Enantioselective formal [2+2] cycloaddition of ketenes with nitroso compounds catalyzed by N-heterocyclic carbenes†

Tong Wang, Xue-Liang Huang and Song Ye*

Received 13th June 2010, Accepted 11th August 2010
DOI: 10.1039/c0ob00249f

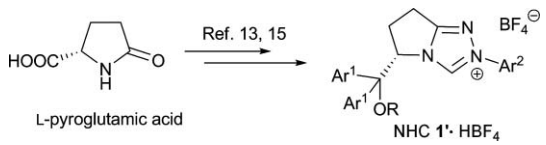
Chiral N-heterocyclic carbenes were found to be efficient catalysts for the formal [2+2] cycloaddition reaction of alkyl(aryl)ketenes and nitroso compounds to give the corresponding 1,2-oxazetidin-3-ones in moderate to good yields with high enantioselectivities. Reductive ring-opening of the oxazetidinones give the corresponding α-hydroxy acid derivatives in good yields.

Introduction

Optically active α-hydroxy acids and their derivatives are important building blocks for asymmetric synthesis of natural products and biologically interesting compounds.[1] As a consequence, numerous efforts have been made to their asymmetric synthesis.[2] In the subtype of tertiary α-hydroxy acid derivatives, several efficient routes have been developed. Representative approaches include the α-alkylation of oxazolidin-2,4-diones,[3] hydroxylation of enolates,[2a] dihydroxylation of ketene acetals,[4] addition of organometallic reagents or nitromethane to α-ketoesters,[5] allylic alkylation of 1,2-enediol carbonates or related compounds,[6] and cyanosilylation of ketones.[7]

The asymmetric cycloaddition reaction of ketenes provided an interesting approach to masked chiral α-hydroxy acids. Lectka reported an enantioselective [4+2] cycloaddition of *monosubstituted* ketenes and *o*-quinones to give the corresponding chiral secondly α-hydroxy acid derivatives.[8] We recently reported an enantioselective [4+2] cycloaddition of *disubstituted* ketenes and *o*-quinones, but the transformation of the resulted cycloadduct to α-hydroxy acid failed.[9] Interestingly, Fu *et al.* reported the planar-chiral DMAP derivative-catalyzed cycloaddition of *disubstituted* ketenes and nitroso compounds and the corresponding tertiary α-hydroxy acid derivatives were obtained in good yields and high enantioselectivities. However, aryl(methyl)ketenes wherein the aryl group is unhindered, lead to low enantioselectivties (3–13% ee).[10] During the preparation of this manuscript, Chatterjee *et al.* reported a copper-catalyzed enantioselective [2+2] cycloaddition of 2-nitrosopyridine with ketenes.[11]

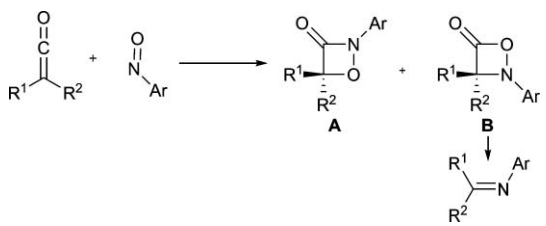
The use of N-heterocylic carbenes (NHC) as organocatalysts has been received great attentions in the past decades.[12] In the line of our research on NHC-catalyzed reactions,[13] we, simultaneously with Smith *et al.*,[14] found that NHCs are efficient catalysts for the reactions of ketenes. The easy preparation of the NHCs **1′** derived from L-pyrogultamic acid[15] and the high enantioselectivities of the catalytic reactions promoted us to investigate the cycloaddtion of ketenes and nitroso compounds using NHCs **1′** as catalysts (Scheme 1).



Scheme 1 Chiral NHC precursors derived from L-pyroglutamic acid.

Results and discussion

Initially, the cycloaddition of phenyl(ethyl)ketene **2a** and nitrosobenzene catalyzed by NHCs was investigated. However, only trace of desired cycloadduct was detected for these NHCs-catalyzed reactions. According to literatures, two regioisomers, 1,2-oxazetidin-4-ones (**A**) and 1,2-oxazetidin-3-ones (**B**) could be formed for the uncatalyzed reaction of ketenes and nitroso compounds, while the cycloadducts **B** are unstable and further decarboxylate to imines (Scheme 2).[16]



Scheme 2 Regioisomers for the cycloaddition of ketenes and nitroso compounds.

