Diastereo- and enantioselective preparation of oxazolines *via* the base-catalysed aldol reaction of isocyanoacetates with aldehydes using cinchona alkaloids

Rui-Chuan Diao, Wen-Tao Zhao and Shen Li*

Department of Chemistry, School of Science, Tianjin University, Tianjin 300354, P.R. China

A diastereo- and enantioselective base-catalysed aldol reaction of *t*-butyl isocyanoacetate with aldehydes under phase-transfer catalytic conditions yielded 19 4,5-disubstituted oxazolines, 16 of which are novel. Key to success was the use of a free 9-OH-containing cinchona alkaloid-based quaternary ammonium salt bearing bulky and electron-withdrawing aryl groups on the N-benzyl moiety. This process tolerates both aromatic and aliphatic aldehydes, affording the corresponding chiral oxazoline products in diastereoselectivities up to 20:1 and enantioselectivities up to 78% ee.

Keywords: aldol reaction, phase-transfer catalysis, isocyanoacetate, cinchona alkaloids, oxazoline

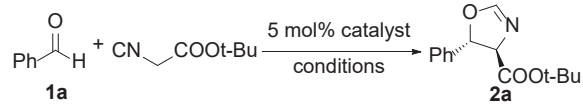
Optically active oxazolines are among the most commonly used chiral ligands for metal-catalysed reactions,[1] and are also core components present in many bioactive natural products.[2,3] Moreover, they are precursors to β-hydroxy-α-amino acids, which are useful building blocks for peptides and other biological compounds.[4] Consequently, great efforts have been devoted to the development of efficient methods for the synthesis of chiral oxazolines. The aldol reaction of isocyanoacetates with carbonyl compounds represents one of the most efficient routes to construct the oxazoline rings.[5] Since Ito and cowriters reported the first example of an asymmetric aldol reaction of isocyanoacetates with aldehydes catalysed by a chiral gold complex,[6] a number of transition-metal complexes, including those of gold,[7–11] silver,[12–16] platinum,[17–19] palladium,[18–21] and cobalt,[22] have been demonstrated to be effective for this reaction. In sharp contrast, organocatalysts have been largely neglected in the asymmetric aldol reaction of isocyanoacetates with carbonyl compounds despite the explosive growth of organocatalysis in the last decade.[23–25]

In recent years, asymmetric phase-transfer catalysis has emerged as an area of intense interest in asymmetric synthesis owing to its operational simplicity and transition metal-free reaction conditions.[26,27] Considering the acidic CH fragment in isocyanoacetates, we envisioned that an isocyanoacetate would be deprotonated to form a chiral ion pair in the presence of a chiral quaternary ammonium salt under basic conditions, which was capable of reacting with appropriate carbonyl compounds to generate chiral oxazolines. Here we report our preliminary results on this subject.

Results and discussion

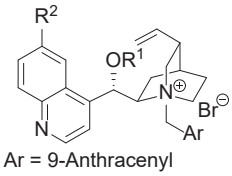
A preliminary experiment showed that it was possible to carry out the reaction of benzaldehyde **1a** and *t*-butyl isocyanoacetate in toluene at –30 °C with Cs_2CO_3 as the base and cinchonine-derived chiral quaternary ammonium salt **3a** as the catalyst (Table 1, entry 1). The desired oxazoline product **2a** was obtained in a modest yield of 60% with a high diastereoselectivity of 7:1, but the enantioselectivity for the major diastereomer was disappointing (only 11% ee). We then optimised that result by varying the base, the solvent and the catalyst and the results are shown in Table 1. We conducted the catalyst screening experiments with several cinchoninium bromides **3b**–**d** under the same conditions (entries 2–4). Gratifyingly, the ee value was improved to 49% by employing catalyst **3d** bearing bulky and electron-withdrawing aryl groups on the N-benzyl moiety

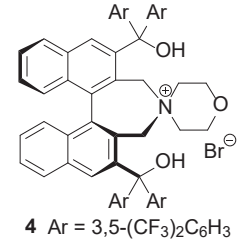
Table 1 Catalyst screening and reaction optimisation in the phase-transfer catalysed aldol reaction of *t*-butyl isocyanoacetate with benzaldehyde (**1a**)[a]



1a **2a**

Chiral phase-transfer catalysts:





