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Organocatalytic synthesis of optically active β-branched α-amino esters *via* asymmetric biomimetic transamination†

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This paper describes an efficient asymmetric biomimetic transamination of α-keto esters with a quinine-derived chiral base as the catalyst, giving a variety of β-branched α-amino esters in 50–96% yield and 87–95% ee.

Introduction

β-Branched α-amino acids are present in various biologically and medicinally important compounds, such as epelsiban (**1a**) (agent for delaying preterm birth),[1,2] inhibitor of MMP-13 (**1b**) (treatment of cartilage degradation),[3] anthrax lethal factor inhibitor (**1c**),[4] and VX-950 (**1d**) (hepatitis C virus serine protease inhibitor) (Fig. 1).[5,6] The availability of optically active unnatural β-branched α-amino acids would provide great opportunities for the drug design. Various methods have been developed for the synthesis of enantiomerically enriched β-branched α-amino acids and their derivatives,[7,8] including enzymatic reactions,[9] chiral auxiliary-based processes,[10] asymmetric nucleophilic additions to imine-esters,[11] and asymmetric hydrogenation of β,β′-disubstituted dehydro amino acids.[12,13] Nevertheless, the development of new and complementary methods towards this class of amino acids is still highly desired. Recently, we reported an efficient biomimetic transamination of α-keto esters with a quinine-derived chiral base as the catalyst and 2-ClPhCH$_2$NH$_2$ as the nitrogen source, giving the corresponding α-amino esters in high ees (Scheme 1).[14] When β-branched α-keto esters were subjected to the reaction conditions, only low yields or ees were obtained for the corresponding α-amino esters. However, it was found that, in addition to the catalyst, the choice of the benzyl amine had a large effect on the transamination of β-branched α-keto esters,[15] and optically active β-branched α-amino esters could be prepared in good yields and high ees with a proper combination of the catalyst and benzyl amine. Herein we report our preliminary results on this subject.

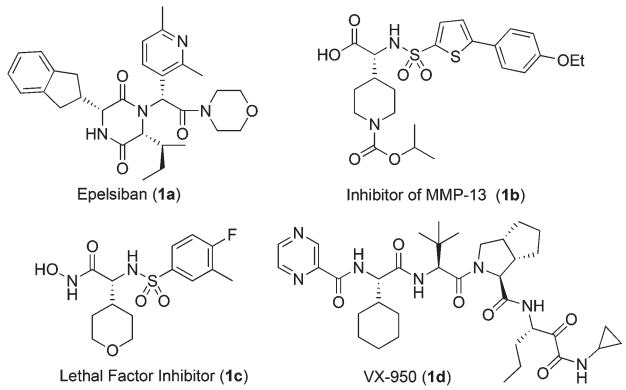
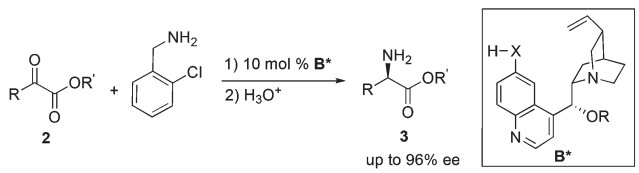


Fig. 1 Selected examples of medicinally significant compounds.



Scheme 1 Chiral base-catalyzed biomimetic transamination.

Results and discussion

Our studies started with *t*-butyl 2-cyclohexyl-2-oxoacetate (**4c**) as the test substrate. Little conversion was observed when **4c**

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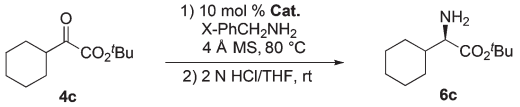
† Electronic supplementary information (ESI) available: Experimental, characterization data, HPLC data for determination of enantiomeric excesses, X-ray structure of *N*-benzoyl amino ester **14j**, and NMR spectra. CCDC 994330. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00684d

Table 1 Studies on the reaction conditions[a]