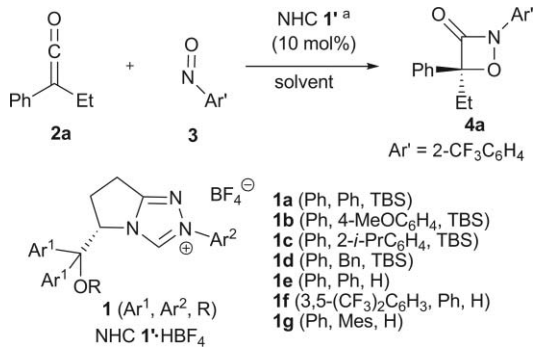
During our investigation of the NHC-catalyzed reaction, Fu *et al.* reported that nitroso compound **3** with a 2-trifluoromethylphenyl group was the best choice for their chiral DMAP derivative-catalyzed reaction.[10] Thus, the NHC-catalyzed reaction of ketenes and nitroso compounds was re-investigated by using nistroso compound **3** as the reagent (Table 1).

It was found that the NHC **1a′** could catalyze the reaction of ketene **2a** and nitroso compound **3** to give the desired cycloadduct of 1,2-oxazetidin-3-one **4a** in good yield with high enantioselectivity (entry 1).[17] Solvent screening revealed that THF is the solvent of choice (entries 1–4). It is interesting that the reaction at –20 °C gave the best result. Lowering or elevating the reaction temperature resulted in inferior yields and enantioselectivities (entries 1 *vs.* 5–8).

The NHCs synthesized from different aryl hydrazines were then investigated.[15,18] NHC **1b′** and **1c′** with an electron-donating group

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. E-mail: songye@iccas.ac.cn
† Electronic supplementary information (ESI) available: Copy of ^{1}H NMR, ^{13}C NMR and CD spectra. See DOI: 10.1039/c0ob00249f

Table 1 Optimization of reaction conditions



Entry	NHC[a]	Solvent	T/°C	Yield[b] (%)	ee[c,d] (%)
1	**1a′**	THF	–20	88	94
2	**1a′**	DME	–20	79	83
3	**1a′**	DCM	–20	23	40
4	**1a′**	ether	–20	14	46
5	**1a′**	THF	–10	89	91
6	**1a′**	THF	0	35	79
7	**1a′**	THF	–30	83	87
8	**1a′**	THF	–40	46	72
9	**1b′**	THF	–20	85	91
10	**1c′**	THF	–20	90	92
11	**1d′**	THF	–20	80	93
12	**1e′**	THF	–20	Trace	/
13	**1f′**	THF	–20	45	82
14	**1g′**	THF	–20	7	–55

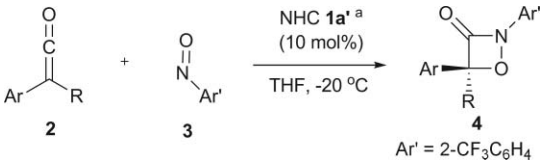
[a] NHCs **1a′–g′** were generated from their precursors **1a–g** (10 mol%) and Cs_2CO_3 (10 mol%) at room temperature for 20 min, and used immediately. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The minus value indicates an opposite enantioselectivity observed.

(Ar^2 = 4-$MeOC_6H_4$ or 2-*i*-PrC_6H_4)[19] afforded comparable results (entries 1 and 9–10). NHC **1d′** with a *N*-benzyl group[20] gave cycloadduct in 80% yield with 93% ee (entry 11). NHCs with a free hydroxy group were also examined (entries 12–14).[21] Although the NHC **1e′** (Ar^1 = Ar^2 = Ph, R = H) gave only trace cycloadduct, NHC **1f′** (Ar^1 = 3,5-$(CF_3)_2C_6H_3$, Ar^2 = Ph, R = H) showed some catalytic activity for the reaction. The NHC **1g′** with bulky mesity group and a free hydoxy group gave the cycloadduct in very low yield but with opposite enantioselectivity (entry 1 *vs.* 14).[11d]