3a Ar = 9-Anthracenyl, R^1 = H, R^2 = H

3b Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = H, R^2 = H

4 Ar = 3,5-$(CF_3)_2C_6H_3$

3c Ar = C_6F_5, R^1 = H, R^2 = H

3d Ar = 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$, R^1 = H, R^2 = H

3e Ar = 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$, R^1 = allyl, R^2 = H

3f Ar = 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$, R^1 = H, R^2 = OCH_3

3g Ar = 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$, R^1 = H, R^2 = OH

Entry	Catalyst	Base	Solvent	Temp./ °C	Time/ h	d.r.[b]	Yield/ %[c]	ee/ %[d]
1	**3a**	Cs_2CO_3	Toluene	–30	24	7:1	60	11
2	**3b**	Cs_2CO_3	Toluene	–30	24	8:1	67	13
3	**3c**	Cs_2CO_3	Toluene	–30	24	7:1	45	2
4	**3d**	Cs_2CO_3	Toluene	–30	24	8:1	57	49
5	**3e**	Cs_2CO_3	Toluene	–30	24	8:1	64	14
6	**3f**	Cs_2CO_3	Toluene	–30	24	8:1	61	46
7	**3g**	Cs_2CO_3	Toluene	–30	24	7:1	68	19
8	**3d**	Cs_2CO_3	Mesitylene	–30	24	8:1	59	46
9	**3d**	Cs_2CO_3	CH_2Cl_2	–30	24	8:1	61	15
10	**3d**	Cs_2CO_3	Et_2O	–30	24	8:1	97	13
11	**3d**	K_2CO_3	Toluene	–30	30	8:1	75	64
12	**3d**	KOH	Toluene	–30	24	7:1	63	25
13	**3d**	K_3PO_4	Toluene	–30	40	10:1	70	72
14	**3d**	K_2HPO_4	Toluene	–30	24	–	nr[e]	––
15	**3d**	K_3PO_4	Toluene	–40	96	10:1	67	70
16	**4**	K_3PO_4	Toluene	–30	40	8:1	64	26

[a]Unless otherwise noted in Table 1, all reactions were carried out with benzaldehyde **1a** (0.10 mmol), *t*-butyl isocyanoacetate (0.12 mmol), base (0.30 mmol) and catalyst (0.005 mmol) in 1.0 mL of solvent.

[b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

[c]Isolated yield of major diastereomer.

[d]ee of the major diastereomer. Determined by HPLC analysis using a chiral stationary phase. The absolute configuration was assigned by comparison of the optical rotation with literature reported data.

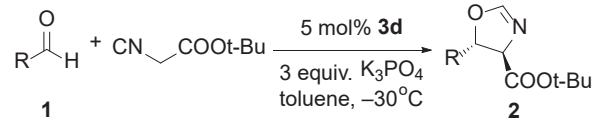
[e]No reaction.

* Correspondent. E-mail: shenli@tju.edu.cn

(entry 4). It is worth mentioning that the presence of a free 9-OH group in the catalysts proved to be a crucial factor in achieving high levels of asymmetric induction, since the *O*-allylated catalyst **3e** gave a significantly reduced enantioselectivity (entry 5). A comparable result to that with **3d** was achieved by using the corresponding quinidine-derived catalyst **3f**, which indicates that the 6′-OMe group has a negligible effect on the catalyst performance (entry 6). In sharp contrast, a free 6′-OH-containing bifunctional catalyst **3g** was found to be unsuitable for this transformation (entry 7). Toluene proved to be the best among the commonly used solvents for phase-transfer catalysis (entries 8–10 *versus* 4). Comparing a series of inorganic bases, anhydrous K_3PO_4 was the most promising one with respect to yield, diastereoselectivity and enantioselectivity (entry 13). Lowering the temperature to –40 °C had no beneficial effect on enantiocontrol but did significantly decrease the reaction rate (entry 15). Therefore, the reaction conditions as shown in Table 1, entry 13 were selected as the optimal conditions. An attempt to further improve the reaction outcome by the employment of Maruoka's bifunctional N-spiro quaternary ammonium salt **4** was unsuccessful (entry 16).[28]

