Enantioselective Synthesis of Endocyclic β-Amino Acids with Two Contiguous Stereocenters via Hydrogenation of 3-Alkoxycarbonyl-2-Substituted Quinolines

Zhang-Pei Chen, Zhi-Shi Ye, Mu-Wang Chen, Yong-Gui Zhou*

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, P. R. of China
Fax +86(411)84379220; E-mail: ygzhou@dicp.ac.cn

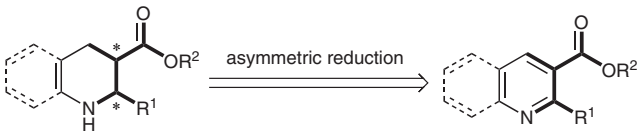
Received: 18.07.2013; Accepted after revision: 25.08.2013

Abstract: An enantioselective iridium-catalyzed hydrogenation of 3-alkoxycarbonyl-2-substituted quinoline derivatives is described. This methodology provides a convenient route to enantiopure endocyclic β-amino acids with two contiguous stereocenters with up to 90% ee.

Key words: β-amino acids, iridium, asymmetric hydrogenation, functionalized quinolines

The tremendous importance of enantiomerically pure β-amino acids has been well elucidated over the past few decades.[1] Among them, conformationally constrained cyclic β-amino acids have received considerable attention due to their potential in pharmaceutical and agrochemical drugs.[2] In addition, when incorporation into peptides or peptido-mimetics, cyclic β-amino acids have a striking ability to induce conformational restriction and create specific structural effects; this has been used in structural and biomechanistic investigations.[3] However, only limited methods have been reported for the synthesis of enantioenriched cyclic β-amino acids, especially endocyclic β-amino acids.[4] Although there are a number of reported methods for their synthesis available, for example, ring opening of chiral epoxides,[4a] intramolecular nitrone cycloaddition,[4b,c] and stereoselective Michael addition,[4d] most of these routes failed to achieve high stereoselectivity and good atom or step economy. Consequently, the development of efficient routes for their synthesis is of great significance.

Considering that N-heteroarenes containing an alkoxycarbonyl group are abundant, asymmetric reduction of these compounds is an efficient and economical way to obtain enantiopure structurally diverse endocyclic β-amino acids (Scheme 1).[5] In 2000, Studer reported the homogenous rhodium-catalyzed asymmetric hydrogenation of 3-(alkoxycarbonyl)pyridines in moderate yield with 17% ee.[6] Subsequently, Zhang and co-workers developed a multistep strategy of combining the Pd/C catalyzed partial hydrogenation with a homogeneous rhodium-catalyzed hydrogenation to afford N-protecting 3-(alkoxycarbonyl)piperidines.[7] Recently, a relay catalytic Friedländer condensation and transfer hydrogenation in the presence of an achiral Lewis acid and chiral Brønsted acid to furnish 3-alkoxycarbonyl-substituted tetrahydroquinolines was successfully described by Gong's group.[8] Very recently, our research group reported an efficient iridium-catalyzed asymmetric hydrogenation of 4-(alkoxycarbonyl)isoquinolines with excellent enantioselectivity and diastereoselectivity.[9] Despite these advances, in virtue of highly stabilizing aromatic structure and the two contiguous prochiral centers, asymmetric hydrogenation of functionalized 2,3-disubstituted quinolines remains a challenge.[10] As 3-alkoxycarbonyl-2-substituted tetrahydroquinolines are novel, conformationally constrained endocyclic β-amino acids, and together with our ongoing efforts to promote the development of asymmetric hydrogenation of heteroaromatic compounds,[11] herein, we report an efficient asymmetric hydrogenation of 3-alkoxycarbonyl-2-substituted quinolines with excellent enantio- and diastereoselectivity.

