Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8960

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COMMUNICATION

Organocatalytic asymmetric biomimetic transamination of aromatic ketone to optically active amine†

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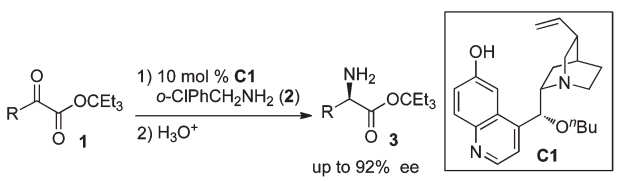
Received 11th September 2012, Accepted 4th October 2012
DOI: 10.1039/c2ob26782a

An asymmetric biomimetic transamination of aromatic ketones to optically active amines with *o*-HOPhCH$_2$NH$_2$ as amine source catalyzed by hydroquinine-derived chiral base is described. Up to 85% ee was obtained.

Enantiomerically enriched amines are present in many bioactive compounds, and are also important intermediates in organic synthesis.[1–3] Asymmetric transamination of ketones provides an attractive strategy for the syntheses of chiral amines. Great progress has been made for biocatalytic transamination.[4] However, non-enzymatic asymmetric transamination of unactivated ketones still remains challenging.[5–8] In 1995, Zwanenburg and coworkers reported that chiral amines can be obtained with up to 44% ee *via* R*OK-catalyzed isomerization of *N*-benzylimines.[8] Recently, we reported that α-amino esters can be obtained in high ee's *via* chiral base-catalyzed transamination of α-keto esters with benzylamines as amine sources (Scheme 1).[9] As part of our continuing efforts on this subject, we have been investigating related asymmetric transaminations of other carbonyl compounds. Herein, we wish to report our preliminary results on asymmetric biomimetic transamination of unactivated ketones (Scheme 2).

Initial studies were carried out with acetophenone (**11**) as substrate and quinine derivative **C1** as catalyst. Little amine products were detected when the reactions were performed in refluxing



Scheme 1 Chiral base-catalyzed transamination of α-keto ester.

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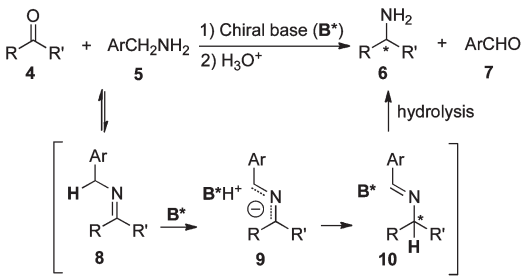
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, HPLC data for determination of enantiomeric excesses, and NMR spectra. See DOI: 10.1039/c2ob26782a



Scheme 2 Chiral base-catalyzed transamination of ketone.

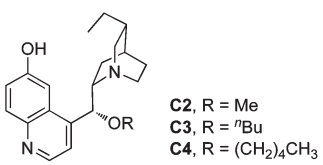
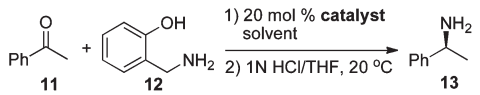


Fig. 1 Selected examples of catalyst examined.

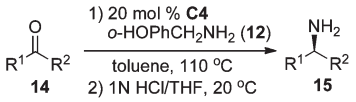
Table 1 Studies on reaction conditions[a]

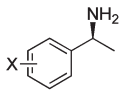
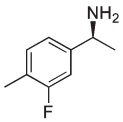
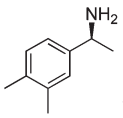
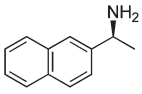
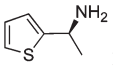
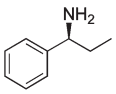


Entry	Cat	Solvent	Conv[b] (%)	ee[c] (%)
1	**C1**	Toluene	87	77
2	**C1**	Benzene	42	82
3	**C1**	MeCN	33	72
4	**C1**	EtOH	34	27
5	**C2**	Toluene	83	80
6	**C3**	Toluene	91	80
7	**C4**	Toluene	96	80

[a] All reactions were carried out with acetophenone (**11**) (0.20 mmol), *o*-HOPhCH$_2$NH$_2$ (**12**) (0.30 mmol), and catalyst (0.04 mmol) in solvent (1.0 mL) at reflux for 72 h. [b] The conversion was determined by ^{1}H NMR of the crude reaction mixture based on ketone **11** and its ketimine. [c] The ee's were determined by chiral HPLC (Chiralpak AD-H column) after the amines were converted into their *N*-benzoyl derivatives.