Having established the reaction conditions, the generality of this aldol reaction was explored with structurally diverse aldehydes **1a**–**s**. As summarised in Table 2, this reaction has proven to be general for both aromatic and aliphatic aldehydes, affording a broad range of chiral oxazolines **2a**–**s** in good yields with high diastereoselectivities ranging from 6:1 to 20:1. The enantioselectivity was strongly dependent on the structure of the aldehydes. Generally speaking, aromatic aldehydes with *para*-substituents on the phenyl ring offered higher ee values than their *ortho*- or *meta*-substituted counterparts (entries 2, 3 *versus* 4 and 6 *versus* 9). In addition, aromatic aldehydes with electron-donating groups exhibited better enantioselectivity than those with electron-withdrawing substituents (entries 4, 5 *versus* 8–10). Accordingly, the highest enantioselectivity of 78% ee was achieved when aldehyde **1e** with a *para*-benzyloxy group was employed (entry 5). The heteroaromatic aldehydes **1m** and **1n** were also well-tolerated, delivering the corresponding oxazolines **2m** and **2n** in 69% and 77% ee, respectively (entries 13 and 14). Aliphatic aldehydes as exemplified by **2o**–**s** were equally reactive with *t*-butyl isocyanoacetate under the same reaction conditions, leading to moderate enantioselectivities ranging from 44% to 60% ee (entries 15–19).

Table 2 Scope of the phase-transfer catalysed aldol reaction of *t*-butyl isocyanoacetate with various aldehydes[a]



1 2

Entry	R	Product	Time/h	d.r.[b]	Yield/%[c]	ee/%[d]
1	C_6H_5	**2a**	40	10:1	72	72
2	2-$OMeC_6H_4$	**2b**	40	7:1	74	50
3	3-$OMeC_6H_4$	**2c**	36	8:1	76	65
4	4-$OMeC_6H_4$	**2d**	26	8:1	72	75
5	4-$OBnC_6H_4$	**2e**	36	8:1	72	78
6	2-BrC_6H_4	**2f**	40	6:1	72	40
7	3-ClC_6H_4	**2g**	40	8:1	65	53
8	4-FC_6H_4	**2h**	40	8:1	65	71
9	4-BrC_6H_4	**2i**	40	8:1	65	70
10	4-$CF_3C_6H_4$	**2j**	40	8:1	64	66
11	1-naphthyl	**2k**	28	5:1	80	54
12	2-naphthyl	**2l**	28	7:1	79	44
13	2-furyl	**2m**	36	17:1	66	69
14	2-thienyl	**2n**	36	20:1	72	77
15	(*E*)-styryl	**2o**	28	6:1	73	50
16	phenethyl	**2p**	28	20:1	86	60
17	*n*-heptyl	**2q**	40	13:1	69	44
18	isopropyl	**2r**	36	10:1	74	52
19	cyclohexyl	**2s**	30	12:1	80	52

[a]Reaction conditions: **1** (0.10 mmol), *t*-butyl isocyanoacetate (0.12 mmol), anhydrous K_3PO_4 (0.30 mmol), **3d** (0.005 mmol) in toluene (1.0 mL) at –30 °C for the stated time.
[b]Determined by ^1H NMR analysis of the crude reaction mixture.
[c]Isolated yield of major diastereomer.
[d]ee of the major diastereomer. Determined by HPLC analysis using a chiral stationary phase.

Conclusion

In summary, we have developed a diastereo- and enantioselective aldol reaction of *t*-butyl isocyanoacetate with aldehydes under phase-transfer catalytic conditions. Key to success was the use of a free 9-OH-containing cinchona alkaloid-based quaternary ammonium salt bearing bulky and electron-withdrawing aryl groups on the N-benzyl moiety. This process tolerates both aromatic and aliphatic aldehydes, affording a broad range of chiral oxazolines in diastereoselectivities up to 20:1 and enantioselectivities up to 78% ee. Further investigations to expand the scope of this transformation are ongoing in our laboratory.

Experimental

NMR spectra were recorded on a Bruker Avance III spectrometer operating at 400 MHz (^1H NMR) or 101 MHz (^{13}C NMR) in $CDCl_3$. Chemical shifts were reported in ppm downfield from internal Me_4Si (0 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). Coupling constants (*J*) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on a VG ZAB-HS spectrometer with an ESI resource. Optical rotations were determined using an Autopol IV automatic polarimeter. HPLC analyses were carried out on a Hewlett Packard Model HP 1200 instrument. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected.