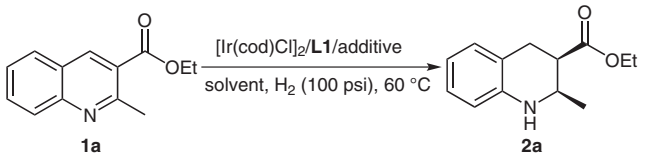


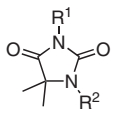
Scheme 1 Enantioselective synthesis of endocyclic β-amino acids

Our initial study began with readily available ethyl 2-methylquinoline-3-carboxylate (**1a**) as a model substrate[12] and the catalytic system $[Ir(cod)Cl]_2$/bisphosphine/halogen, which has been used advantageously as a catalyst in the hydrogenation of aromatic compounds.[5] However, the reaction proceeded with both low diastereoselectivity and enantioselectivity at 60 °C under 7 bar (100 psi) of hydrogen gas (Table 1, entry 1). Subsequently, the effects of various solvents on the diastereoselectivity and enantioselectivity were investigated (entries 2–4). Gratifyingly, benzene was the most suitable solvent with 69% ee and >20:1 dr (entry 4). Considering that recent research on the halogen effect could be utilized to enhance significantly the performance in the iridium-catalyzed asymmetric hydrogenation of heteroarenes,[13] various commercial available halogen sources were further surveyed (entries 4–7). As expected, all additives delivered full conversion and moderate enantioselectivity; the reaction failed to proceed in the absence of halogen (entry 8). After a systematic screening, we found that 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH) gave the best results.

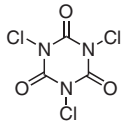
SYNTHESIS 2013, 45, 3239–3244
Advanced online publication: 25.09.2013
DOI: 10.1055/s-0033-1339849; Art ID: SS-2013-H0500-OP

Table 1 The Effect of Solvents and Additives[a]





BCDMH, R^1 = Br, R^2 = Cl
DCDMH, R^1 = Cl, R^2 = Cl

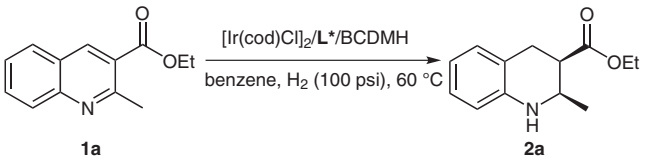


TCCA

Entry	Solvent	Additive	Conv.[b] (%)	dr[b] (*cis*/*trans*)	ee[c] (%)
1	THF	BCDMH	>95	7:1	37
2	toluene	BCDMH	>95	5:1	62
3	*o*-xylene	BCDMH	>95	8:1	67
4	benzene	BCDMH	>95	>20:1	69
5	benzene	TCCA	>95	13:1	57
6	benzene	DCDMH	>95	13:1	66
7	benzene	I_2	>95	10:1	69
8	benzene	–	< 5	–	–

[a] Conditions: **1a** (0.2 mmol), $[Ir(cod)Cl]_2$ (1.25 mol%), **L1** (2.75 mol%), additive (12.5 mol%), H_2 [7 bar (100 psi)], solvent (3 mL), 60 °C, 20 h.
[b] Determined by ^{1}H NMR spectroscopy analysis of the crude product.
[c] Determined by HPLC on a chiral stationary phase.

Table 2 The Effect of Ligands[a]



Entry	Ligand	Conv.[b] (%)	dr[b] (*cis*/*trans*)	ee[c] (%)
1	**L1**	>95	>20:1	69
2	**L2**	93	>20:1	72
3	**L3**	93	>20:1	71
4	**L4**	>95	>20:1	75
5	**L5**	93	>20:1	76
6	**L6**	93	>20:1	73
7	**L7**	92	>20:1	80
8[d]	**L7**	>95	>20:1	80
9	**L8**	>95	1:1	1

[a] Conditions: **1a** (0.2 mmol), $[Ir(cod)Cl]_2$ (1.25 mol%), ligand (2.75 mol%), BCDMH (12.5 mol%), H_2 [7 bar (100 psi)], benzene (3 mL), 60 °C, 20 h.
[b] Determined by ^{1}H NMR spectroscopy analysis of the crude product.
[c] Determined by HPLC on a chiral stationary phase.
[d] 26 h.

