Tetrahedron 68 (2012) 6862–6867

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

The effect of benzyl amine on the efficiency of the base-catalyzed transamination of α-keto esters

Fazhen Xue [a], Xiao Xiao [a], Haining Wang [a], Yian Shi [a,b,*]

[a] Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China
[b] Department of Chemistry, Colorado State University, Fort Collins, CO 80523, United States

ARTICLE INFO

Article history:
Received 8 May 2012
Received in revised form 5 June 2012
Accepted 6 June 2012
Available online 15 June 2012

Keywords:
Transamination
Base-catalyzed
Benzyl amine
α-Keto esters
α-Amino esters
Enantioselective

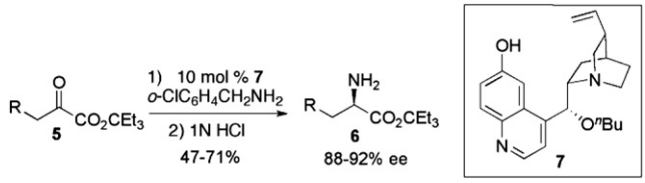
ABSTRACT

This paper describes the effect of benzyl amine on the base-catalyzed transamination of α-keto esters. Among various benzyl amines examined, *o*-$HOC_6H_4CH_2NH_2$ was found to be highly effective for the reaction, affording a wide variety of α-amino esters in good yields. The *o*-OH group of the benzyl amine facilitates the transamination process likely via H-bond. Moderate enantiomeric excess was obtained for α-amino ester when a quinine derived catalyst was used.

1. Introduction

α-Amino acids and their derivatives are important compounds in biological systems, drug development, and organic synthesis.[1] Great progress has been made in the development of various efficient methods for the synthesis of α-amino acids.[2] In biological systems, an important process to form α-amino acids involves transamination of α-keto acids **1** from pyridoxamine 5′-phosphate **2** catalyzed by transaminase (Scheme 1).[3–5] Non-enzymatic transamination presents an attractive strategy to α-amino acid derivatives and has received intensive studies.[6–12] During our studies, we have shown that a variety of α-amino esters can be obtained in high enantioselectivities and reasonable yields with quinine derived catalyst **7** and *o*-$ClC_6H_4CH_2NH_2$ as amine source (Scheme 2).[13] However, this transamination system was not effective for certain substrates, such as phenyl keto ester. In search for more effective transamination system, various benzyl amines were examined. It was found that the transamination efficiency could be significantly enhanced with *o*-$HOC_6H_4CH_2NH_2$ as amine source. Herein we wish to report our preliminary studies on this subject.

Scheme 1. Biological transamination.



Scheme 2. Asymmetric transamination.

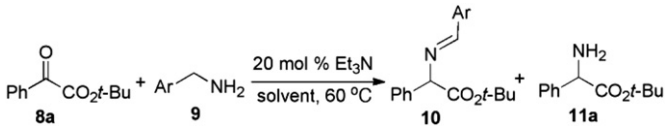
2. Results and discussion

Our studies were carried out with phenyl keto ester **8a** as substrate and Et_3N as catalyst, and substituted benzyl amine as amine donor. As shown in Table 1, only trace amounts of transamination products could be detected, when **8a** was treated with 20 mol % Et_3N and most of the substituted benzyl amines in $CDCl_3$ at 60 °C for 3 days (Table 1, entries 1–10). However, 65% conversion was

* Corresponding author. Fax: +1 970 4911801; e-mail address: yian@lamar.colostate.edu (Y. Shi).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.06.023

Table 1
Effect of benzyl amine on transamination[a]



Entry	9	Solvent	Conv (%)[b]
1	**9a**, Ar=Ph	$CDCl_3$	Trace
2	**9b**, Ar=*o*-ClC_6H_4	$CDCl_3$	Trace
3	**9c**, Ar=*o*-$MeOC_6H_4$	$CDCl_3$	Trace
4	**9d**, Ar=*o*-MeC_6H_4	$CDCl_3$	Trace
5	**9e**, Ar=*o*-FC_6H_4	$CDCl_3$	Trace
6	**9f**, Ar=*m*-BrC_6H_4	$CDCl_3$	Trace
7	**9g**, Ar=*m*-$CF_3C_6H_4$	$CDCl_3$	Trace
8	**9h**, Ar=*p*-F, *o*-ClC_6H_3	$CDCl_3$	Trace
9	**9i**, Ar=*p*-CNC_6H_4	$CDCl_3$	Trace
10	**9j**, Ar=Nap	$CDCl_3$	Trace
11	**9k**, Ar=*o*-HOC_6H_4	$CDCl_3$	65
12	**9k**	$ClCH_2CH_2Cl$	61
13	**9k**	THF	51
14	**9k**	Toluene	58
15	**9k**	EtOAc	46
16	**9k**	CH_3CN	65
17	**9k**	MeOH	88
18[c]	**9k**	MeOH	100

[a] The reactions were carried out with **8a** (0.05 mmol), **9** (0.05 mmol), and Et_3N (0.01 mmol) in solvent (0.50 mL) at 60 °C for 3 d unless otherwise stated.
[b] The conversion of **8a** into **10** and **11** was determined by ^1H NMR of the crude reaction mixture based on α-keto ester **8a**.
[c] The reactions were carried out with **8a** (0.05 mmol), **9** (0.1 mmol), and Et_3N (0.01 mmol) in MeOH (0.25 mL) at 60 °C for 1 d.