Entry	Cat.	Solvent	X	Yield[b] (%)	ee[c] (%)
1	**C1**	Benzene	2-Cl	—	—
2	**C2**	Benzene	2-Cl	—	—
3	**C1**	Toluene	2-Cl	27	63
4	**C1**	Toluene	H	—	—
5	**C1**	Toluene	2-Me	—	—
6	**C1**	Toluene	4-MeO	—	—
7	**C1**	Toluene	2-Cl, 4-CN	25	53
8	**C1**	Toluene	2-OH	90	−4
9	**C1**	Toluene	4-NO_2	73	63
10	**C1**	Toluene	4-CN	78	71
11	**C2**	Toluene	4-CN	73	90
12	**C3**	Toluene	4-CN	78	93
13	**C4**	Toluene	4-CN	85	94
14	**C4**	Toluene	2-Cl	2	90
15	**C4**	Toluene	H	—	—
16	**C4**	Toluene	2-Me	—	—
17	**C4**	Toluene	4-MeO	—	—
18	**C4**	Toluene	2-Cl, 4-CN	35	88
19	**C4**	Toluene	2-OH	61	0
20	**C4**	Toluene	4-NO_2	75	92
21	**C4**	Benzene	4-CN	78	93
22	**C4**	^{i}PrOH	4-CN	46	30
23	**C4**	CH_3CN	4-CN	88	59
24	**C4**	$ClCH_2CH_2Cl$	4-CN	69	87
25	**C4**	Dioxane	4-CN	56	70
26	**C5**	Toluene	4-CN	80	−86

[a] All reactions were carried out with α-keto ester **4c** (0.30 mmol), benzyl amine **5** (0.90 mmol), catalyst (0.030 mmol), and 4 Å molecular sieves (0.15 g) in solvent (3.0 mL) at 80 °C for 72 h unless otherwise noted. For entries 1 and 2, the reactions were carried out at 50 °C for 60 h. [b] Isolated yield based on α-keto esters **4c**. [c] The ees were determined by chiral HPLC (Chiralcel OD-H column) after the amino esters were converted into their *N*-benzoyl derivatives.

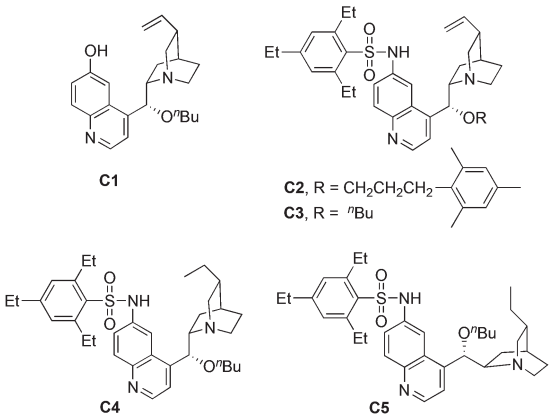


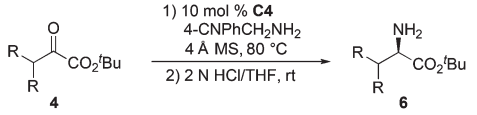
Fig. 2 Selected examples of catalysts examined.

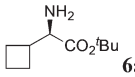
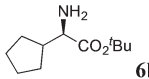
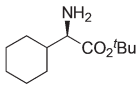
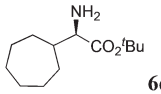
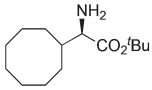
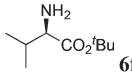
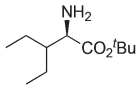
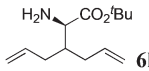
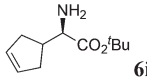
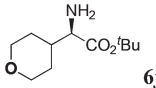
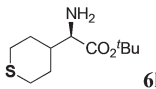
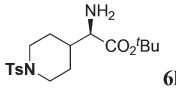
was subjected to our previous conditions using **C1** or **C2** as the catalyst (Fig. 2) and 2-$ClPhCH_2NH_2$ as the nitrogen source in benzene at 50 °C (Table 1, entries 1 and 2).[14] When the reaction was run in toluene with the catalyst **C1** at 80 °C, the amino ester was obtained in 27% yield and 63% ee (Table 1, entry 3). Benzyl amines were subsequently examined for the reaction with **C1** as the catalyst (Table 1, entries 4–10). Little conversions were observed with $PhCH_2NH_2$, 2-$MePhCH_2NH_2$ and 4-$MeOPhCH_2NH_2$ with the catalyst **C1** (Table 1, entries 4–6). Amino ester **6c** was obtained in 90% yield but only 4% ee with 2-$OHPhCH_2NH_2$, which was previously shown to be highly effective for the transamination (Table 1, entry 8).[15] However, 78% yield and 71% ee were achieved with 4-$CNPhCH_2NH_2$ (Table 1, entry 10). Encouraged by this result, additional catalysts were investigated for the reaction with 4-$CNPhCH_2NH_2$ (Table 1, entries 11–13). To our delight, the amino ester was obtained in 85% yield and 94% ee with the catalyst **C4** (Table 1, entry 13). The re-examination of the benzyl amines for the transamination with the catalyst **C4** (Table 1, entries 14–20) revealed a similar trend as the catalyst **C1** (Table 1, entries 3–10). Results showed that the electronic effect of the substituents of benzyl amines had significant impact on the reactivity and enantioselectivity of the transamination. In general, benzyl amines with electron-withdrawing groups were more effective than those with electron-donating groups. Among the solvents tested (Table 1, entries 13, 21–25), toluene and benzene gave the best overall results. The opposite enantiomer of the amino ester was obtained in 80% yield and 86% ee with the quinidine-derived catalyst **C5** (Table 1, entry 26).