Finally, the effects of the ligand were evaluated with BCDMH as an additive (Table 2, Figure 1). The axial chiral bisphosphine ligands performed very well, good enantio- and diastereoselectivity were obtained. However, the central chirality ligand **L8** displayed poor stereoselectivity. Remarkably, the ligand **L7**, which was developed by our group and the group of Tang in 2007,[14] showed obvious superiority with up to 80% ee. Full conversion was achieved without loss of enantioselectivity when the reaction time was prolonged to 26 hours (entry 8). Hence, the optimized conditions were established to be $[Ir(cod)Cl]_2$/**L7**/BCDMH in benzene.

Having established the optimal conditions, the exploration of substrate scope was carried out (Table 3). The substrates were hydrogenated smoothly with full conversion and in excellent enantio- and diastereoselectivity, as summarized in Table 3. Notably, altering the alkoxycarbonyl group on the C3 position of quinolines resulted in slightly fluctuant enantioselectivity and reactivity (entries 1–7). The various 2-alkyl-substituted quinolines were reduced successfully with high yields and excellent enantioselectivity regardless of the side chain length (entries 8–11). It was noted that the best result of up to 90% ee was provided when C2 isopropyl was introduced (entry 11), while replacement of the alkyl substituent at C2 by phenyl resulted in moderate enantioselectivity (entry 12). For the substrates possessing a substituent group at C5, excellent yields and enantioselectivities were achieved and the electronic properties of the substituent had little effect on the catalytic activity and enantioselectivity (entries 13–15).

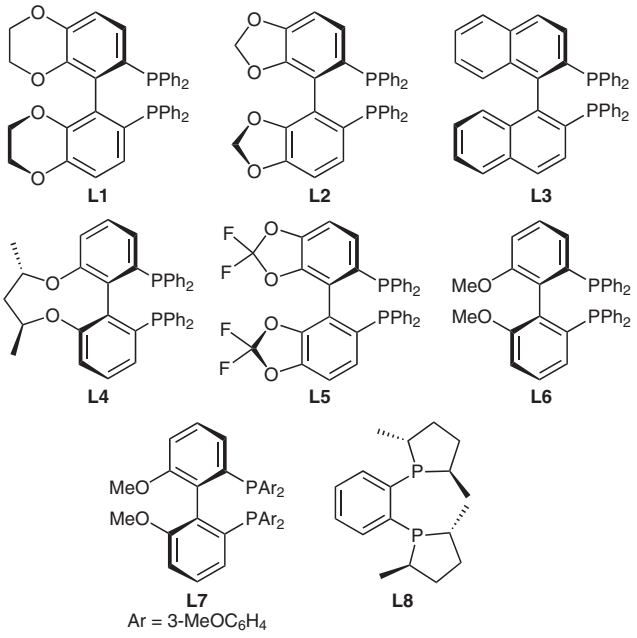
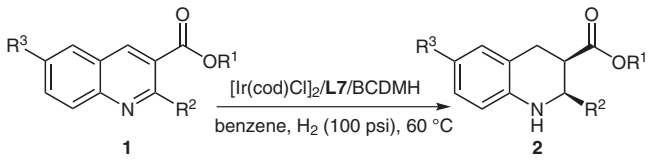


Figure 1

Table 3 The Substrate Scope[a]



Entry	R^1	R^2	R^3	Yield[b] (%)	ee[c,d] (%)
1	Et	Me	H	92 (**2a**)	80 (+)
2	Me	Me	H	95 (**2b**)	83 (2*R*,3*R*)
3	Pr	Me	H	94 (**2c**)	85 (+)
4	Bu	Me	H	91 (**2d**)	84 (+)
5	*i*-Pr	Me	H	90 (**2e**)	81 (+)
6	*t*-Bu	Me	H	91 (**2f**)	83 (+)
7	Bn	Me	H	87 (**2g**)	81 (+)
8	Me	Et	H	89 (**2h**)	89 (+)
9	Et	Pr	H	85 (**2i**)	88 (+)
10	Me	$(CH_2)_4Me$	H	94 (**2j**)	84 (+)
11	Me	*i*-Pr	H	86 (**2k**)	90 (+)
12	Et	Ph	H	89 (**2l**)	69 (+)
13	Me	*i*-Pr	OMe	94 (**2m**)	85 (+)
14	Me	*i*-Pr	Cl	94 (**2n**)	89 (+)
15	Me	*i*-Pr	F	94 (**2o**)	89 (+)