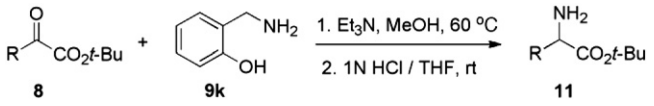
obtained when *o*-$HOC_6H_4CH_2NH_2$ was used (Table 1, entry 11). The conversion increased to 88% using MeOH as solvent (Table 1, entry 17). Essentially 100% conversion was obtained at 60 °C for 1 day with 2 equiv of *o*-$HOC_6H_4CH_2NH_2$ at higher reaction concentration (Table 1, entry 18). These results showed that *o*-$HOC_6H_4CH_2NH_2$ displayed uniquely high reactivity toward the transamination of phenyl keto ester **8a**, which was not effective substrate for other substituted benzyl amines examined.

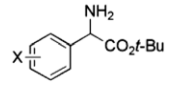
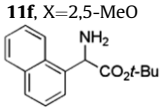
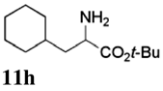
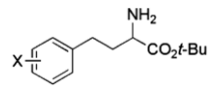
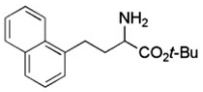
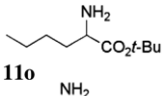
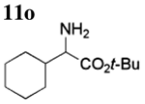
As shown in Table 2, the transamination system with *o*-$HOC_6H_4CH_2NH_2$ can be extended to a wide variety of keto esters. In general, the reaction proceeded cleanly in all cases examined. Remarkably high yields were obtained for various aryl keto esters (Table 2, entries 1–7), which were challenging substrates in our previous studies.[13] The transamination process was also highly effective for a variety of alkyl keto esters (Table 2, entries 8–15). Relatively good yield was also obtained for cyclohexyl keto ester **8p** (Table 2, entry 16), which was ineffective with *o*-$ClC_6H_4CH_2NH_2$ likely due to the steric hindrance of the cyclohexyl group.

To further understand the effect of benzyl amine on the transamination, comparative studies for the transamination of phenyl keto ester **8a** were carried out with *o*-$ClC_6H_4CH_2NH_2$ (**9b**), *o*-$MeOC_6H_4CH_2NH_2$ (**9c**), and *o*-$HOC_6H_4CH_2NH_2$ (**9k**) (Scheme 3). The reactions were run with 20 mol % Et_3N and 3 equiv of benzyl amine in $CDCl_3$ at 60 °C and monitored by ^1H NMR. Some ketimines were observed with **9b** and **9c**, but no such ketimine was detected with **9k**. The plots of the conversions of substrate **8a** into products **10** and **11a** against reaction times clearly show that the transamination with *o*-$HOC_6H_4CH_2NH_2$ (**9k**) is much faster than that with *o*-$ClC_6H_4CH_2NH_2$ (**9b**) or *o*-$MeOC_6H_4CH_2NH_2$ (**9c**). The hydroxyl group of **9k** greatly facilitates the transamination likely via the H-bond (Scheme 4).[3–5]

In the biological system, pyridoxamine derivatives are involved in transaminations. Pyridoxamine (**9l**) also contains an *ortho* hydroxyl group. The transamination of phenyl keto ester **8a** with

Table 2
Transamination using *o*-$HOC_6H_4CH_2NH_2$[a]

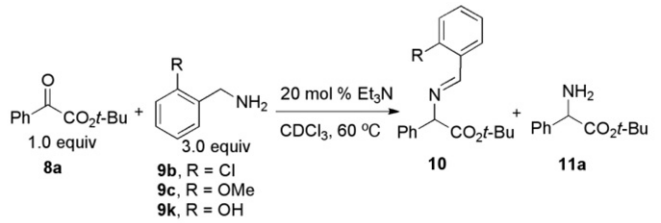


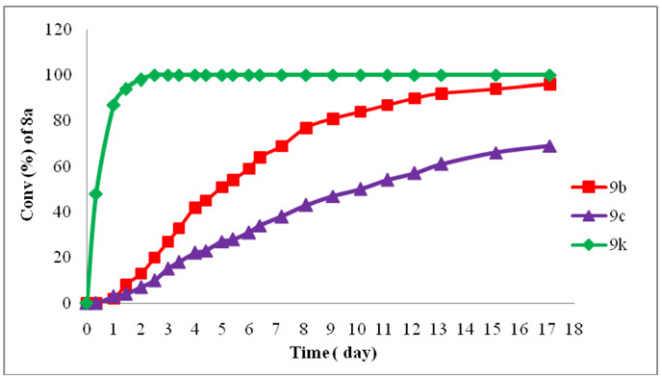
Entry	11	Yield (%)
		
