2g** to the product **3**.

In summary, we have developed a direct and efficient aldol condensation reaction of diazoacetate with trifluoromethyl ketones in the presence of dialkyl zinc. Me_2Zn simultaneously provide the best base and Lewis acidity required for this successful reaction. A series of fluorinated products were obtained in good to excellent yields. In a preliminary experiment, a moderate to good enantioselectivity was obtained. Further tailored reagents and reaction conditions in order to improve stereoselectivity of this transformation as well as additional mechanistic studies are ongoing in our laboratory and will be reported in due course.

2. Experimental section

2.1. General details

NMR was recorded on Varian Mercury Plus 500 instruments at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR) and 376 MHz (^{19}F NMR). Chemical shifts were reported in parts per million down field from internal Me_4Si. MS were recorded on a VG-7070E or VG ZAB-HS spectrometer with the ESI resource. Optical rotations were determined using an Autopol IV-T. IR spectra were recorded on an AVATAR 360 FT-IR spectrometer. HPLC analyses were carried out on a Hewlett Packard Model HP 1200 instrument. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium/benzophenone prior to use; Dichloromethane, dichloroethane, and acetonitrile were distilled from CaH_2. All other purchased reagents were used without further purification. Ethyl diazoacetate,[9] ligand **I**,[10] and **VIII**[11] were prepared according to the literature procedures. All of the reactions were carried out under an argon atmosphere with the exclusion of moisture.

2.2. Representative procedure for the aldol condensation reaction of ethyl diazoacetate with trifluoromethyl ketone

Dimethyl zinc (0.36 mL, 1.1 M in hexane, 0.4 mmol) was added to a solution of ethyl diazoacetate (30 μL, 0.3 mmol) in dichloromethane (2.0 mL) under argon at room temperature. After the resulting mixture was stirred for 10 min, 1,1,1-trifluoroacetophenone **1a** (34.8 mg, 0.2 mmol) was added into the solution. The mixture was stirred at the same temperature until the completion of the reaction with monitoring by TLC. Then, the reaction solution was quenched with saturated NH_4Cl solution (10 mL), and extracted with AcOEt (10 mL×3). The combined organic layers were washed with brine (10 mL×3), dried over $MgSO_4$, and the solvent was removed in vacuum to yield the crude product, which was purified by silica gel flash column chromatography (petroleum ether/AcOEt: 8:1) to give the slightly yellow oil (54.7 mg).

*2.2.1. Ethyl 4,4,4-trifluoro-3-hydroxy-3-phenyl-2-diazobutanoate (**2a**).* Slightly yellow oil, 95% yield, ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.1 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 4.32 (q, J=6.8 Hz, 2H), 6.47 (br s, 1H), 7.45–7.49 (m, 3H), 7.69–7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 134.8, 129.6, 128.7, 126.4, 125.1 (q, $^1J_{C-F}$=285.7 Hz), 75.6 (q, $^2J_{C-F}$=30.9 Hz), 62.9, 59.3 (d, J=4.8 Hz), 14.2; MS (ESI): m/z 288.47 $[M]^+$, 259.16 $[M-N_2-H]^+$, 226.87 [M−OH−OEt]; IR (KBr) ν 2110, 1670, 1311, 1158, 712 cm^{-1}.

*2.2.2. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-fluorophenyl)-2-diazobutanoate (**2b**).* Slightly yellow oil, 86% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.4 (s, 3F), −111.6 (s, 1F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.0 Hz, 3H), 4.28–4.36 (m, 2H), 6.46 (br s, 1H), 7.14 (t, J=8.8 Hz, 2H), 7.68 (dd, J=8.4 and 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 163.3 (d, $^1J_{C-F}$=248.1 Hz), 130.7 (d, $^4J_{C-F}$=3.2 Hz), 128.6 (d, $^3J_{C-F}$=7.6 Hz), 125.0 (q, $^1J_{C-F}$=285.7 Hz), 115.7 (d, $^2J_{C-F}$=21.7 Hz), 75.4 (q, $^2J_{C-F}$=30.9 Hz), 62.0, 59.1, 14.2; MS (ESI): m/z 306.06 $[M]^+$, 277.17 $[M-N_2-H]^+$, 226.87 [M−OH−OEt]; IR (KBr) ν 2105, 1675, 1311, 1163, 1107, 721 cm^{-1}.