[a] Conditions: **1** (0.2 mmol), $[Ir(cod)Cl]_2$ (1.25 mol%), **L7** (2.75 mol%), BCDMH (12.5 mol%), H_2 [7 bar (100 psi)], benzene (3 mL), 60 °C, 26 h.
[b] Isolated yields.
c Determined by HPLC on a chiral stationary phase.
[d] dr >20:1, determined by ^{1}H NMR analysis of crude product.

The absolute configuration of hydrogenation product (+)-methyl 2-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (**2b**) was unambiguously assigned to be *cis*-(2*R*,3*R*) by X-ray crystallographic analysis (Figure 2); the relative and absolute configurations of **2a**,**c**–**o** were tentatively assigned by comparison. Notably, this was complementary to Gong's work that provided *trans*-3-alkoxycarbonyl-2-substituted tetrahydroquinolines via a relay catalytic Friedländer condensation and transfer hydrogenation in the presence of achiral Lewis acid and chiral Brønsted acid.[8]

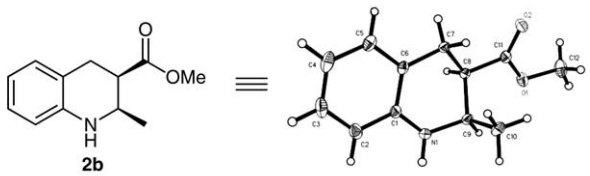


Figure 2 X-ray crystal structure of **2b**

In conclusion, an efficient enantioselective iridium-catalyzed hydrogenation of 3-alkoxycarbonyl-2-substituted quinolines has been developed with up to 90% ee. The new methodology provides a direct and facile route for the construction of novel enantiopure endocyclic β-amino acids with two contiguous stereocenters.

Commercially available reagents were used without further purification. Solvents were treated prior to use according to standard methods. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at r.t. in $CDCl_3$ on a 400 MHz instrument with TMS as internal standard. Enantiomeric excess was determined by HPLC analysis using a chiral column. Optical rotations were measured by polarimeter. Flash column chromatography was performed on silica gel (200–300 mesh).

(+)-Ethyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2a); Typical Procedure

A mixture of $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol) and ligand **L7** (3.9 mg, 0.0055 mmol) in benzene (1.0 mL) was stirred at r.t. for 10 min in a glovebox, then BCDMH (6.0 mg, 0.025 mmol) and substrate **1a** (43.1 mg, 0.2 mmol) together with benzene (2.0 mL) were added and the mixture was stirred for a further 10 min. The hydrogenation was performed at 60 C under H_2 [7 bar (100 psi)] for 26 h. After carefully releasing the H_2, the mixture was purified by column chromatography (silica gel, EtOAc–petroleum ether) to give pure product.

(+)-Ethyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2a)

Colorless oil; yield: 40.3 mg (92%); 80% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 8.0, 8.9 min (major).

$[\alpha]_D^{20}$ +28.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (m, 2 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 7.9 Hz, 1 H), 4.19 (m, 2 H), 3.98–3.80 (m, 2 H), 3.12–2.87 (m, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.13 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 143.0, 129.7, 127.2, 119.2, 117.6, 114.8, 60.7, 47.5, 42.3, 25.6, 18.0, 14.5.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{17}NO_2Na$: 242.1157; found: 242.1152.

(+)-Methyl (2*R*,3*R*)-2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2b)[15]

White solid; yield: 40.0 mg (95%); 83% ee; ; mp 73–75 C; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 9.4, 10.5 min (major).