1	**11a**, X=H	86
2	**11b**, X=*p*-F	84
3	**11c**, X=*p*-MeO	84
4	**11d**, X=*p*-Me	91
5	**11e**, X=*o*-Me	89
6	**11f**, X=2,5-MeO	85
7	 **11g**	87
8[b]	 **11h**	75
		
9	**11i**, X=H	91
10	**11j**, X=*p*-MeO	90
11	**11k**, X=*p*-F	89
12	**11l**, X=*o*-F	93
13	**11m**, X=*m*-Cl	90
14[b]	 **11n**	95
15[b]	 **11o**	80
16[b]	 **11p**	63

[a] The reactions were carried out with **8** (0.6 mmol), **9k** (1.2 mmol), and Et_3N (0.12 mmol) in MeOH (3.0 mL) at 60 °C for 1 d unless otherwise stated.
[b] Reacted for 2 d.

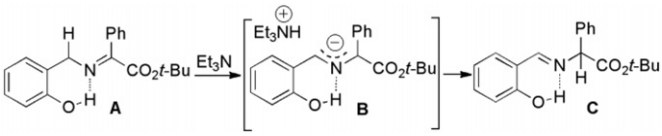
pyridoxamine proceeded smoothly, affording α-amino ester **11a** in 94% yield after 6 h (Scheme 5). A comparison between **9k** and **9l** was carried out for the transamination of phenyl keto ester **8a** using in situ IR by measuring the decrease of the absorbance at 1695 cm^{-1} (the keto group of **8a**) (Scheme 6). The data show that the transamination of phenyl keto ester **8a** with pyridoxamine (**9l**) was even faster as compared to *o*-$HOC_6H_4CH_2NH_2$ (**9k**), indicating that the transamination with **9l** could be further facilitated by the pyridine ring. A combination of an *ortho* hydroxyl group and a pyridine ring along with other factors makes pyridoxamine and its derivatives very effective cofactors for the transaminations in nature.[5a]

The asymmetric transamination of keto ester **8i** with *o*-$HOC_6H_4CH_2NH_2$ was also investigated with 10 mol % quinine derived base **7**. The reaction proceeded at rt, giving α-amino ester **11i** in 86% yield and 57% ee with the opposite configuration as

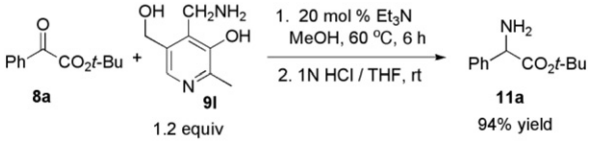




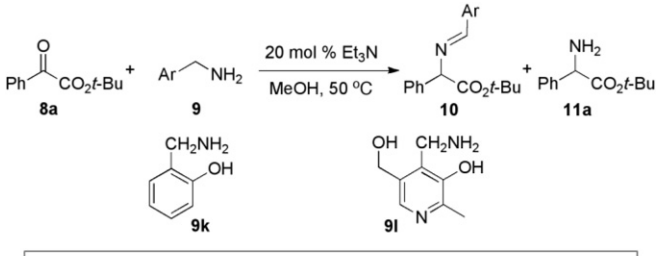
Scheme 3. Comparison studies between different benzyl amines. The conversions of **8a** into **10** and **11a** were determined by ^{1}H NMR of the crude reaction mixtures based on α-keto ester **8a**.

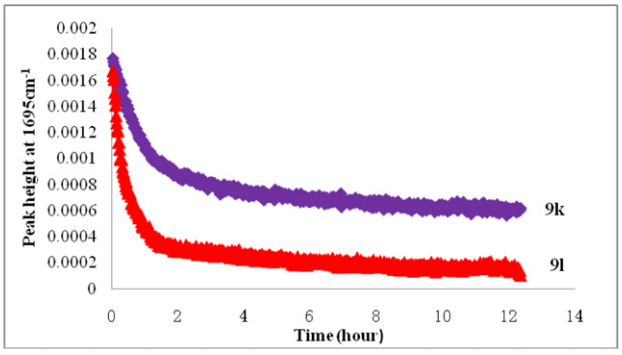


Scheme 4. The effect of the hydroxyl group on transamination.

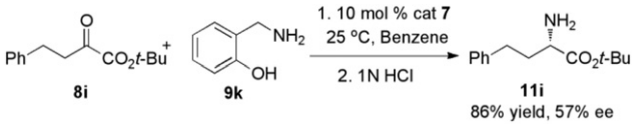


Scheme 5.





Scheme 6. Comparison studies between **9k** and **9l**.



Scheme 7. Asymmetric transamination with *o*-$HOC_6H_4CH_2NH_2$.

compared to the transamination of **8i** with *o*-$ClC_6H_4CH_2NH_2$.[13] While a precise understanding of the enantioselectivity awaits further study, a plausible transition state model is proposed in Fig. 1. It appears that the OH group of *o*-$HOC_6H_4CH_2NH_2$ also alters the stereodifferentiation process in addition to the reactivity, which provides an additional controlling factor for the development of enantioselective transamination.