*2.2.3. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-chlorophenyl)-2-diazobutanoate (**2c**).* Slightly yellow oil, 85% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.4 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.0 Hz, 3H), 4.28–4.35 (m, 2H), 6.46 (br s, 1H), 7.43 (d, J=8.4 Hz, 2H), 7.63 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 135.8, 133.5, 128.9, 128.0, 124.8 (q, $^1J_{C-F}$=285.7 Hz), 75.4 (q, $^2J_{C-F}$=31.1 Hz), 62.1, 59.0, 14.2; MS (ESI): m/z 322.32 $[M]^+$; IR (KBr) ν 2105, 1680, 1311, 1199, 1091 cm^{-1}.

*2.2.4. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-bromophenyl)-2-diazobutanoate (**2d**).* Slightly yellow oil, 90% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.3 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 4.28–4.34 (m, 2H), 6.45 (br s, 1H), 7.57 (dd, J=14.4 and 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 134.0, 131.9, 128.3, 124.8 (q, $^1J_{C-F}$=285.7 Hz), 123.4, 75.5 (q, $^2J_{C-F}$=31.1 Hz), 62.1, 58.9, 14.2; MS (ESI): m/z 226.83 [M−OH−OEt−Br]; IR (KBr) ν 2105, 1670, 1317, 1158, 1009 cm^{-1}.

*2.2.5. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(3,4,5-trifluorophenyl)-2-diazobutanoate (**2e**).* Slightly yellow oil, 86% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.6 (s, 3F), −131.9 (d, J=20.3 Hz, 2F), −157.5 (t, J=20.5 Hz, 1F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.2 Hz, 3H), 4.30–4.36 (m, 2H), 6.52 (br s, 1H), 7.35 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.1 (ddd, J_{C-F}=250.0 and 10.1 and 3.8 Hz), 140.4 (dt, J_{C-F}=254.1 and 15.0 Hz), 131.5 (dd, J_{C-F}=11.4 and 6.7 Hz), 124.3 (q, $^1J_{C-F}$=285.4 Hz), 111.7–111.5 (m), 75.0 (q, $^2J_{C-F}$=31.9 Hz), 62.3, 58.4, 14.2; MS (ESI): m/z 342.25 $[M]^+$; IR (KBr) ν 2100, 1690, 1531, 1440, 1311, 1265, 1189, 1040, 1020 cm^{-1}.

*2.2.6. Ethyl 4,4,4-trifluoro-3-hydroxy-3-biphenyl-2-diazobutanoate (**2f**).* Yellow oil, 82% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.1 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J=7.2 Hz, 3H), 4.35 (q, J=7.2 Hz, 2H), 6.53 (br s, 1H), 7.42 (t, J=7.4 Hz, 1H), 7.50 (t, J=7.6 Hz, 2H), 7.65 (d, J=7.2 Hz, 2H), 7.70 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 142.4, 140.0, 133.7, 128.9, 127.8, 127.3, 127.2, 127.0, 125.2 (q, $^1J_{C-F}$=285.8 Hz), 75.6 (q, $^2J_{C-F}$=31.0 Hz), 62.0, 59.3, 14.3; MS (ESI): m/z 363.10 $[M-H]^-$; IR (KBr) ν 2100, 1670, 1312, 1168, 1086, 738, 657 cm^{-1}.