The generality of the transamination was subsequently examined with the catalyst **C4** and 4-$CNPhCH_2NH_2$ in toluene at 80 °C. α-Keto esters containing different cycloalkanes (ranging from four-membered ring to eight-membered ring) were found to be effective substrates, giving α-amino esters in 75–87% yield and 87–95% ee (Table 2, entries 1–5). The side chains of α-keto esters could also have saturated and unsaturated aliphatic groups. The corresponding α-amino esters were obtained in 50–77% yield and 91–92% ee (Table 2, entries 6–8). Cyclopentenyl keto ester was transaminated to the amino ester in 96% yield and 92% ee (Table 2, entry 9). β-Branched α-amino esters containing heterocycles like tetrahydro-2*H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine were obtained from the corresponding α-keto esters in 65–95% yield and 90–93% ee (Table 2, entries 10–12).

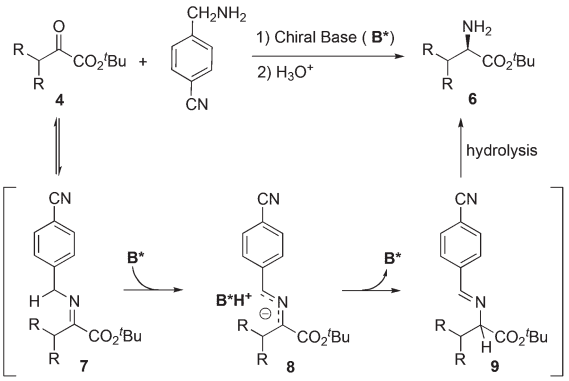
A possible mechanism for the transamination of β-branched α-keto esters is proposed in Scheme 2.[14] It is likely that the electron-withdrawing 4-CN group of the benzyl amine increases the acidity of the benzylic hydrogen of ketimine **7**, and consequently facilitates the proton shift.[16] The imine is also activated by forming a H-bonding with the substituent at the 6′-position of the catalyst. At the same time, the H-bonding also influences the stereoselectivity of the proton shift.[14,16] Thus, the electronic and steric nature of the H-bond donor at the 6′-position of the catalyst have significant effect on the reactivity and enantioselectivity of the transamination process. In the current case, a combination of the catalyst **C4** and 4-$CNPhCH_2NH_2$ leads to β-branched α-amino esters in good yields and high ees.

Table 2 Catalytic asymmetric transamination of α-keto esters[a]



Entry	Amino ester (6)	Yield[c] (%)	ee[d] (%)
1	 6a	75	87
2	 6b	87	94
3[b]	 6c	82	94
4	 6d	82	94
5	 6e	75	95
6[b]	 6f	72	92
7	 6g	50	91
8	 6h	77	92
9	 6i	96	92
10	 6j	65	91
11	 6k	87	93
12	 6l	95	90

[a] All reactions were carried out with α-keto esters **4** (0.50 mmol), 4-CNPhCH$_2$NH$_2$ (1.50 mmol), catalyst **C4** (0.050 mmol), and 4 Å molecular sieves (0.25 g) in dry toluene (5.0 mL) at 80 °C for 72 h unless otherwise noted. For entry 7, the reaction time was 96 h. [b] The absolute configurations (*R*) were determined by comparing optical rotations after hydrolysis to the acids with reported ones of α-amino acids (for entry 3, see: ref. 17). The absolute configurations of remaining amino esters are tentatively proposed by analogy. [c] Isolated yield based on α-keto esters **4**. [d] The ees were determined by chiral HPLC (Chiralcel OD-H column) after the amino esters were converted into their *N*-benzoyl derivatives.



Scheme 2 Chiral base-catalyzed transamination of β-branched α-keto esters.

Conclusions

In summary, we have developed an efficient asymmetric biomimetic transamination process for β-branched α-keto esters with a hydroquinine-derived chiral base as the catalyst and 4-CNPhCH$_2$NH$_2$ as the nitrogen source. A wide variety of β-branched α-amino esters have been obtained in 50–96% yield and 87–95% ee. The current transamination method provides ready access to optically active β-branched α-amino acids and their derivatives which can be potentially used for the synthesis of various biologically active molecules.[1–6] Further efforts will be devoted to understanding the reaction mechanism as well as developing more effective catalytic systems.

Acknowledgements

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