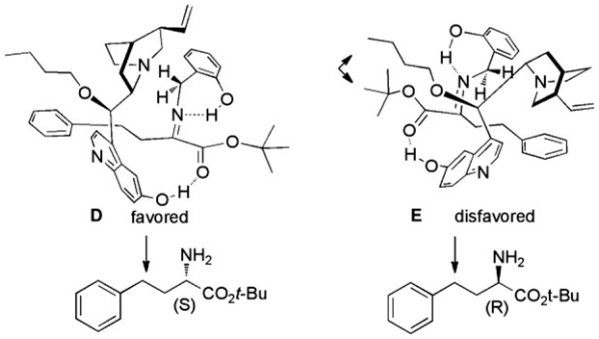


Fig. 1. Possible transition states for transamination.

3. Conclusion

In summary, the transamination of α-keto esters has been investigated with Et_3N as catalyst and various substituted benzyl amines as amine donors. Studies show that *o*-$HOC_6H_4CH_2NH_2$ is highly effective for the transamination process. A wide variety of α-amino esters can be obtained in high yields. Moderate enantioselectivity was also obtained with a chiral base. It appears that the hydroxyl group has a large impact on both reactivity and stereoselectivity likely via H-bond. Further efforts will be devoted to better understanding the transamination mechanism as well as developing effective catalytic asymmetric transamination processes for α-keto esters and other carbonyl compounds.

4. Experimental section

4.1. General information and materials

All commercially available reagents were used without further purification. All solvents were freshly distilled under nitrogen from appropriate drying agents before use. Column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz NMR spectrometer. IR spectra were recorded on a FT-IR spectrometer. In situ IR spectra were recorded on a Mettler Toledo React IR™ 15 spectrometer fitted with a DiComp probe. Commercially available reagents were used without further purification. Compounds **8a**–**p** were prepared from the mono-*tert*-butyloxalic acid-*N*-methoxy-*N*-methylamide by the addition of appropriate Grignard reagents according to published procedures.[14] *o*-$HOC_6H_4CH_2NH_2$ (**9k**) was prepared from 2-methoxybenzylamine via demethylation using BBr_3.[15] Pyridoxamine (**9l**) was obtained by neutralization of pyridoxamine dihydrochloride with aqueous NaOH to pH 9.[16]

4.2. Representative procedure for transamination of α-keto esters

A mixture of α-keto ester **8a** (0.1237 g, 0.60 mmol), *o*-$HOC_6H_4CH_2NH_2$ (0.1477 g, 1.20 mmol), and Et_3N (0.0121 g, 0.120 mmol) in MeOH (3.0 mL) was stirred at 60 °C for 24 h and concentrated. The resulting residue was dissolved in THF (6.0 mL), followed by the addition of aqueous 1 N HCl (6.0 mL). Upon stirring at rt for 5 h, the mixture was diluted with water (15 mL) then washed with hexane (3×10 mL). The organic phase was extracted with aqueous 1 N HCl (1×15 mL). The aqueous phases were combined, brought to pH 8.0 with solid $NaHCO_3$, extracted with CH_2Cl_2 (5×10 mL), and the organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, petroleum ether/EtOAc=5/1 then EtOAc) to give α-amino ester **11a** as yellow oil (0.1069 g, 86% yield).

*4.2.1. tert-Butyl 2-amino-2-phenylacetate (**11a**) (Table 2, entry 1).* Yellow oil; IR (film) 3377, 1731, 1368, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 4.48 (s, 1H), 1.88 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 141.2, 128.8, 127.9, 126.9, 81.7, 59.6, 28.1; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ (M+H): 208.1332; found: 208.1327.

*4.2.2. tert-Butyl 2-amino-2-(4-fluorophenyl)acetate (**11b**) (Table 2, entry 2).* Yellow oil; IR (film) 3384, 1731, 1509, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 2H), 7.06–6.98 (m, 2H), 4.47 (s, 1H), 2.06 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.7, 161.3, 136.9, 128.6, 128.5, 115.7, 115.5, 81.9, 58.8, 28.1; Anal. Calcd for $C_{12}H_{16}FNO_2$: C, 63.98; H, 7.16; N, 6.22; found: C, 63.80; H, 6.80; N, 6.14.

*4.2.3. tert-Butyl 2-amino-2-(4-methoxyphenyl)acetate (**11c**) (Table 2, entry 3).* Yellow oil; IR (film) 3383, 1729, 1511, 1249, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 6.89–6.84 (m, 2H), 4.43 (s, 1H), 3.80 (s, 3H), 1.98 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.3, 133.4, 128.0, 114.2, 81.6, 58.9, 55.4, 28.1; HRMS (ESI) calcd for $C_{13}H_{20}NO_3$ (M+H): 238.1438; found: 238.1434.

*4.2.4. tert-Butyl 2-amino-2-p-tolylacetate (**11d**) (Table 2, entry 4).* Yellow oil; IR (film) 3384, 1731, 1368, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.0 Hz, 2H), 7.14 (d, *J*=8.0 Hz, 2H), 4.44 (s, 1H), 2.34 (s, 3H), 1.90 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 138.2, 137.5, 129.5, 126.7, 81.6, 59.3, 28.1, 21.3; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ (M+H): 222.1489; found: 222.1486.