*2.2.7. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(naphthalen-1-yl)-2-diazobutanoate (**2g**).* Light yellow viscous liquid, 88% yield; ^{19}F

NMR (376 MHz, $CDCl_3$) δ −76.1 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J=7.0 Hz, 3H), 4.36–4.42 (m, 2H), 6.73 (br s, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.54–7.61 (m, 2H), 7.74 (br s, 1H), 7.94 (t, J=8.8 Hz, 2H), 8.63 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 134.9, 131.5, 130.9, 129.4, 128.5, 126.8, 126.0, 125.9 (q, $^1J_{C-F}$=286.6 Hz), 125.8 (q, $^3J_{C-F}$=3.9 Hz), 125.2, 124.1, 77.4 (q, $^2J_{C-F}$=30.3 Hz), 61.9, 59.2, 14.2; MS (ESI): m/z 312.20 [M−N_2], 226.79 [M−N_2CCO_2Et]; IR (KBr) ν 2105, 1669, 1311, 1259, 1157, 773 cm^{-1}.

*2.2.8. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(naphthalen-2-yl)-2-diazobutanoate (**2h**).* Light yellow viscous liquid, 82% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.8 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.0 Hz, 3H), 4.31–4.37 (m, 2H), 6.61 (br s, 1H), 7.55–7.61 (m, 2H), 7.79 (d, J=8.8 Hz, 1H), 7.89–7.96 (m, 3H), 8.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 133.5, 132.7, 132.1, 128.8, 128.7, 127.6, 127.3, 126.7, 126.4, 125.5 (q, $^1J_{C-F}$=285.8 Hz), 123.5, 75.9 (q, $^2J_{C-F}$=30.8 Hz), 62.0, 59.4, 14.3; MS (ESI): m/z 312.26 [M−N_2], 226.80 [M−N_2CCO_2Et]; IR (KBr) ν 2105, 1675, 1301, 1188, 1153, 748 cm^{-1}.

*2.2.9. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-methoxylphenyl)-2-diazobutanoate (**2i**).* Yellow oil, 80% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.3 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 3.84 (s, 3H), 4.31 (q, J=7.2 Hz, 2H), 6.40 (br s, 1H), 6.96 (d, J=8.8 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 160.3, 127.9, 126.7, 125.2 (q, $^1J_{C-F}$=285.7 Hz), 114.0, 75.5 (q, $^2J_{C-F}$=30.9 Hz), 61.9, 59.5, 55.2 (d, J=5.5 Hz), 14.2; MS (ESI): m/z 318.54 [M]$^+$; IR (KBr) ν 2105, 1670, 1516, 1312, 1260, 1168, 1030 cm^{-1}.

*2.2.10. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-methylphenyl)-2-diazobutanoate (**2j**).* Slightly yellow oil, 75% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.2 Hz, 3H), 2.40 (s, 3H), 4.32 (q, J=7.2 Hz, 2H), 6.43 (br s, 1H), 7.27 (d, J=8.0 Hz, 2H), 7.58 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 139.6, 131.8, 129.4, 126.3, 125.2 (q, $^1J_{C-F}$=285.7 Hz), 75.6 (q, $^2J_{C-F}$=30.9 Hz), 61.9, 59.4, 21.1 (d, J=4.4 Hz), 14.2; MS (ESI): m/z 302.65 [M]$^+$; IR (KBr) ν 2105, 1680, 1306, 1158, 1020, 922 cm^{-1}.

*2.2.11. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(2-methylphenyl)-2-diazobutanoate (**2k**).* Slightly yellow oil, 60% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.1 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.2 Hz, 3H), 2.58 (s, 3H), 4.35 (q, J=7.2 Hz, 2H), 6.42 (br s, 1H), 7.22 (t, J=8.0 Hz, 1H), 7.29–7.35 (m, 2H), 7.49 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 138.7, 133.4, 131.7, 129.7, 126.9 (d, $^3J_{C-F}$=3.8 Hz), 125.7, 125.7 (q, $^1J_{C-F}$=286.4 Hz), 76.9 (q, $^2J_{C-F}$=30.0 Hz), 61.9, 57.9, 21.1 (d, J=4.1 Hz), 14.3; MS (ESI): m/z 302.05 [M]$^+$; IR (KBr) ν 2100, 1670, 1306, 1260, 1153, 922, 743, 723 cm^{-1}.