$[\alpha]_D^{20}$ +41.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–7.00 (m, 2 H), 6.66 (t, *J* = 7.2 Hz, 1 H), 6.51 (d, *J* = 7.9 Hz, 1 H), 3.98–3.81 (m, 2 H), 3.74 (s, 3 H), 3.12–2.89 (m, 3 H), 1.13 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 143.0, 129.7, 127.3, 119.1, 117.6, 114.8, 52.0, 47.5, 42.3, 25.7, 18.1.

(+)-Propyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2c)

Colorless oil; yield: 43.9 mg (94%); 85% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 7.8, 8.4 min (major).

$[\alpha]_D^{20}$ +23.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.96 (m, 2 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 6.50 (d, *J* = 7.8 Hz, 1 H), 4.12–4.05 (m, 2 H), 3.91–3.85 (m, 2 H), 3.07–2.85 (m, 3 H), 1.72–1.61 (m, 2 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 143.1, 129.7, 127.2, 119.3, 117.6, 114.8, 66.4, 47.6, 42.4, 25.7, 22.2, 18.1, 10.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_2$: 234.1494; found: 234.1481.

(+)-Butyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2d)

Colorless oil; yield: 45.0 mg (91%); 84% ee; HPLC (Chiracel AD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 6.7, 9.4 min (major).

$[\alpha]_D^{20}$ +25.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03–6.97 (m, 2 H), 6.65 (t, *J* = 7.3 Hz, 1 H), 6.51 (d, *J* = 7.9 Hz, 1 H), 4.15–4.10 (m, 2 H), 3.90–3.86 (m, 2 H), 3.06–2.90 (m, 3 H), 1.67–1.58 (m, 2 H), 1.40–1.34 (m, 2 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 143.0, 129.7, 127.2, 119.2, 117.6, 114.8, 64.6, 47.5, 42.4, 30.9, 25.7, 19.4, 18.1, 13.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_2$: 248.1651; found: 248.1642.

(+)-Isopropyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2e)

Colorless oil; yield: 42.0 mg (90%); 81% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 75/25, flow = 0.7 mL/min): t_R = 7.3, 7.8 min (major).

$[\alpha]_D^{20}$ +80.4 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.96 (m, 2 H), 6.66 (t, *J* = 7.4 Hz, 1 H), 6.52 (d, *J* = 7.9 Hz, 1 H), 5.09–5.03 (m, 1 H), 3.88–3.82 (m, 1 H), 3.08–2.86 (m, 3 H), 1.26 (d, *J* = 6.3 Hz, 6 H), 1.14 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 142.9, 129.7, 127.2, 119.4, 117.6, 114.8, 68.1, 47.5, 42.4, 25.5, 22.0, 22.0, 17.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_2$: 234.1494; found: 234.1480.

(+)-*tert*-Butyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2f)

Colorless oil; yield: 45.0 mg (91%); 83% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 6.5, 6.8 min (major).

$[\alpha]_D^{20}$ +12.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.96 (m, 2 H), 6.64 (t, *J* = 7.3 Hz, 1 H), 6.50 (d, *J* = 7.9 Hz, 1 H), 3.90 (s, 1 H), 3.84–3.81 (m, 1 H), 3.04–2.95 (m, 1 H), 2.89–2.82 (m, 2 H), 1.46 (s, 9 H), 1.13 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 143.1, 129.8, 127.1, 119.4, 117.5, 114.7, 80.9, 47.6, 43.0, 28.3, 25.5, 17.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_2$: 248.1651; found: 248.1649.

(+)-Benzyl 2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2g)

Colorless oil; yield: 50.0 mg (87%); 81% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 11.7, 13.5 min (major).

$[\alpha]_D^{20}$ +21.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5 H), 7.00–6.99 (m, 2 H), 6.65 (t, *J* = 7.0 Hz, 1 H), 6.50 (d, *J* = 7.9 Hz, 1 H), 5.20–5.12 (m, 2 H), 3.89–3.83 (m, 2 H), 3.12–2.90 (m, 3 H), 1.11 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 143.1, 136.1, 129.8, 128.8, 128.4, 128.3, 127.3, 119.2, 117.7, 114.8, 66.6, 47.6, 42.5, 25.9, 18.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1494; found: 282.1481.