Several other aryl(alkyl)ketenes were then tested for cycloaddition with nitroso compound **3** (Table 2). Aryl(ethyl)ketenes **2a–d** with either electron-withdrawing (4-Cl) or electron-donating groups (4-Me, 4-MeO) gave the cycloadduct in good to high yield with good to excellent enantioselectivity (entries 2–4). Aryl(alkyl)ketenes with *ortho*- or *meta*-substituted aryl group (3-MeC_6H_4, 2-ClC_6H_4) (**2e–f**) and 1-naphthyl(ethyl) ketene (**2g**) worked well (entries 5–7). For phenyl(methyl)ketene, which gave cycloadduct in 72% yield with 13% ee in Fu's report,[10] low yield but good enantioselectivity (70% ee) was observed in the NHC-catalyzed reaction (entry 8). Another aryl(methyl)ketene **2i** (Ar = 3-MeC_6H_4) gave product in 43% yield with 95% ee (entry 9). Phenyl(*n*-alkyl)ketene (**2j–k**, R = *n*-Pr, *n*-Bu) worked well (entries 10–11).

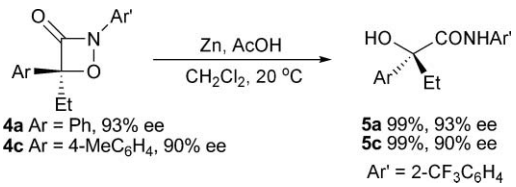
The resulted optically active 1,2-oxazetidin-3-ones are valuable in organic synthesis.[22] For examples, α-hydroxy amides could be easily prepared by the reductive cleavage of the N–O bond of 1,2-oxazetidin-3-ones **4a** and **4c** (Scheme 3).

Table 2 Enantioselecitive [2+2] cycloaddition reaction of ketenes and nitroso compound **3** catalyzed by chiral NHC **1a′**



Entry	**2**	Ar	*R*	**4**	Yield[b] (%)	ee[c] (%)
1	**2a**	Ph	Et	**4a**	88	94
2	**2b**	4-ClC_6H_4	Et	**4b**	54	79
3	**2c**	4-MeC_6H_4	Et	**4c**	80	95
4	**2d**	4-$MeOC_6H_4$	Et	**4d**	57	72
5	**2e**	3-MeC_6H_4	Et	**4e**	80	94
6	**2f**	2-ClC_6H_4	Et	**4f**	82	90
7	**2g**	1-Naphthyl	Et	**4g**	81	85
8	**2h**	Ph	Me	**4h**	35	70
9	**2i**	3-MeC_6H_4	Me	**4i**	43	95
10	**2j**	Ph	*n*-Pr	**4j**	83	88
11	**2k**	Ph	*n*-Bu	**4k**	86	95

[a] See note a in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC.



Scheme 3 Synthesis of α-hydroxy amides.

In conclusion, chiral N-heterocyclic carbenes were found to be efficient catalysts for the cycloaddition of aryl(alkyl)ketenes and a nitroso compound. Ketenes with methyl, ethyl, n-propyl and n-butyl subsitutent all worked well to give the corresponding 1,2-oxazetidin-3-ones in moderate to good yields with high enantioselectivities.

Experimental

Unless otherwise indicated, all starting materials were obtained from commercial supplies and used as received. Anhydrous ether, DME and THF were distilled from sodium and benzophenone. Anhydrous CH_2Cl_2 was distilled from CaH_2. Chiral triazoliums **1a–g** and ketenes were synthesized according to our previous reports.[13] 1-Nitroso-2-(trifluoromethyl)benzene was prepared according to literature.[10] All reactions utilizing air or moisture sensitive reagents were performed in oven-dried glasswares with magnetic stirring under nitrogen atmosphere. Column chromatograph was performed with silica gel 200~300 mesh.

General procedure for the [2+2] cycloaddition of ketenes with 1-nitroso-2-(trifluoromethyl)benzene catalyzed by NHC

To an oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with triazolium salt **1a** (28.5 mg, 0.05 mmol) and anhydrous Cs_2CO_3 (16.3 mg, 0.05 mmol). This tube was closed with a septum, evacuated, and back-filled with nitrogen. To this mixture was added freshly distilled THF (5 mL) and stirred for 20 min at room temperature. The resulting solution was cooled to –20 °C, and 1-nitroso-2-(trifluoromethyl)benzene (131.3 mg,

0.75 mmol) was added in one portion, followed by slow addition of the ketene (0.5 mmol). After stirring for 24 h, the reaction mixture was diluted with ethyl acetate and passed through a short silica pad. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether/ethylacetate, typically 100 : 1) to give the desired product.