Diethyl ether and toluene were distilled from sodium/benzophenone prior to use; CH_2Cl_2 was distilled from CaH_2. All purchased reagents were used without further purification. Cinchona alkaloid-based phase-transfer catalysts were synthesised according and in analogy to literature-known methods.[29–31]

Phase-transfer catalysed aldol reaction of t-*butyl isocyanoacetate with aldehydes; general procedure*

t-Butyl isocyanoacetate (16.9 mg, 0.12 mmol), catalyst (0.005 mmol), K_3PO_4 (63.6 mg, 0.30 mmol) and toluene (1 mL) were added to a 10 mL Schlenk flask equipped with a stirring bar. The mixture was cooled to –30 °C before aldehyde **1** (0.10 mmol) was added in one portion. The vigorous stirring was maintained until the reaction was complete (monitored by TLC). Filtration of the resulting mixture through a Celite pad then concentration under vacuum gave the crude product, which was analysed by ^1H NMR to determine the diastereomer ratio. The major diastereomer was obtained after column chromatography on silica gel using EtOAc/petroleum ether (1:4) as eluent.

t-*Butyl (4*R,*5*S*)-5-phenyl-4,5-dihydrooxazole-4-carboxylate* (**2a**)[14]

10:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 72% yield (17.8 mg); the enantioselectivity was determined by HPLC using a Chiralpak AD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 95:5, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 9.89 min (major) and 11.82 min (minor) as 72% ee; $[\alpha]_D^{25} = -46.5$ (*c* 1.0, CH_2Cl_2), [ref: $[\alpha]_D^{25} = +99.6$ (*c* 0.64, CH_2Cl_2) for (4*S*,5*R*)-configuration, 96% ee]; ^1H NMR (400 MHz,

$CDCl_3$): δ 7.33–7.24 (m, 5H, ArH), 7.02 (d, *J* = 4.0 Hz, 1H, N=CH), 5.54 (d, *J* = 7.8 Hz, 1H, CH), 4.44 (dd, *J* = 7.8, 2.1 Hz, 1H, CH), 1.45 (s, 9H, CH_3).

t-*Butyl (4*R,*5*S*)-5-(2-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate* (**2b**)

7:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 74% yield (20.5 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 7.87 min (minor) and 11.37 min (major) as 50% ee; $[\alpha]_D^{25}$ = −47.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.25 (m, 2H, ArH), 7.06 (d, *J* = 1.9 Hz, 1H, N=CH), 6.97 (t, *J* = 7.5 Hz, 1H, ArH), 6.91 (d, *J* = 8.2 Hz, 1H, ArH), 5.88 (d, *J* = 7.6 Hz, 1H, CH), 4.40 (dd, *J* = 7.6, 2.0 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 1.54 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.02, 156.17, 155.87, 129.47, 127.44, 126.07, 120.64, 110.55, 81.80, 79.17, 75.63, 55.26, 27.99; HRMS (ESI) for $C_{15}H_{20}NO_4^+$ calcd 278.1387; found: 278.1399.

t-*Butyl (4*R,*5*S*)-5-(3-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate* (**2c**)

8:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 76% yield (21.1 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 8.77 min (minor) and 10.34 min (major) as 65% ee; $[\alpha]_D^{25}$ = −53.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.9 Hz, 1H, ArH), 7.09 (d, *J* = 2.0 Hz, 1H, N=CH), 6.89 (m, 3H, ArH), 5.60 (d, *J* = 7.8 Hz, 1H, CH), 4.52 (dd, *J* = 7.8, 2.1 Hz, 1H, CH), 3.83 (s, 3H, OCH_3), 1.54 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.49, 160.03, 155.98, 140.85, 130.05, 117.69, 114.10, 111.05, 82.55, 82.14, 76.23, 55.29, 28.01; HRMS (ESI) for $C_{15}H_{20}NO_4^+$ calcd 278.1387; found: 278.1391.

t-*Butyl (4*R,*5*S*)-5-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate* (**2d**)[14]

8:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 72% yield (20.0 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 230 nm, 1.0 mL min^{-1} flow rate] t_R = 8.64 min (minor) and 9.94 min (major) as 75% ee; $[\alpha]_D^{25}$ = −78.6 (*c* 1.0, CH_2Cl_2), [ref: $[\alpha]_D^{25}$ = +118.4 (c 0.25, CH_2Cl_2) for (4*S*,5*R*)-configuration, 89% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H, ArH), 7.07 (d, *J* = 1.9 Hz, 1H, N=CH), 6.93 (d, *J* = 8.7 Hz, 2H, ArH), 5.57 (d, *J* = 7.8 Hz, 1H, CH), 4.51 (dd, *J* = 7.8, 2.0 Hz, 1H, CH), 3.83 (s, 3H, O–CH_3), 1.53 (s, 9H, CH_3).

t-*Butyl (4*R,*5*S*)-5-(4-(benzyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate* (**2e**)

8:1 dr of crude product, the *trans* isomer was obtained as a white solid after column chromatography, 72% yield (25.4 mg); m.p.: 65−66 °C; the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 15.94 min (minor) and 21.58 min (major) as 78% ee; $[\alpha]_D^{25}$ = −172 (*c* 1.0, CH_2Cl_2): ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.41 (m, 5H, ArH), 7.26 (d, *J* = 8.6 Hz, 2H, ArH), 7.08 (d, *J* = 1.8 Hz, 1H, N=CH), 7.01 (d, *J* = 8.7 Hz, 2H, ArH), 5.58 (d, *J* = 7.8 Hz, 1H, CH), 5.10 (s, 2H, CH_2), 4.53 (dd, *J* = 7.8, 2.0 Hz, 1H, CH), 1.53 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.60, 159.15, 156.03, 136.72, 131.49, 128.63, 128.07, 127.43, 127.28, 115.25, 82.46, 82.29, 76.05, 70.10, 28.01; HRMS (ESI) for $C_{21}H_{24}NO_4^+$ calcd 354.1700; found: 354.1710.

t-*Butyl (4*R,*5*S*)-5-(2-bromophenyl)-4,5-dihydrooxazole-4-carboxylate* (**2f**)

6:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 72% yield (23.5 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 6.32 min (minor) and 10.55 min (major) as 40% ee; $[\alpha]_D^{25}$ = –30 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.9 Hz, 1H, ArH), 7.34 (t, *J* = 7.2 Hz, 1H, ArH), 7.30–7.27 (m, 1H, ArH), 7.20 (t, *J* = 6.7 Hz, 1H, ArH), 7.14 (d, *J* = 1.8 Hz, 1H, N=CH), 6.01 (d, *J* = 6.5 Hz, 1H, CH), 4.40 (dd, *J* = 6.5, 2.0 Hz, 1H, CH), 1.53 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.26, 156.01, 138.54, 133.09, 129.86, 127.87, 126.65, 121.03, 82.46, 81.38, 76.15, 27.91; HRMS (ESI) for $C_{14}H_{17}BrNO_3^+$ calcd 326.0386; found: 326.0387.

t-*Butyl (4*R,*5*S*)-5-(3-chlorophenyl)-4,5-dihydrooxazole-4-carboxylate* (**2g**)

8:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 65% yield (18.3 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 6.59 min (minor) and 8.61 min (major) as 53% ee; $[\alpha]_D^{25}$ = –36.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.36 (m, 3H, ArH), 7.24–7.18 (m, 1H, ArH), 7.09 (d, *J* = 2.0 Hz, 1H, N=CH), 5.59 (d, *J* = 7.8 Hz, 1H, CH), 4.49 (dd, *J* = 7.8, 2.1 Hz, 1H, CH), 1.54 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.17, 155.85, 141.30, 134.90, 130.25, 128.78, 125.69, 123.57, 82.84, 81.39, 76.25, 28.00; HRMS ESI for $C_{14}H_{17}ClNO_3^+$ calcd 282.0891; found: 282.0894.

t-*Butyl (4*R,*5*S*)-5-(4-fluorophenyl)-4,5-dihydrooxazole-4-carboxylate* (**2h**)[14]

8:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 65% yield (17.3 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 230 nm, 1.0 mL min^{-1} flow rate] t_R = 6.39 min (minor) and 7.82 min (major) as 71% ee; $[\alpha]_D^{25}$ = –88.1 (*c* 1.0, CH_2Cl_2), [ref: $[\alpha]_D^{25}$ = +248.4 (c 1.5, CH_2Cl_2) for (4*S*,5*R*)-configuration, 92% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 5.2 Hz, 2H, ArH), 7.15–7.06 (m, 3H, ArH and N=CH), 5.61 (d, *J* = 7.8 Hz, 1H, CH), 4.50 (dd, *J* = 7.8, 2.0 Hz, 1H, CH), 1.54 (s, 9H, CH_3).

t-*Butyl (4*R,*5*S*)-5-(4-bromophenyl)-4,5-dihydrooxazole-4-carboxylate* (**2i**)

8:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 65% yield (21.2 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 6.77 min (minor) and 8.37 min (major) as 70% ee; $[\alpha]_D^{25}$ = –68.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.4 Hz, 2H, ArH), 7.20 (d, *J* = 8.4 Hz, 2H, ArH), 7.08 (d, *J* = 2.0 Hz, 1H, N=CH), 5.58 (d, *J* = 7.9 Hz, 1H, CH), 4.47 (dd, *J* = 7.9, 2.1 Hz, 1H, CH), 1.53 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.23, 155.88, 138.30, 132.08, 127.23, 122.68, 82.78, 81.60, 76.24, 28.00; HRMS (ESI) for $C_{14}H_{17}BrNO_3^+$ calcd 326.0386; found: 326.0383.

t-*Butyl (4*R,*5*S*)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazole-4-carboxylate* (**2j**)

8:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 64% yield (20.2 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 7.25 min (minor) and 9.01 min (major) as 66% ee; $[\alpha]_D^{25}$ = –38.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.2 Hz, 2H, ArH), 7.45 (d, *J* = 8.2 Hz, 2H, ArH), 7.11 (d, *J* = 2.1 Hz, 1H, N=CH), 5.67 (d, *J* = 7.9 Hz, 1H, CH), 4.48 (dd, *J* = 7.9, 2.1 Hz, 1H, CH), 1.54 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.12, 155.89, 143.24, 130.85 (q, *J* = 32.4), 125.95 (q, *J* = 3.8 Hz), 125.79, 123.88 (q, *J* =270.5), 83.00, 81.37, 76.33, 28.01; HRMS (ESI) $C_{15}H_{17}F_3NO_3^+$ calcd 316.1161; found: 316.1167.

t-*Butyl (4*R,*5*S*)-5-(naphthalen-1-yl)-4,5-dihydrooxazole-4-carboxylate* (**2k**)

5:1 dr of crude product, the *trans* isomer was obtained as a white solid after column chromatography, 80% yield (23.8 mg); m.p.: 87–89 °C;

the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 11.78 min (minor) and 17.53 min (major) as 54% ee; $[\alpha]_D^{25}$ = –28.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.90 (m, 2H, ArH), 7.85–7.88 (m, 1H, ArH), 7.60–7.52 (m, 2H, ArH), 7.52–7.44 (m, 2H, ArH), 7.24 (d, *J* = 1.9 Hz, 1H, N=CH), 6.45 (d, *J* = 7.2 Hz, 1H, CH), 4.59 (dd, *J* = 7.2, 2.0 Hz, 1H, CH), 1.58 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.79, 156.22, 134.43, 133.94, 129.83, 129.13, 126.64, 126.05, 125.37, 123.01, 122.76, 82.70, 80.29, 75.79, 27.98; HRMS (ESI) for $C_{18}H_{20}NO_3^+$ calcd 298.1443; found: 298.1458.

t-*Butyl (4*R,*5*S*)-5-(naphthalen-2-yl)-4,5-dihydrooxazole-4-carboxylate* (**2l**)