*4.2.5. tert-Butyl 2-amino-2-o-tolylacetate (**11e**) (Table 2, entry 5).* Yellow oil; IR (film) 3384, 1731, 1368, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 7.20–7.14 (m, 3H), 4.70 (s, 1H), 2.44 (s, 3H), 1.84 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 139.7, 136.1, 130.8, 127.7, 126.6, 125.9, 81.6, 55.9, 28.1, 19.6; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ (M+H): 222.1489; found: 222.1485.

*4.2.6. tert-Butyl 2-amino-2-(2,5-dimethoxyphenyl)acetate (**11f**) (Table 2, entry 6).* Yellow oil; IR (film) 3382, 1729, 1500, 1227, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84–6.74 (m, 3H), 4.58 (s, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.01 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 153.9, 151.2, 130.9, 114.7, 113.5, 112.0, 81.2, 56.1, 56.0, 55.7, 28.1; HRMS (ESI) calcd for $C_{14}H_{22}NO_4$ (M+H): 268.1543; found: 268.1549.

*4.2.7. tert-Butyl 2-amino-2-(naphthalen-1-yl)acetate (**11g**) (Table 2, entry 7).* Yellow oil; IR (film) 3382, 1729, 1368, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*=8.4 Hz, 1H), 7.87 (d, *J*=7.6 Hz, 1H), 7.84–7.76 (m, 1H), 7.59–7.39 (m, 4H), 5.22 (s, 1H), 2.17 (s, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 137.3, 134.3, 131.3, 129.0, 128.6, 126.5, 125.9, 125.6, 124.6, 123.8, 81.9, 56.5, 28.1; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ (M+H): 258.1489; found: 258.1486.

*4.2.8. tert-Butyl 2-amino-3-cyclohexylpropanoate (**11h**) (Table 2, entry 8).* Yellow oil; IR (film) 3380, 1729, 1367, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.36 (dd, *J*=8.4, 5.6 Hz, 1H), 1.80–1.06 (m, 13H), 1.45 (s, 9H), 0.99–0.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 80.9, 53.0, 43.1, 34.5, 33.9, 33.0, 28.3, 26.7, 26.5, 26.4; HRMS (ESI) calcd for $C_{13}H_{26}NO_2$ (M+H): 228.1958; found: 228.1953.

*4.2.9. tert-Butyl 2-amino-4-phenylbutanoate (**11i**) (Table 2, entry 9).* Yellow oil; IR (film) 3381, 1727, 1368, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.23–7.16 (m, 3H), 3.35 (dd, *J*=7.6, 5.2 Hz, 1H), 2.79–2.64 (m, 2H), 2.08–1.97 (m, 1H), 1.88–1.76 (m, 1H), 1.60 (s, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 141.8, 128.62, 128.60, 126.1, 81.2, 54.8, 37.0, 32.2, 28.3; HRMS (ESI) calcd for $C_{14}H_{21}NNaO_2$ (M+Na): 258.1465; found: 258.1457.

*4.2.10. tert-Butyl 2-amino-4-(4-methoxyphenyl)butanoate (**11j**) (Table 2, entry 10).* Yellow oil; IR (film) 3382, 1727, 1513, 1367, 1246, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J*=8.0 Hz, 2H), 6.83 (d, *J*=8.4, 2H), 3.78 (s, 3H), 3.33 (dd, *J*=7.2, 5.2 Hz, 1H), 2.73–2.58 (m, 2H), 2.04–1.92 (m, 1H), 1.87–1.73 (m, 1H), 1.70 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 158.1, 133.8, 129.5, 114.1, 81.2, 55.5, 54.8, 37.2, 31.3, 28.3; HRMS (ESI) calcd for $C_{15}H_{24}NO_3$ (M+H): 266.1751; found: 266.1744.

*4.2.11. tert-Butyl 2-amino-4-(4-fluorophenyl)butanoate (**11k**) (Table 2, entry 11).* Yellow oil; IR (film) 3383, 1727, 1510, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.10 (m, 2H), 6.96 (t, *J*=8.4 Hz, 2H), 3.31 (dd, *J*=7.6, 5.6 Hz, 1H), 2.76–2.61 (m, 2H), 2.05–1.92 (m, 1H), 1.84–1.72 (m, 1H), 1.52 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 162.8, 160.3, 137.4, 137.3, 130.0, 129.9, 115.4, 115.2, 81.3, 54.7, 37.0, 31.4, 28.3; HRMS (ESI) calcd for $C_{14}H_{21}FNO_2$ (M+H): 254.1551; found: 254.1545.

*4.2.12. tert-Butyl 2-amino-4-(2-fluorophenyl)butanoate (**11l**) (Table 2, entry 12).* Yellow oil; IR (film) 3384, 1728, 1492, 1368, 1229, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.12 (m, 2H), 7.09–6.94 (m, 2H), 3.35 (dd, *J*=7.6, 5.6 Hz, 1H), 2.84–2.63 (m, 2H), 2.07–1.92 (m, 1H), 1.89–1.75 (m, 1H), 1.55 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 162.6, 160.2, 130.9, 130.8, 128.7, 128.5, 127.9, 127.8, 124.2, 124.1, 115.6, 115.3, 81.3, 54.9, 35.5, 28.2, 25.5; HRMS (ESI) calcd for $C_{14}H_{20}FNNaO_2$ (M+Na): 276.1370; found: 276.1365.