Racemic samples for the standard of chiral HPLC spectra were prepared using racemic NHC precursor *rac*-**1a**, prepared from racemic pyroglutamic acid, as catalyst.

(–)-4-Ethyl-4-phenyl-2-(2-(trifluoromethyl)phenyl) -1,2-oxazetidin-3-one (4a)[10]. Yield: 141 mg, 88%; colorless oil; R_f 0.35 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.60–7.55 (m, 3H), 7.49–7.36 (m, 4H), 2.44–2.20 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 135.8, 134.5, 132.9, 128.9, 128.8, 128.1, 127.5 (q, J = 5.3 Hz), 124.9, 124.2, 123.8 (q, J = 32.3 Hz), 122.9 (q, J = 271.5 Hz), 101.9, 30.0, 7.9; $[\alpha]_D^{20}$ –47.8 ($CHCl_3$, c = 1.0; literature:[10] $[\alpha]_D^{20}$ –39, $CHCl_3$, c = 0.30); HPLC analysis: 94% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 5.9 min (major), 7.4 min (minor)].

(–)-4-(4-Chlorophenyl)-4-ethyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4b). Yield: 96 mg, 54%; colorless oil; R_f 0.30 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (d, J = 7.8 Hz, 1H), 7.66–7.56 (m, 2H), 7.51–7.47 (m, 2H), 7.45–7.40 (m, 3H), 2.41–2.16 (m, 2H), 1.15 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.2, 134.8, 134.3, 134.2 (q, J = 0.75 Hz), 132.9, 129.0, 128.3, 127.5 (q, J = 5.3 Hz), 126.3, 124.3, 124.0 (q, J = 32.3 Hz), 122.8 (q, J = 271.5 Hz), 101.2, 29.8, 7.8; HRMS (ESI) calcd for $C_{17}H_{14}ClF_3NO_2$ $[M+H]^+$ 356.0665, found 356.0667; IR (KBr): ν 3459, 2922, 1798, 1634, 1492, 1454, 1318, 1270, 1174, 1141, 1093, 1057, 1036, 1015, 896, 830, 763, 657, 635 cm^{-1}; $[\alpha]_D^{20}$ –37.4 ($CHCl_3$, c = 1.0); HPLC analysis: 79% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 7.6 min (major), 10.6 min (minor)].

(–)-4-Ethyl-4-*p*-tolyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4c). Yield: 135 mg, 80%; colorless oil; R_f 0.35 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.45–7.37 (m, 3H), 7.26–7.24 (m, 2H), 2.38 (s, 3H), 2.42–2.19 (m, 2H), 1.16 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 138.7, 134.5 (q, J = 1.5 Hz), 132.9, 132.8, 129.5, 128.0, 127.4 (q, J = 5.3 Hz), 124.9, 124.1, 123.7 (q, J = 32.3 Hz), 122.9 (q, J = 271.5 Hz), 101.9, 29.8, 21.2, 7.8; HRMS (ESI) calcd for $C_{18}H_{17}ClF_3NO_2$ $[M+H]^+$ 336.1211, found 336.1210; IR (KBr): ν 3501, 1798, 1603, 1491, 1454, 1318, 1269, 1173, 1138, 1057, 1036, 893, 810, 763, 661 cm^{-1}; $[\alpha]_D^{20}$ –32.4 ($CHCl_3$, c = 1.0); HPLC analysis: 95% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 6.6 min (major), 9.2 min (minor)].

(–)-4-Ethyl-4-(4-methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4d). Yield: 95 mg, 57%; colorless oil; R_f 0.20 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.60–7.45 (m, 2H), 7.40 (t, J = 7.8 Hz, 1H), 6.99–6.94 (m, 2H), 3.83 (s, 3H), 2.42–2.19 (m, 2H), 1.16 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 160.0, 134.5 (q, J = 1.5 Hz), 132.8, 130.2, 127.9, 127.7, 127.3 (q, J = 5.3 Hz), 126.4, 124.0, 123.7 (q, J = 32.3 Hz), 122.8 (q, J = 271.5 Hz), 114.2, 55.3, 29.5, 7.9; HRMS (ESI) calcd for $C_{18}H_{17}F_3NO_3$ $[M+H]^+$ 352.1161, found 352.1152; IR (KBr): ν 2925, 1798, 1605, 1513, 1454, 1318, 1253, 1175, 1139, 1057, 1035, 834, 763 cm^{-1}; $[\alpha]_D^{20}$ –33.4 ($CHCl_3$, c = 1.0); HPLC analysis: 72% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 11.0 min (major), 16.8 min (minor)].