*2.2.12. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(3,5-dimethylphenyl)-2-diazobutanoate (**2l**).* Slightly yellow oil, 89% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.0 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.2 Hz, 3H), 2.38 (s, 6H), 4.30–4.35 (m, 2H), 6.44 (br s, 1H), 7.08 (s, 1H), 7.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 138.3, 134.6, 131.2, 125.2 (q, $^1J_{C-F}$=285.7 Hz), 124.1, 75.6 (q, $^2J_{C-F}$=30.7 Hz), 61.9, 59.4, 21.4, 14.2; MS (ESI): m/z 317.76 [M+H]$^+$; IR (KBr) ν 2100, 1675, 1312, 1260, 1152, 1086, 1024 cm^{-1}.

*2.2.13. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(thiophen-2-yl)-2-diazobutanoate (**2m**).* Slightly yellow oil, 76% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.8 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.0 Hz, 3H), 4.34 (q, J=7.2 Hz, 2H), 7.01 (br s, 1H), 7.05 (t, J=4.4 Hz, 1H), 7.16 (br s, 1H), 7.44 (d, J=5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 138.3, 127.3, 127.1, 125.7, 124.9 (q, $^1J_{C-F}$=285.8 Hz), 74.3 (q, $^2J_{C-F}$=32.7 Hz), 62.1, 59.2, 14.2; MS (ESI): m/z 294.33 [M]$^+$; IR (KBr) ν 2115, 1670, 1311, 1193, 1163, 1101, 707 cm^{-1}.

*2.2.14. Ethyl 4,4-difluoro-3-hydroxy-3-phenyl-2-diazobutanoate (**2n**).* Slightly yellow oil, 74% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −127.5 (dd, J=294.1 Hz and 276.4 Hz, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J=7.0 Hz, 3H), 4.25–4.33 (m, 2H), 5.20 (br s, 1H), 6.16 (t, J=55.4 Hz, 1H), 7.40–7.47 (m, 3H), 7.65 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 136.6, 129.3, 128.7, 126.5, 115.5 (t, $^1J_{C-F}$=249.6 Hz), 75.3 (t, $^2J_{C-F}$=22.8 Hz), 61.6, 60.0, 14.3; MS (ESI): m/z 271.16 [M+H]$^+$; IR (KBr) ν 2110, 1685, 1306, 1117, 1081 cm^{-1}.

*2.2.15. Ethyl 4,4,4-trifluoro-3-hydroxy-3-methyl-2-diazobutanoate (**2o**).* Slightly yellow oil, 88% yield; ^{19}F NMR (376 MHz, $CDCl_3$) δ −83.4 (s, 3F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J=7.2 Hz, 3H), 1.58 (s, 3H), 4.29 (q, J=7.2 Hz, 2H), 5.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 125.7 (q, $^1J_{C-F}$=285.3 Hz), 71.0 (q, $^2J_{C-F}$=31.7 Hz), 61.7, 60.8, 19.7, 14.2; IR (KBr) ν (cm^{-1}): 2106, 1682, 1307, 1249, 1035; MS (ESI) m/z: 226.16 [M]$^+$.

2.3. Representative enantioselective version of the aldol condensation procedure, ethyl 4,4,4-trifluoro-3-hydroxy-3-phenyl-2-diazobutanoate (2a)

To a solution of (*S*)-diphenylprolinol **3** (10 mg, 0.04 mmol) in toluene (3.0 mL) was added dimethyl zinc (0.36 mL, 1.1 M in hexane, 0.4 mmol) under argon at 0 °C and the resulting solution was stirred for 10 min. Ethyl diazoacetate (30 μL, 0.3 mmol) was added into the solution. After stirring for 30 min, 1,1,1-trifluoroacetophenone **1a** (34.8 mg, 0.2 mmol) was added into the above solution. The mixture was stirred at the same temperature for the stated time. Then, the reaction solution was quenched with saturated NH_4Cl solution (10 mL), and extracted with AcOEt (10 mL×3). The combined organic layers were washed with brine (10 mL×3), dried over $MgSO_4$, and the solvent was removed in vacuum to yield the crude product, which was purified by silica gel flash column chromatography (petroleum ether/AcOEt: 8:1) to give the slightly yellow oil (43.2 mg). 75% yield, $[\alpha]_D^{20}$ +6.5 (*c* 1.0, CH_2Cl_2), 34% ee, Daicel Chiralcel AS-H, hexane/*i*-PrOH=99.5/0.5, 0.8 mL/min, 254 nm, t_R (major)=7.5 min, t_R (minor)=8.1 min.