7:1 dr of crude product, the *trans* isomer was obtained as a white solid after column chromatography, 79% yield (23.5 mg); m.p.: 82–83 °C; the enantioselectivity was determined by HPLC using a Chiralpak AD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 95:5, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 13.16 min (major) and 16.00 min (minor) as 44% ee; $[\alpha]_D^{25}$ = –34.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.6 Hz, 1H, ArH), 7.88–7.84 (m, 2H, ArH), 7.82 (s, 1H, ArH), 7.57–7.50 (m, 2H, ArH), 7.41 (dd, *J* = 8.5, 1.6 Hz, 1H, ArH), 7.17 (d, *J* = 2.0 Hz, 1H, N=CH), 5.81 (d, *J* = 7.8 Hz, 1H, CH), 4.62 (dd, *J* = 7.8, 2.1 Hz, 1H, CH), 1.56 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.54, 156.13, 136.42, 133.33, 133.09, 129.12, 128.07, 127.79, 126.66, 126.56, 125.05, 122.86, 82.62, 82.55, 76.23, 28.04; HRMS (ESI) for $C_{18}H_{20}NO_3^+$ calcd 298.1443; found: 298.1435.

t-*Butyl (4*R,*5*S*)-5-(furan-2-yl)-4,5-dihydrooxazole-4-carboxylate* (**2m**)

17:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 66% yield (15.6 mg); the enantioselectivity was determined by HPLC using a Chiralpak AD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 95:5, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 13.26 min (major) and 14.95 min (minor) as 69% ee; $[\alpha]_D^{25}$ = –136.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 1.1 Hz, 1H, ArH), 6.96 (d, *J* = 2.0 Hz, 1H, N=CH), 6.46 (d, *J* = 3.2 Hz, 1H, ArH), 6.39 (dd, *J* = 3.3, 1.8 Hz, 1H, ArH), 5.66 (d, *J* = 7.7 Hz, 1H, CH), 4.80 (dd, *J* = 7.7, 2.1 Hz, 1H, CH), 1.50 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.03, 155.65, 150.12, 143.85, 110.65, 109.97, 82.69, 75.25, 72.25, 27.93; HRMS (ESI) for $C_{12}H_{15}NNaO_4^+$ calcd 260.0893; found: 260.0902.

t-*Butyl (4*R,*5*S*)-5-(thiophen-2-yl)-4,5-dihydrooxazole-4-carboxylate* (**2n**)

20:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 72% yield (18.2 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 95:5, λ 220 nm, 0.8 mL min^{-1} flow rate] t_R = 12.90 min (minor) and 14.23 min (major) as 77% ee; $[\alpha]_D^{25}$ = –110.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 5.0, 0.9 Hz, 1H, ArH), 7.09 (d, *J* = 3.4 Hz, 1H, N=CH), 7.02–6.97 (m, 2H, ArH), 5.85 (d, *J* = 7.6 Hz, 1H, CH), 4.64 (dd, *J* = 7.6, 2.1 Hz, 1H, CH), 1.50 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.96, 155.55, 141.52, 127.13, 126.44, 125.90, 82.72, 78.31, 76.05, 27.96; HRMS (ESI) for $C_{12}H_{15}NNaO_3S^+$ calcd 276.0665; found: 276.0673.

t-*Butyl (4*R,*5*S*)-5-((*E*)-styryl)-4,5-dihydrooxazole-4-carboxylate* (**2o**)

6:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 73% yield (20.0 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 10.63 min (major) and 13.39 min (minor) as 50% ee; $[\alpha]_D^{25}$ = –30.6 (c 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.0 Hz, 2H, ArH), 7.36 (d, *J* = 7.0 Hz, 1H, ArH), 7.34–7.29 (m, 2H, ArH), 7.00 (d, *J* = 1.9 Hz, 1H, N=CH), 6.72 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.19 (dd, *J* = 15.8, 7.4 Hz, 1H, CH=CH), 5.26 (t, *J* = 7.6 Hz, 1H, CH), 4.42 (dd, *J* = 7.8, 2.0 Hz, 1H, CH), 1.53 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.40, 156.14, 135.59, 133.89, 128.70, 128.49, 126.78, 125.49, 82.48, 82.00, 73.89, 28.00; HRMS (ESI) for $C_{16}H_{20}NO_3^+$ calcd 274.1438; found: 274.1444.

t-*Butyl (4*R,*5*S*)-5-phenethyl-4,5-dihydrooxazole-4-carboxylate* (**2p**)

20:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 86% yield (23.7 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 10.43 min (major) and 12.23 min (minor) as 60% ee; $[\alpha]_D^{25}$ = –15.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H, ArH), 7.22 (t, *J* = 6.8 Hz, 3H, ArH), 6.94 (d, *J* = 1.5 Hz, 1H, N=CH), 4.61 (q, *J* = 7.2, 1H, CH), 4.25 (dd, *J* = 7.4, 1.9 Hz, 1H, CH), 2.82–2.72 (m, 2H, CH_2), 2.05–1.99 (m, 2H, CH_2), 1.49 (s, 9H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.76, 156.34, 140.54, 128.55, 128.38, 126.23, 82.22, 80.92, 73.07, 36.82, 31.21, 27.95; HRMS (ESI) for $C_{16}H_{22}NO_3^+$ calcd 276.1594; found: 276.1604.

t-*Butyl (4*R,*5*S*)-5-heptyl-4,5-dihydrooxazole-4-carboxylate* (**2q**)

13:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 69% yield (18.6 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 4.66 min (minor) and 5.58 min (major) as 44% ee; $[\alpha]_D^{25}$ = –28.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.6 Hz, 1H, N=CH), 4.58 (q, *J* = 7.2 Hz, 1H, CH), 4.18 (dd, *J* = 7.4, 1.9 Hz, 1H, CH), 1.74–1.60 (m, 2H, CH_2), 1.50 (s, 9H, CH_3), 1.42–1.25 (m, 10H, CH_2), 0.89 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.04, 156.32, 82.0, 81.79, 73.07, 35.05, 31.70, 29.16, 29.08, 27.96, 24.75, 22.59, 14.04; HRMS (ESI) for $C_{15}H_{28}NO_3^+$ calcd 270.2064; found: 270.2074.

t-*Butyl (4*R,*5*S*)-5-isopropyl-4,5-dihydrooxazole-4-carboxylate* (**2r**)

10:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 74% yield (15.8 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 90:10, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 5.10 min (minor) and 5.81 min (major) as 52% ee; $[\alpha]_D^{25}$ = –28.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.5 Hz, 1H, N=CH), 4.34 (t, *J* = 6.9 Hz, 1H, CH), 4.22 (dd, *J* = 7.4, 1.7 Hz, 1H, CH), 1.88–1.76 (m, 1H, CH), 1.47 (s, 9H, CH_3), 0.94 (dd, *J* = 12.6, 6.8 Hz, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.27, 156.42, 86.53, 81.96, 70.65, 32.06, 27.90, 17.31, 17.16; HRMS (ESI) for $C_{11}H_{20}NO_3^+$ calcd 214.1438; found: 214.1448.

t-*Butyl (4*R,*5*S*)-5-cyclohexyl-4,5-dihydrooxazole-4-carboxylate* (**2s**)

12:1 dr of crude product, the *trans* isomer was obtained as a colourless oil after column chromatography, 80% yield (11.2 mg); the enantioselectivity was determined by HPLC using a Chiralpak OD-H column (25 cm × 0.46 cm ID), [hexane/*iso*-propanol = 95:5, λ 220 nm, 1.0 mL min^{-1} flow rate] t_R = 6.91 min (minor) and 8.02 min (major) as 52% ee; $[\alpha]_D^{25}$ = –18.2 (c 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.7 Hz, 1H, N=CH), 4.35 (t, *J* = 7.1 Hz, 1H, CH), 4.26 (dd, *J* = 7.5, 1.9 Hz, 1H, CH), 1.82–1.73 (m, 3H, CH and CH_2), 1.71–1.63 (m, 2H, CH_2), 1.47 (s, 9H, CH_3), 1.28–0.96 (m, 6H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.31, 156.37, 85.77, 81.95, 70.77, 41.77, 27.92, 27.90, 27.70, 26.19, 25.61, 25.46; HRMS (ESI) for $C_{14}H_{24}NO_3^+$ calcd 254.1751; found: 254.1760.

This work was supported by the National Natural Science Foundation of China (no. 21302137), the Specialized Research Fund for the Doctoral Program of Higher Education of China (no. 20130032120071), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry and the Elite Scholar Program of Tianjin University.

Electronic Supplementary Information

The ^1H NMR and ^{13}C NMR spectra of new oxazoline products, and HPLC charts of chiral oxazoline products are available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

Received 30 April 2016; accepted 18 June 2016
Paper 1604079 doi: 10.3184/174751916X14683198156665
Published online: 6 September 2016

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