(–)-4-Ethyl-4-*m*-tolyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4e)[10]. Yield: 133 mg, 80%; colorless oil; R_f 0.35 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.43–7.30 (m, 4H), 7.20–7.18 (m, 1H), 2.40 (s, 3H), 2.40–2.19 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.8, 138.7, 135.8, 134.6 (q, J = 1.5 Hz), 132.9, 129.6, 128.8, 128.0, 127.5 (q, J = 5.25 Hz), 125.5, 124.2, 123.8 (q, J = 32.3 Hz), 122.9 (q, J = 271.5 Hz), 122.0, 102.0, 30.1, 21.6, 7.9; $[\alpha]_D^{20}$ –47.8 ($CHCl_3$, c = 1.0; literature:[10] $[\alpha]_D^{20}$ –36, $CHCl_3$, c = 0.36); HPLC analysis: 94% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 5.4 min (major), 6.7 min (minor)].

(–)-4-(2-Chlorophenyl)-4-ethyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4f). Yield: 147 mg, 82%; colorless oil; R_f 0.38 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77–7.65 (m, 3H), 7.58 (t, J = 7.5 Hz, 1H), 7.48–7.38 (m, 2H), 7.36–7.30 (m, 2H), 2.62–2.39 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 134.2 (q, J = 1.5 Hz), 133.5, 132.9, 131.9, 131.3, 130.1, 128.2, 127.5 (q, J = 5.25 Hz), 127.3, 126.9, 124.3, 124.0 (q, J = 32.3 Hz), 122.9 (q, J = 271.5 Hz), 102.0, 28.7, 8.2; HRMS (ESI) calcd for $C_{17}H_{14}ClF_3NO_2$ $[M+H]^+$ 356.0665, found 356.0657; IR (KBr): ν 3460, 1797, 1603, 1453, 1318, 1267, 1139, 1056, 1037, 759 cm^{-1}; $[\alpha]_D^{20}$ –36.0 ($CHCl_3$, c = 1.0); HPLC analysis: 90% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 6.7 min (minor), 7.6 min (major)].

(–)-4-Ethyl-4-(naphthalen-1-yl)-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4g)[10]. Yield: 150 mg, 81%; colorless oil; R_f 0.35 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (d, J = 8.1 Hz, 1H), 7.91–7.86 (m, 3H), 7.72 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.56–7.47 (m, 4H), 7.38 (t, J = 7.5 Hz, 1H), 2.59–2.50 (m, 2H), 1.21 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 133.4 (q, J = 1.5 Hz), 133.3, 131.8, 131.1, 128.7, 128.4, 127.9, 127.0, 126.4 (q, J = 5.25 Hz), 125.4, 125.2, 124.4, 123.9, 123.2, 122.8 (q, J = 32.3 Hz), 122.1, 121.9 (q, J = 271.5 Hz), 102.8, 29.9, 7.4; $[\alpha]_D^{20}$ –27.4 ($CHCl_3$, c = 1.0; literature:[10] $[\alpha]_D^{20}$ +36, $CHCl_3$, c = 0.27); HPLC analysis: 85% ee [Daicel CHIRALPAK AD-H column; 20 °C; 0.5 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 13.7 min (minor), 16.1 min (major)].

(–)-4-Methyl-4-phenyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4h)[10]. Yield: 53 mg, 35%; colorless oil; R_f 0.25 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76–7.69 (m, 2H), 7.64–7.57 (m, 3H), 7.49–7.37 (m, 4H), 2.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 136.3, 134.5, 132.9, 129.0, 128.9, 128.2, 127.4 (q, J = 5.3 Hz), 124.9, 124.4, 124.1 (q, J = 32.3 Hz), 122.8 (q, J = 271.5 Hz), 98.3, 22.4;

$[\alpha]_D^{20}$ −6.9 ($CHCl_3$, c = 1.0; literature:[10] $[\alpha]_D^{20}$ −8.1, $CHCl_3$, c = 0.28); HPLC analysis: 70% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 7.6 min (major), 9.8 min (minor)].