*2.3.1. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-chlorophenyl)-2-diazobutanoate (**2c**).* Yield 72%, $[\alpha]_D^{20}$ +11.3 (*c* 1.0, CH_2Cl_2), 32% ee, Daicel Chiralcel AD-H, hexane/*i*-PrOH=99.5/0.5, 0.8 mL/min, 254 nm, t_R (major)=9.7 min, t_R (minor)=10.4 min.

*2.3.2. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-bromophenyl)-2-diazobutanoate (**2d**).* Yield 90%, $[\alpha]_D^{20}$ +9.0 (*c* 1.0, CH_2Cl_2), 32% ee Daicel Chiralcel AD-H, hexane/*i*-PrOH=99.5/0.5, 0.8 mL/min, 254 nm, t_R (major)=10.6 min, t_R (minor)=11.4 min.

*2.3.3. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(naphthalen-1-yl)-2-diazobutanoate (**2g**).* Yield 83%, $[\alpha]_D^{20}$ +60.8 (*c* 1.0, CH_2Cl_2), 72% ee, Daicel Chiralcel OJ-H, hexane/*i*-PrOH=99.5/0.5, 1.0 mL/min, 254 nm, t_R (major)=18.4 min, t_R (minor)=27.4 min.

*2.3.4. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(4-methoxylphenyl)-2-diazobutanoate (**2i**).* Yield 85%, $[\alpha]_D^{20}$ +8.7 (*c* 1.0, CH_2Cl_2), 30% ee, Daicel Chiralcel AS-H, hexane/*i*-PrOH=99.5/0.5, 0.8 mL/min, 254 nm, t_R (major)=10.8min, t_R (minor)=12.3 min.

*2.3.5. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(naphthalen-1-yl)butanoate **3**.* A suspension of Pd/C (100 mg, 10% Pd) and **2g** (101.4 mg, 0.3 mmol) in ethyl acetate (5 mL) under an atmosphere of hydrogen (1 atm) was stirred for 3 h at room temperature. The reaction was

filtered through Celite and concentrated. Silica gel chromatography using diethyl ether/hexanes gave final product as a white solid (69.3 mg, 74% yield). $[\alpha]_D^{25}$ +25.4 (*c* 1.0, CH_2Cl_2); HPLC (Chiralpak OJ-H, *i*-PrOH/hexane=10/90, flow rate=0.8 mL/min, λ=254 nm): t_{major}=25.6 min, t_{minor}=37.0 min, ee=71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J*=7.2 Hz, 3H), 2.30 (dd, *J*=26.8, 16.0 Hz, 2H); 3.69–3.84 (m, 2H), 5.38 (s, 1H), 7.30–7.39 (m, 3H), 7.76–7.90 (m, 3H), 8.10–8.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 134.6, 132.1, 131.2, 129.7, 129.0, 126.4, 126.0, 125.3 (q, $^1J_{C-F}$=283.6 Hz), 124.3, 119.1 (d, $^3J_{C-F}$=1.3 Hz), 74.5 (q, $^2J_{C-F}$=30.5 Hz), 60.4, 38.5, 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.3 (s, 3F); IR (KBr): 3406, 2990, 2938, 2906, 1687, 1584, 1544, 1369, 1305, 1274, 1212, 1176, 1060 cm^{-1}; MS (ESI): *m*/*z* 310.9 ($[M-H]^+$).

Acknowledgements

This work was supported financially by the National Natural Science Foundation of China (No. 20972110 and 21002068).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.09.009.