*4.2.13. tert-Butyl 2-amino-4-(3-chlorophenyl)butanoate (**11m**) (Table 2, entry 13).* Yellow oil; IR (film) 3382, 1727, 1368, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.12 (m, 3H), 7.08 (d, *J*=7.6 Hz, 1H), 3.31 (dd, *J*=7.6, 5.2 Hz, 1H), 2.78–2.60 (m, 2H), 2.06–1.92 (m, 1H), 1.85–1.72 (m, 1H), 1.52 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 143.9, 134.4, 129.9, 128.8, 126.9, 126.4, 81.3, 54.7, 36.6, 31.9, 28.3; HRMS (ESI) calcd for $C_{14}H_{21}ClNO_2$ (M+H): 270.1255; found: 270.1258.

*4.2.14. tert-Butyl 2-amino-4-(naphthalen-1-yl)butanoate (**11n**) (Table 2, entry 14).* Yellow oil; IR (film) 3382, 1726, 1367, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J*=8.4, 1H), 7.86 (d, *J*=8.4, 1H), 7.72 (d, *J*=7.6 Hz, 1H), 7.57–7.43 (m, 2H), 7.43–7.31 (m, 2H), 3.47 (dd, *J*=7.2, 5.6 Hz, 1H), 3.28–3.08 (m, 2H), 2.22–2.08 (m, 1H), 2.05–1.90 (m, 1H), 1.76 (s, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 138.0, 134.1, 132.1, 129.0, 127.0, 126.3, 126.0, 125.8,

125.7, 123.9, 81.3, 55.3, 36.3, 29.4, 28.3; HRMS (ESI) calcd for $C_{18}H_{24}NO_2$ (M+H): 286.1802; found: 286.1804.

*4.2.15. tert-Butyl 2-aminohexanoate (**11o**) (Table 2, entry 15).* Yellow oil; IR (film) 3381, 1731, 1368, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.29 (dd, J=7.2, 5.6 Hz, 1H), 1.77–1.57 (m, 3H), 1.57–1.48 (m, 1H), 1.45 (s, 9H), 1.39–1.22 (m, 4H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 81.0, 55.2, 34.9, 28.3, 27.9, 22.7, 14.1; HRMS (ESI) calcd for $C_{10}H_{21}NNaO_2$ (M+Na): 210.1465; found: 210.1460.

*4.2.16. tert-Butyl 2-amino-2-cyclohexylacetate (**11p**) (Table 2, entry 16).* Yellow oil; IR (film) 3383, 1727, 1367, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.15 (d, J=4.8 Hz, 1H), 1.84–1.52 (m, 8H), 1.47 (s, 9H), 1.34–1.02 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 81.0, 60.3, 42.5, 29.9, 28.3, 28.0, 26.51, 26.49, 26.4; HRMS (ESI) calcd for $C_{12}H_{24}NO_2$ (M+H): 214.1802; found: 214.1797.

4.3. Procedure for transamination of phenyl keto ester 8a with pyridoxamine (9l)

A mixture of **8a** (0.0618 g, 0.30 mmol), pyridoxamine (**9l**) (0.0605 g, 0.36 mmol), and Et_3N (0.0061 g, 0.06 mmol) in MeOH (1.5 mL) was stirred at 60 °C for 6 h and concentrated. The resulting residue was dissolved in THF (3.0 mL), followed by the addition of aqueous 1 N HCl (3.0 mL). Upon stirring at rt for 5 h, the mixture was diluted with water (8 mL) then washed with hexane (3×10 mL). The organic phase was extracted with aqueous 1 N HCl (1×10 mL). The aqueous phases were combined, brought to pH 8.0 with solid $NaHCO_3$, extracted with CH_2Cl_2 (5×10 mL), and the organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, petroleum ether/EtOAc=5/1 then EtOAc) to give α-amino ester **11a** as yellow oil (0.0582 g, 94% yield).

4.4. General procedure for comparison experiment between 9k and 9l using in situ IR (Scheme 6)

A mixture of phenyl keto ester **8a** (0.0412 g, 0.20 mmol), o-$HOC_6H_4CH_2NH_2$ (**9k**) (0.0246 g, 0.20 mmol) or pyridoxamine (**9l**) (0.0336 g, 0.20 mmol), and Et_3N (0.0040 g, 0.04 mmol) in MeOH (2.0 mL) at 50 °C was monitored by in situ IR every 1 min.