(–)-4-Methyl-4-*m*-tolyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4i). Yield: 69 mg, 43%; colorless oil; R_f 0.25 (petroleum ether/ethyl acetate = 20 : 1); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75–7.68 (m, 2H), 7.6 (t, J = 7.8 Hz, 1H), 7.45–7.31 (m, 4H), 7.20 (d, J = 7.2 Hz, 1H), 2.40 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3, 138.7, 136.2, 134.6 (q, J = 1.5 Hz), 132.9, 129.8, 128.8, 128.2, 127.4 (q, J = 5.3 Hz), 125.4, 124.3, 124.0 (q, J = 32.3 Hz), 122.8 (q, J = 271.5 Hz), 121.9, 98.4, 22.4, 21.5; HRMS (ESI) calcd for $C_{17}H_{15}F_3NO_2$ $[M+H]^+$ 322.1055, found 322.1049; $[\alpha]_D^{20}$ −55.3 ($CHCl_3$, c = 1.0); IR (KBr): ν 3500, 1807, 1644, 1455, 1319, 1267, 1177, 1139, 764, 741 cm^{-1}; HPLC analysis: 95% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 7.4 min (major), 9.5 min (minor)].

(–)-4-Phenyl-4-propyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4j). Yield: 139 mg, 83%; colorless oil; R_f 0.35 (petroleum ether/ethyl acetate = 20 : 1); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.57–7.52 (m, 3H), 7.46–7.34 (m, 4H), 2.36–2.16 (m, 2H), 1.74–1.47 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 136.1, 134.6 (q, J = 1.5 Hz), 132.9, 128.9, 128.8, 128.1, 127.5 (q, J = 5.3 Hz), 124.9, 124.1, 123.8 (q, J = 32.3 Hz), 122.9 (q, J = 271.5 Hz), 101.5, 38.9, 17.0, 14.1; HRMS (ESI) calcd for $C_{18}H_{17}F_3NO_2$ $[M+H]^+$ 336.1211, found 336.1208; IR (KBr): ν 3500, 1806, 1495, 1454, 1318, 1267, 1173, 1138, 1057, 1036, 763, 708 cm^{-1}; $[\alpha]_D^{20}$ −45.0 ($CHCl_3$, c = 1.0); HPLC analysis: 88% ee [Daicel CHIRALPAK AD-H column; 20 °C; 0.5 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 16.2 min (major), 18.7 min (minor)].

(–)-4-Butyl-4-phenyl-2-(2-(trifluoromethyl)phenyl)-1,2-oxazetidin-3-one (4k). Yield: 150 mg, 86%; colorless oil; R_f 0.35 (petroleum ether/ethyl acetate = 20 : 1); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.60–7.54 (m, 3H), 7.47–7.37 (m, 4H), 2.33–2.23 (m, 2H), 1.60–1.50 (m, 2H), 1.46–1.36 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 135.9, 134.4 (q, J = 1.5 Hz), 132.8, 128.8, 128.7, 128.0, 127.4 (q, J = 5.3 Hz), 124.8, 124.1, 123.7 (q, J = 32.3 Hz), 122.8 (q, J = 271.5 Hz), 101.4, 36.4, 25.4, 22.6, 13.8; HRMS (ESI) calcd for $C_{19}H_{19}F_3NO_2$ $[M+H]^+$ 350.1368, found 350.13568; IR (KBr): ν 3497; 2965, 1799, 1651, 1603, 1557, 1504, 1494, 1455, 1318, 1267, 1137, 1057, 1035, 762, 696 cm^{-1}; $[\alpha]_D^{20}$ −43.6 ($CHCl_3$, c = 0.5); HPLC analysis: 95% ee [Daicel CHIRALPAK AD-H column; 20 °C; 0.5 mL min^{-1}; solvent system: 2-propanol/hexane = 1 : 99; retention times: 13.2 min (major), 14.7 min (minor)].

Reductive cleavage of the N–O bond of 1,2-oxazetidin-3-ones

To the suspension of 1,2-oxazetidin-3-one **4a** (110.8 mg, 0.35 mmol; 93% ee; prepared from 1.5 mmol phenylethyl ketene) and zinc powder (112.8 mg, 1.73 mmol) in CH_2Cl_2 (6 mL) was added dropwise the solution of acetic acid (0.1 mL, 1.73 mmol) in CH_2Cl_2 (2 mL) in 1 h. The mixture was stirred for an additional 3 h at rt, and then the solids were removed by filtration through Celite. The filtrate was concentrated under reduced pressure to give the desired product without further purification.