References and notes

1. Selected reviews, see: (a) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555; (b) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635; (c) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1; (d) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214; (e) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15; (f) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975; (g) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1; (h) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305; (i) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633; (j) Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2745.
2. Recent reviews, see: (a) Gong, Y.-F.; Kato, K. *Curr. Org. Chem.* **2004**, *8*, 1659; (b) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B.; Legros, J. *Chem. Soc. Rev.* **2005**, *34*, 562; (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455.
3. (a) Qiu, L.-H.; Shen, Z.-X.; Shi, C.-Q.; Liu, Y.-H.; Zhang, Y.-W. *Chin. J. Chem.* **2005**, *23*, 584; (b) Song, J. J.; Tan, Z.; Reeves, J. T.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007**, *9*, 1013; (c) Song, J. J.; Tan, Z.; Reeves, J. T.; Fandrick, D. R.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 877.
4. Selected reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, NY, 1998; (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911; (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
5. (a) Burkoth, T. L. *Tetrahedron Lett.* **1969**, *57*, 5049; (b) Schöllkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 301; (c) Wenkert, E.; Pherson, A. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084; (d) Woolsey, N. F.; Khalil, M. H. *J. Org. Chem.* **1972**, *37*, 2405; (e) Schollkopf, U.; Banhidai, B.; Frasnelli, H.; Meyer, R.; Beckhaus, H. *Liebigs Ann. Chem.* **1974**, 1767; (f) Pellicciari, R.; Natalini, B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1882; (g) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959; (h) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1987**, *28*, 5351; (i) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144; (j) Ye, T.; McKervey, M. A. *Tetrahedron* **1992**, *48*, 8007; (k) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, *118*, 1; (l) Jiang, N.; Wang, J. *Org. Lett.* **2001**, *3*, 2989; (m) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285; (n) Yao, W.; Wang, J. *Org. Lett.* **2003**, *5*, 1527; (o) Zhao, Y.; Ma, Z.; Zhang, X.; Zou, Y.; Jin, X.; Wang, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5977; (p) Uraguchi, D.; Sorimachi, K. *J. Am. Chem. Soc.* **2005**, *127*, 9360; (q) Hasegawa, K.; Arai, S.; Nishida, A. *Tetrahedron* **2006**, *62*, 1390; (r) Xiao, F.; Liu, Y.; Wang, J. *Tetrahedron Lett.* **2007**, *48*, 1147; (s) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054; (t) Wang, W.; Shen, K.; Wang, J.; Liu, H. X.; Feng, X. *Synlett* **2009**, 1665; (u) Trost, B. M.; Malhotra, S.; Fried, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 1674.
6. (a) Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, 1039; (b) Benfatti, F.; Yilmaz, S.; Cozzi, P. G. *Adv. Synth. Catal.* **2009**, *351*, 1763; (c) Wang, F.; Liu, X.; Zhang, Y.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 7297.
7. (a) Zhang, G.-W.; Wang, L.; Nie, J.; Ma, J.-A. *Adv. Synth. Catal.* **2008**, *350*, 1457; (b) Nie, J.; Zhang, G.-W.; Wang, L.; Fu, A.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2009**, 2356; (c) Nie, J.; Zhang, G.-W.; Wang, L.; Zheng, D.-H.; Zheng, Y.; Ma, J.-A. *Eur. J. Org. Chem.* **2009**, 3145; (d) Zhang, G.-W.; Zheng, D.-H.; Nie, J.; Wang, T.; Ma, J.-A. *Org. Biomol. Chem.* **2010**, *8*, 1399; (e) Pei, Z.-K.; Zheng, Y.; Nie, J.; Ma, J.-A. *Tetrahedron Lett.* **2010**, *51*, 4658; (f) Wang, T.; Zhang, G.-W.; Teng, Y.; Nie, J.; Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2773.
8. (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028; (b) Jimeno, C.; Rios, R.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2004**, *60*, 4543.
9. Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135.
10. (a) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; (b) Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R. *Org. Synth.* **1997**, *74*, 50.
11. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621.