4.5. The procedure for asymmetric transamination of α-keto ester (Scheme 7)

*4.5.1. Asymmetric transamination of α-keto ester **8i**.* A well-dried Schlenk tube charged with molecular sieves 4 Å (0.030 g), α-keto ester **8i** (0.0702 g, 0.30 mmol), o-$OHC_6H_4CH_2NH_2$ (0.0739 g, 0.60 mmol), and catalyst **7** (0.0110 g, 0.030 mmol) was evacuated and refilled with N_2. The process was repeated three times. Dry benzene (3.0 mL) was added. Upon stirring at 25 °C for 48 h, the reaction mixture was concentrated. The resulting residue was treated with THF (3.0 mL), followed by the addition of aqueous 1 N HCl (3.0 mL). Upon stirring at rt for 5 h, the mixture was diluted with water (10 mL) then washed with hexane (3×10 mL). The organic phase was extracted with aqueous 1 N HCl. The aqueous phases were combined, brought to pH 8.0 with solid $NaHCO_3$, extracted with CH_2Cl_2 (5×10 mL), and the organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, petroleum ether/EtOAc=5/1 then EtOAc/CH_3OH=10/1) to give α-amino ester **11i** (0.0607 g, 86% yield); $[\alpha]_D^{20}$ +13.1 (c 0.89, $CHCl_3$) (57% ee).

4.5.2. Preparation of N-benzoyl derivative of amino ester for the determination of the enantiomeric excess. To a solution of **11i** (0.0509 g, 0.22 mmol) in CH_2Cl_2 (1.5 mL) were added Et_3N (0.0404 g, 0.40 mmol) and PhCOCl (0.0464 g, 0.33 mmol) successively. The reaction mixture was stirred at rt for 30 min and purified by flash chromatography (silica gel, petroleum ether/EtOAc=10/1 to 5/1) to afford *N*-benzoyl amino ester **12i** (0.0622 g, 83%) as white solid. The sample was subjected to chiral HPLC (chiralcel OD-H column) to determine the enantiomeric excess.

Acknowledgements

We gratefully acknowledge the National Basic Research Program of China (973 program, 2010CB833300) and the Chinese Academy of Sciences for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.023.

References and notes

1. For a recent book, see:*Amino Acids, Peptides and Proteins in Organic Chemistry*; Hughes, A. B., Ed.; Wiley-VCH: Weinheim, Germany, 2009.
2. For leading reviews on asymmetric syntheses of α-amino acids, see: (a) Cintas, P. *Tetrahedron* **1991**, *47*, 6079; (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889; (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013; (e) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10; (f) Ma, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290; (g) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506; (h) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; (i) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584; (j) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406; (k) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem.* **2007**, *11*, 801; (l) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176; (m) Michaux, J.; Niel, G.; Campagne, J. M. *Chem. Soc. Rev.* **2009**, *38*, 2093.
3. For leading reviews on biological syntheses of α-amino acids, see: (a) Martell, A. E. *Acc. Chem. Res.* **1989**, *22*, 115; (b) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146; (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721; (d) De Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. *Acc. Chem. Res.* **2007**, *40*, 1260; (e) Zhu, D.; Hua, L. *Biotechnol. J.* **2009**, *4*, 1420; (f) Ward, J.; Wohlgemuth, R. *Curr. Org. Chem.* **2010**, *14*, 1914.
4. For leading reviews on Vitamin B6 see: (a) Voziyan, P. A.; Hudson, B. G. *Ann. N. Y. Acad. Sci.* **2005**, 807; (b) Toney, M. D. *Biochim. Biophys. Acta* **2011**, 1407; (c) Mann, S.; Ploux, O. *Biochim. Biophys. Acta* **2011**, 1459.
5. For leading references on the mechanistic study of transamination based on Vitamin B6, see: (a) Metzler, D. E.; Ikawa, M.; Snell, E. E. *J. Am. Chem. Soc.* **1954**, *76*, 648; (b) Tobias, P. S.; Kallen, R. G. *J. Am. Chem. Soc.* **1975**, *97*, 6530; (c) Chang, Y. C.; McCalmont, T.; Graves, D. J. *Biochemistry* **1983**, *22*, 4987; (d) Martel, A. E.; Taylor, P. *Inorg. Chem.* **1984**, *23*, 2734; (e) Ortega-Castro, J.; Adrover, M.; Frau, J.; Salva, A.; Donoso, J.; Munoz, F. *J. Phys. Chem.* **2010**, *114*, 4634; (f) Chan-Huot, M.; Sharif, S.; Tolstoy, P. M.; Toney, M. D.; Limbach, H.-H. *Biochemistry* **2010**, *49*, 10818; (g) Griswold, W. R.; Toney, M. D. *J. Am. Chem. Soc.* **2011**, *133*, 14823; (h) Cerqueira, N. M. F. S. A.; Fernandes, P. A.; Ramos, M. J. *J. Chem. Theory Comput.* **2011**, *7*, 1356; (i) Oliveira, E. F.; Cerqueira, N. M. F. S. A.; Fernandes, P. A.; Ramos, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 15496.
6. For leading references on transamination with pyridoxamine analogues, see: (a) Murakami, Y.; Kikuchi, J.; Akiyoshi, K. *Chem. Lett.* **1984**, 1185; (b) Murakari, Y.; Kikuchi, J.; Akiyoshi, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1200; (c) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212; (d) Pham, T. R.; Schultz, P. G.; Sugasawara, R.; Schultz, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 6670; (e) Wu, Y.; Ahlberg, P. *J. Org. Chem.* **1992**, *57*, 6324; (f) Liu, L.; Breslow, R. *J. Am. Chem. Soc.* **2002**, *124*, 4978; (g) Liu, L.; Rozenman, M.; Breslow, R. *J. Am. Chem. Soc.* **2002**, *124*, 12660; (h) Liu, L.; Breslow, R. *J. Am. Chem. Soc.* **2003**, *125*, 12110; (i) Liu, L.; Zhou, W.; Chruma, J.; Breslow, R. *J. Am. Chem. Soc.* **2004**, *126*, 8136; (j) Svenson, J.; Zheng, N.; Nicholls, I. A. *J. Am. Chem. Soc.* **2004**, *126*, 8554; (k) Skouta, R.; Wei, S.; Breslow, R. *J. Am. Chem. Soc.* **2009**, *131*, 15604.
7. For leading references on syntheses of chiral α-amino acids with chiral pyridoxamine analogues, see: (a) Breslow, R.; Hammond, M.; Lauer, M. *J. Am. Chem. Soc.* **1980**, *102*, 421; (b) Tachibana, Y.; Ando, M.; Kuzuhara, H. *Chem. Lett.* **1982**, 1765; (c) Tachibana, Y.; Ando, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3652; (d) Zimmerman, S. C.; Breslow, R. *J. Am. Chem. Soc.* **1984**, *106*, 1490; (e) Ando, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 244; (f) Kuang, H.; Brown, M. L.; Davies, R. R.; Young, E. C.; Distefano, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 10702; (g) Zhou, W.; Yerkes, N.; Chruma, J.; Liu, L.; Breslow, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1351; (h) Breslow, R.; Wei, S.; Kenesky, C. *Tetrahedron* **2007**, *63*, 6317; (i) Bandyopadhyay, S.; Zhou, W.; Breslow, R. *Org. Lett.* **2007**, *9*, 1009; (j) Wei, S.; Wang, J.; Venhuizen, S.; Skouta, R.; Breslow, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5543.