(+)-2-Hydroxy-2-phenyl-*N*-(2-(trifluoromethyl)phenyl)butanamide (5a). Yield: 111 mg, 99%; m.p. 109 °C; R_f 0.6 (petroleum ether/ethyl acetate = 5 : 1); ^1H NMR ($CDCl_3$, 300 MHz): δ 9.11 (br s, 1H), 8.23 (d, J = 8.1 Hz, 1 H), 7.67–7.64 (m, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.34–7.29 (m, 2H), 7.19 (t, J = 7.5 Hz, 1H), 2.89 (s, 1H), 2.52–2.40 (m, 1H), 2.23–2.11 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.5, 141.8, 135.0 (q, J = 1.5 Hz), 132.8, 128.5, 128.0, 126.0 (q, J = 5.2 Hz), 125.2, 124.3, 124.0 ((q, J = 271.5 Hz), 123.5, 120.1 (q, J = 30.0 Hz), 79.8, 32.1, 7.7; HRMS (EI) calcd for $C_{17}H_{16}F_3NO_2$ $[M]^+$ 323.1133, found 323.1137; IR (KBr): ν 3488, 1653, 1635, 1590, 1532, 1300, 1286, 1172, 1117, 1059, 1034, 811, 763, 651 cm^{-1}; $[\alpha]_D^{20}$ +8.8 ($CHCl_3$, c = 1.0); HPLC analysis: 93% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 5 : 95; retention times: 12.0 min (major), 15.1 min (minor)].

(+)-2-Hydroxy-2-*p*-tolyl-*N*-(2-(trifluoromethyl)phenyl) butanamide (5c). 1,2-oxazetidin-3-one **4c** (100 mg, 0.3 mmol; 90%ee; prepared from 1.5 mmol *p*-tolyl(ethyl)ketene) was used. Yield: 100 mg, 99%; colorless oil; R_f 0.5 (petroleum ether/ethyl acetate = 5 : 1); ^1H NMR ($CDCl_3$, 300 MHz): δ 9.11 (br s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.53–7.48 (m, 3H), 7.21–7.16 (m, 3H), 2.87 (s, 1H), 2.49–2.40 (m, 1H), 2.38 (s, 3H), 2.19–2.08 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 138.9, 137.7, 135.0 (q, J = 1.5 Hz), 132.8, 129.2, 126.1 (q, J = 5.2 Hz), 125.5, 124.3, 124.1 (q, J = 270.7 Hz), 123.5, 120.0 (q, J = 30.0 Hz), 79.7, 32.0, 21.0, 7.7; HRMS (EI) calcd for $C_{18}H_{18}F_3NO_2$ $[M]^+$ 337.1290, found 337.1293; IR (KBr): ν 3445, 1680, 1635, 1590, 1525, 1457, 1320, 1286, 1172, 1117, 1059, 1034, 993, 811, 763, 651 cm^{-1}; $[\alpha]_D^{20}$ +4.5 ($CHCl_3$, c = 1.0); HPLC analysis: 90% ee [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 5 : 95; retention times: 11.9 min (major), 18.0 min (minor)].

Acknowledgements

Financial support from National Science Foundation of China (20872143, 20932008), the Ministry of Science and Technology of China (2009ZX09501-018) and the Chinese Academy of Sciences are greatly acknowledged.

Notes and references

1 G. M. Coppola, H. F. Schuster, *a-Hydroxy Acids in Enantioselective Synthesis*, VCH: Weinheim, Germany, 1997.
2 (*a*) F. A. Davis and B.-C. Chen, *Chem. Rev.*, 1992, **92**, 919; (*b*) J. M. Janey, *Angew. Chem., Int. Ed.*, 2005, **44**, 4292; (*c*) N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 6038.
3 T. Ooi, K. Fukumoto and K. Maruoka, *Angew. Chem., Int. Ed.*, 2006, **45**, 3839.
4 D. P. Curran and S.-B. Ko, *J. Org. Chem.*, 1994, **59**, 6139.
5 (*a*) S. Yamaguchi, J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1972, **37**, 3174; (*b*) K. Funabashi, M. Jachmann, M. Kanai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2003, **42**, 5489; (*c*) B. Jiang, Z. Chen and X. Tang, *Org. Lett.*, 2002, **4**, 3451; (*d*) K. Zheng, B. Qin, X. Liu and X. Feng, *J. Org. Chem.*, 2007, **72**, 8478; (*e*) H.-L. Wu, P.-Y. Wu, Y.-Y. Shen and B.-J. Uang, *J. Org. Chem.*, 2008, **73**, 6445; (*f*) H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 732; (*g*) A. Loupy and D. A. Monteux, *Tetrahedron*, 2002, **58**, 1541.