(+)-Methyl 2-Ethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2h)

White solid; yield: 39.0 mg (89%); 89% ee; mp 56–58 C; HPLC (Chiracel AD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 6.7, 8.5 min (major).

$[\alpha]_D^{20}$ +67.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01–6.96 (m, 2 H), 6.64 (t, *J* = 7.4 Hz, 1 H), 6.52 (d, *J* = 7.8 Hz, 1 H), 4.12 (s, 1 H), 3.71 (s, 3 H), 3.52–3.49 (m, 1 H), 3.05–2.89 (m, 3 H), 1.47–1.35 (m, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 143.0, 129.8, 127.2, 119.5, 117.5, 114.7, 53.9, 51.9, 41.9, 26.2, 24.1, 11.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_2$: 220.1338; found: 220.1324.

(+)-Ethyl 2-Propyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2i)

Colorless oil; yield: 42.0 mg (85%); 88% ee; HPLC (Chiracel AD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 95:5, flow = 0.6 mL/min): t_R = 13.1, 16.4 min (major).

$[\alpha]_D^{20}$ +46.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.96 (m, 2 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 7.9 Hz, 1 H), 4.23–4.11 (m, 2 H), 4.09 (s, 1 H), 3.65–3.62 (m, 1 H), 3.05–2.91 (m, 3 H), 1.50–1.46 (m, 2 H), 1.27 (t, *J* = 7.1 Hz, 4 H), 0.92 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 143.0, 129.8, 127.2, 119.5, 117.5, 114.7, 60.7, 51.9, 42.0, 33.3, 26.0, 19.7, 14.5, 14.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_2$: 248.1651; found: 248.1648.

(+)-Methyl 2-Pentyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2j)[15]

Yellow oil; yield: 49.1 mg (94%); 84% ee; HPLC (Chiracel AD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 6.8, 8.2 min (major).

$[\alpha]_D^{20}$ +44.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.96 (m, 2 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 6.52 (d, *J* = 7.9 Hz, 1 H), 3.72 (s, 3 H), 3.61 (d, *J* = 9.5 Hz, 1 H), 3.09–2.90 (m, 3 H), 1.48–1.43 (m, 2 H), 1.28–1.25 (m, 6 H), 0.87 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 143.1, 129.8, 127.2, 119.4, 117.5, 114.8, 52.3, 51.9, 42.1, 31.8, 31.3, 26.3, 26.2, 22.8, 14.2.

(+)-Methyl 2-Isopropyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2k)[15]

Colorless oil; yield: 40.1 mg (86%); 90% ee; HPLC (Chiracel OJ-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 12.9 (major), 18.9 min.

$[\alpha]_D^{20}$ +36.1 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (t, *J* = 8.2 Hz, 2 H), 6.65 (t, *J* = 7.3 Hz, 1 H), 6.53 (d, *J* = 7.9 Hz, 1 H), 3.66 (s, 3 H), 3.16–2.99 (m, 4 H), 1.93–1.83 (m, 1 H), 1.03–0.96 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 144.0, 129.5, 127.0, 119.9, 117.9, 114.8, 59.6, 51.7, 40.2, 30.4, 28.6, 20.5, 19.8.

(+)-Ethyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2l)

Yellow oil; yield: 50.1 mg (89%); 69% ee; HPLC (Chiracel AD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 7.7, 9.9 min (major).

$[\alpha]_D^{20}$ +109.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (m, 3 H), 7.16 (m, 2 H), 7.04 (m, 2 H), 6.68 (t, *J* = 6.9 Hz, 1 H), 6.57 (d, *J* = 7.5 Hz, 1 H), 4.96 (d, *J* = 4.4 Hz, 1 H), 4.40 (br, 1 H), 4.10–4.05 (m, 2 H), 3.25–3.20 (m, 1 H), 2.96–2.83 (m, 2 H), 1.20–1.15 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 143.7, 142.3, 129.8, 128.5, 127.9, 127.6, 127.1, 119.1, 117.4, 113.6, 60.8, 56.1, 43.5, 25.1, 14.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1494; found: 282.1497.