8. For a leading reference on chiral guanidine-catalyzed asymmetric syntheses of α-amino acids with α-keto esters as substrates, see: Hjelmencrantz, A.; Berg, U. *J. Org. Chem.* **2002**, *67*, 3585.
9. For leading references on chiral Lewis acid-catalyzed asymmetric syntheses of α-amino acids with α-keto esters as substrates, see: (a) Bernauer, K.; Deschenaux, R.; Taura, T. *Helv. Chim. Acta* **1983**, *66*, 2049; (b) Deschenaux, R.; Bernauer, K. *Helv. Chim. Acta* **1984**, *67*, 373; (c) Knudsen, K. R.; Bachmann, S.; Jørgensen, K. A. *Chem. Commun.* **2003**, 2602; (d) Bachmann, S.; Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 2044.
10. For leading references on 1,3 proton shift of imines, see: (a) Cram, D. J.; Guthrie, R. D. *J. Am. Chem. Soc.* **1965**, *87*, 397; (b) Richer, J.-C.; Perelman, D. *Can. J. Chem.* **1970**, *48*, 570; (c) Ono, T.; Kukhar, V. P.; Soloshonok, V. A. *J. Org. Chem.* **1996**, *61*, 6563; (d) Cainelli, G.; Giacomini, D.; Trerè, A.; Boyl, P. P. *J. Org. Chem.* **1996**, *61*, 5134; (e) Ohkura, H.; Berbasov, D. O.; Soloshonok, V. A. *Tetrahedron* **2003**, *59*, 1647; (f) Han, J.; Sorochinsky, A. E.; Ono, T.; Soloshonok, V. A. *Curr. Org. Synth.* **2011**, *8*, 281.
11. For leading references on chiral base-catalyzed asymmetric syntheses of chiral amines, see: (a) Soloshonok, V. A.; Kirilenko, A. G.; Galushko, S. V.; Kukhar, V. P. *Tetrahedron Lett.* **1994**, *35*, 5063; (b) Willems, J. G.; Vries, J. G.; Nolte, R. J.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 3917; (c) Soloshonok, V. A.; Yasumoto, M. *J. Fluorine Chem.* **2007**, *128*, 170; (d) Michaut, V.; Metz, F.; Paris, J.; Plaquevent, J. *J. Fluorine Chem.* **2007**, *128*, 500.
12. For leading references on asymmetric biomimetic transamination of keto compounds with chiral benzyl amine, see: (a) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *J. Fluorine Chem.* **2006**, *127*, 924; (b) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *J. Fluorine Chem.* **2006**, *127*, 930; (c) Soloshonok, V. A.; Catt, H. T.; Ono, T. *J. Fluorine Chem.* **2010**, *131*, 261.
13. Xiao, X.; Xie, Y.; Su, C.; Liu, M.; Shi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 12914.
14. (a) Chiu, C. C.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 5763; (b) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036.
15. Hallett, A. J.; Kwant, G. J.; Vries, J. G. *Chem.—Eur. J.* **2009**, *15*, 2111.
16. Raja, K.; Roland, K.; Christoph, K. PCT Int. Appl. WO 2005077902, 2005.