6 (*a*) B. M. Trost, J. Xu and T. Schmidt, *J. Am. Chem. Soc.*, 2008, **130**, 11852; (*b*) B. M. Trost, J. Xu and M. Reichle, *J. Am. Chem. Soc.*, 2007, **129**, 282; (*c*) B. M. Trost, K. Dogra and M. Franzini, *J. Am. Chem. Soc.*, 2004, **126**, 1944.
7 Y. Hamashima, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 7412.
8 T. Bekele, M. H. Shah, J. Wolfer, C. J. Abraham, A. Weatherwax and T. Lectka, *J. Am. Chem. Soc.*, 2006, **128**, 1810.
9 P.-L. Shao, X.-Y. Chen, L.-H. Sun and S. Ye, *Tetrahedron Lett.*, 2010, **51**, 2316.
10 M. Dochnahl and G. C. Fu, *Angew. Chem. Int. Ed.*, 2009, **48**, 2391.
11 I. Chatterjee, C. K. Jana, M. Steinmetz, S. Grimme and A. Studer, *Adv. Synth. Catal.*, 2010, **352**, 945.
12 (*a*) For the reviews of NHC-catalyzed reactions, see: D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*b*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988; (*c*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506; (*d*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534.
13 (*a*) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao and S. Ye, *Org. Lett.*, 2008, **10**, 277; (*b*) L. He, H. Lv, Y.-R. Zhang and S. Ye, *J. Org. Chem.*, 2008, **73**, 8101; (*c*) X.-N. Wang, H. Lv, X. L. Huang and S. Ye, *Org. Biomol. Chem.*, 2009, **7**, 346; (*d*) X.-L. Huang, L. He, P.-L. Shao and S. Ye, *Angew. Chem., Int. Ed.*, 2009, **48**, 192; (*e*) F.-G. Sun, X.-L. Huang and S. Ye, *J. Org. Chem.*, 2010, **75**, 273; (*f*) X.-L. Huang and S. Ye, *Chin. Sci. Bull.*, 2010, **55**, 1753.
14 (*a*) N. Duguet, C. D. Campbell, A. M. Z. Slawin and A. D. Smith, *Org. Biomol. Chem.*, 2008, **6**, 1108; (*b*) C. Concellón, N. Duguet and A. D. Smith, *Adv. Synth. Catal.*, 2009, **351**, 3001.
15 (*a*) For the synthesis of chiral NHCs derived from L-pyroglutamic acid, see: D. Enders and J. Han, *Tetrahedron: Asymmetry*, 2008, **19**, 1367; (*b*) L. Baragwanath, C. A. Rose, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2009, **74**, 9214.
16 (*a*) H. Staudinger and S. Jelagin, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 365; (*b*) R. C. Kerber and M. C. Cann, *J. Org. Chem.*, 1974, **39**, 2552.
17 Only an unidentified adduct in 13% isolated yield plus a complex were resulted for the reaction of ketene **2a** and nitros compound **3** in the absence of NHC.
18 T. Rovis, *Chem. Lett.*, 2008, **37**, 2.
19 X.-N. Wang, P.-L. Shao, H. Lv and S. Ye, *Org. Lett.*, 2009, **11**, 4029.
20 D. Enders, J. Han and A. Henseler, *Chem. Commun.*, 2008, 3989.
21 L. He, Y.-R. Zhang, X.-L. Huang and S. Ye, *Synthesis*, 2008, 2825.
22 (*a*) The reduction of the cycloadducts to give the corresponding diols has been reported by Fu *et al.* (ref. 10), and the oxidation of the diols to tertiaryl hydroxyl aicd was reported: P. Gancitano, R. Ciriminna, M. L. Testa, A. Fidalgo, L. M. Ilharco and M. Pagliaro, *Org. Biomol. Chem.*, 2005, **3**, 2389; (*b*) F. J. Aladro, F. M. Guerra, F. J. Moreno-Dorado, J. M. Bustamante, Z. D. Jorge and G. M. Massanet, *Tetrahedron Lett.*, 2000, **41**, 3209.