The relative and absolute configurations were tentatively assigned by comparison with **2b** and NOE experiment.

(+)-Methyl 2-Isopropyl-6-methoxy-1,2,3,4-tetrahydroquinoline-3-carboxylate (2m)

Colorless oil; yield: 49.5 mg (94%), 85% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 8.2 (major), 9.9 min.

$[\alpha]_D^{20}$ +58.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.61 (d, *J* = 7.5 Hz, 2 H), 6.52 (d, *J* = 8.1 Hz, 1 H), 3.73 (s, 3 H), 3.65 (s, 3 H), 3.10–2.98 (m, 4 H), 1.89–1.84 (m, 1 H), 1.02 (dd, *J* = 14.8, 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 152.5, 138.1, 121.4, 116.3, 114.5, 113.3, 60.3, 55.9, 51.7, 40.0, 30.2, 29.3, 20.5, 19.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_3$: 264.1600; found: 264.1584.

(+)-Methyl 6-Chloro-2-isopropyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2n)

White solid; yield: 50.3 mg (94%); 89% ee; mp 82–84 C; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 6.6 (major), 8.6 min.

$[\alpha]_D^{20}$ +58.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97–6.91 (m, 2 H), 6.46 (d, *J* = 8.5 Hz, 1 H), 3.99 (s, 1 H), 3.66 (s, 3 H), 3.10–2.92 (m, 4 H), 1.88–1.82 (m, 1 H), 1.01 (dd, *J* = 11.5, 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 142.7, 129.1, 126.9, 122.2, 121.4, 115.8, 59.7, 51.8, 39.6, 30.4, 28.9, 20.4, 19.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}ClNO_2$: 268.1104; found: 268.1094.

(+)-Methyl 6-Fluoro-2-isopropyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2o)

Yellow oil; yield: 47.2 mg (94%); 89% ee; HPLC (Chiracel OD-H column, 254 nm, 30 C, *n*-hexane–*i*-PrOH, 70:30, flow = 0.7 mL/min): t_R = 6.4 (major), 7.6 min.

$[\alpha]_D^{20}$ +23.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74–6.67 (m, 2 H), 6.48–6.45 (m, 1 H), 3.85 (s, 1 H), 3.66 (s, 3 H), 3.10–2.98 (m, 4 H), 1.93–1.81 (m, 1 H), 1.02 (dd, *J* = 12.2, 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 156.1 (d, $^1J_{F\text{-}C}$ = 234.8 Hz), 140.3, 121.4 (d, $^3J_{F\text{-}C}$ = 6.3 Hz), 115.7 (d, $^3J_{F\text{-}C}$ = 7.7 Hz), 115.6 (d, $^2J_{F\text{-}C}$ = 22.1 Hz), 113.7 (d, $^2J_{F\text{-}C}$ = 22.6 Hz), 60.1, 51.7, 39.7, 30.3, 29.2, 20.4, 19.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –127.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}FNO_2$: 252.1400; found: 268.1094.

Acknowledgment

We are grateful to the financial support from National Science Foundation of China (21125208 & 21032003), National Basic Research Program (2010CB833300) and Chinese Academy of Sciences.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) For selected reviews on β-amino acids, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Sorochinsky, A.; Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J.; Soloshonok, V. *Synthesis* **2011**, 3045. (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (d) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (e) Miller, J. A.; Nguyen, S. B. T. *Mini-Rev. Org. Chem.* **2005**, *2*, 39.

(2) (a) Maison, W.; Kosten, M.; Charpy, A.; Kintscher-Langenhagen, J.; Schlemminger, I.; Lutzen, A.; Westerhoff, O.; Martens, J. *Eur. J. Org. Chem.* **1999**, 2433. (b) Christianson, L. A.; Lucero, M. J.; Appella, D. H.; Klein, D. A.; Gellman, S. H. *J. Comput. Chem.* **2000**, *21*, 763. (c) Yamanaka, T.; Ohkubo, M.; Kato, M.; Kawamura, Y.; Nishi, A.; Hosokawa, T. *Synlett* **2005**, 631. (d) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206.

(3) (a) Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459. (b) Forro, E.; Fulop, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 93. (c) Gais, H. J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500. (d) O'Brien, P.; Porter, D. W.; Smith, N. M. *Synlett* **2000**, 1336. (e) Masesane, I. B.; Steel, P. G. *Tetrahedron Lett.* **2004**, *45*, 5007. (f) Kiss, L.; Fulop, F. *Synlett* **2010**, 1302. (g) Kiss, L.; Forro, E.; Fulop, F. *Tetrahedron Lett.* **2006**, *47*, 2855. (h) Kiss, L.; Kazi, B.; Forro, E.; Fueloep, F. *Tetrahedron Lett.* **2008**, *49*, 339. (i) Davis, F. A.; Theddu, N. *J. Org. Chem.* **2010**, *75*, 3814. (j) Kazi, B.; Kiss, L.; Forro, E.; Fulop, F. *Tetrahedron Lett.* **2010**, *51*, 82.

(4) (a) Songis, O.; Didierjean, C.; Martinez, J.; Calmes, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2135. (b) Basak, R. K.; Dharuman, S.; Vankar, Y. D. *Tetrahedron Lett.* **2012**, *53*, 4283. (c) Davies, S. G.; Osomu, I.; Walters, I. A. S. *Synlett* **1993**, 461. (d) Aggarwal, V. K.; Roseblade, S.; Alexander, R. *Org. Biomol. Chem.* **2003**, *1*, 684. (e) Kuhl, A.; Hahn, M. G.; Dumic, M.; Mittendorf, J. *Amino Acids* **2005**, *29*, 89. (f) Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284. (g) Yu, C.-B.; Gao, K.; Chen, Q.-A.; Chen, M.-W.; Zhou, Y.-G. *Tetrahedron Lett.* **2012**, *53*, 2560.

(5) For selected reviews, see: (a) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (b) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (c) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171. (d) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Chin. J. Org. Chem.* **2005**, *25*, 634.

(6) Studer, M. *Monatsh. Chem.* **2000**, 1335.

(7) Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem.* **2006**, 4343.

(8) Ren, L.; Lei, T.; Ye, J. X.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 771.

(9) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2012**, *51*, 8286.

(10) For recent examples on hydrogenation of functionalized quinolines, see: (a) Maj, A. M.; Suisse, I.; Méliet, C.; Hardouin, C.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2012**, *53*, 4747. (b) Cai, X.-F.; Chen, M.-W.; Ye, Z.-S.; Guo, R.-N.; Shi, L.; Li, Y.-Q.; Zhou, Y.-G. *Chem. Asian J.* **2013**, *8*, 1381. For selected works on hydrogenation of 2,3-disubstituted quinolines, see: (c) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878.

(d) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759. (e) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001. (f) Wang, D.-W.; Wang, X.-B.; Lu, S.-M.; Yu, C.-B.; Zhou, Y.-G. *J. Org. Chem.* **2009**, *74*, 2780.

(11) (a) Wang, D.-S.; Zhou, Y.-G. *Tetrahedron Lett.* **2010**, *51*, 3014. (b) Wang, D.-S.; Tang, J.; Zhou, Y.-G.; Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. *Chem. Sci.* **2011**, *2*, 803. (c) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442.

(12) (a) Shen, Q.; Wang, L.; Yu, J.; Liu, M.; Qiu, J.; Fang, L.; Guo, F.; Tang, J. *Synthesis* **2012**, *44*, 389. (b) Huo, M.; Kuang, Y.-Y.; Chen, F.-E. *Org. Prep. Proced. Int.* **2004**, *36*, 331.

(13) (a) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (b) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (c) Xiao, D.; Zhang, X. *Angew. Chem. Int. Ed.* **2001**, *40*, 3425. (d) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (e) Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7564.

(14) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494.

(15) Bunce, R. A.; Nago, T.; Sonobe, N. *J. Heterocycl. Chem.* **2007**, *44*, 1059.