Table 2 Catalytic asymmetric transamination of aromatic ketones[a]



Entry	Amine[b] (**15**)	Yield[c] (%)	ee[d] (%)
			
1	**15a**, X = H	66	80
2	**15b**, X = *o*-F	65	84
3	**15c**, X = *o*-Br	62	71
4	**15d**, X = *m*-Br	74	78
5	**15e**, X = *m*-CH_3	51	82
6	**15f**, X = *p*-Cl	61	79
7	**15g**, X = *p*-CH_3	52	83
8	**15h**, X = *p*-^{n}Bu	47	78
9	**15i**, X = *p*-^{t}Bu	51	76
10	 **15j**	58	85
11	 **15k**	44	83
12	 **15l**	73	81
13	 **15m**	47	70
14	 **15n**	43	77

[a] All reactions were carried out with ketone **14** (1.0 mmol), *o*-$HOPhCH_2NH_2$ (**12**) (1.50 mmol), and catalyst **C4** (0.20 mmol) in toluene (5.0 mL) at 110 °C for 72 h. [b] For entries 1, 6, 7, and 14, the absolute configurations (*S*) were determined by comparing the optical rotations with reported ones of chiral amines (refs. 11 and 12). The absolute configurations of remaining amines were tentatively proposed by analogy. [c] Isolated yield based on ketone **14**. [d] The ee's were determined by chiral HPLC (Chiralpak AD-H column) after the amines were converted into their *N*-benzoyl derivatives.

toluene with various benzyl amines such as $PhCH_2NH_2$, *o*-$MeOPhCH_2NH_2$, *o*-$ClPhCH_2NH_2$, *m*-$BrPhCH_2NH_2$, *p*-$FPhCH_2NH_2$, *p*-$CNPhCH_2NH_2$, *etc.* Our next attention was then focused on *o*-$HOPhCH_2NH_2$ (**12**), which has displayed unusually high reactivity for the transamination of certain unreactive aryl keto esters with other benzyl amines.[10] To our delight, the desired amine product was obtained with 77% ee when acetophenone (**11**) was treated with *o*-$HOPhCH_2NH_2$ (**12**) and 20 mol% catalyst **C1** in refluxing toluene (Table 1, entry 1). Slightly higher ee's (80% ee) were obtained with catalysts **C2**, **C3**, and **C4** (Fig. 1) (Table 1, entries 5–7). It appears that the transamination is greatly facilitated by the *o*-OH group of *o*-$HOPhCH_2NH_2$ (**12**) likely *via* H-bond.

The asymmetric transamination can be extended to a variety of aromatic ketones (Table 2). Acetophenone and various substituted acetophenones can be transaminated to give the corresponding chiral amines in 44–74% yield and 71–85% ee (Table 2, entries 1–11). Other aromatic ketones such as 2-acetylnaphthalene and 2-acetylthiophene were effective substrates, giving the amines in 81% and 70% ee respectively (Table 2, entries 12 and 13). Similar ee was obtained with propiophenone (Table 2, entry 14).

Conclusion

In summary, we have developed an efficient asymmetric biomimetic transamination of various aromatic ketones with *o*-$HOPhCH_2NH_2$ as amine donor and hydroquinine derivative **C4** as catalyst, giving optically active amines in 43–74% yield and 70–85% ee. This process illustrates the potential of transamination as a viable approach to generate optically active amines from unactivated ketones. Further understanding the mechanism and developing more effective catalytic systems are currently under way.

Acknowledgements

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

Notes and references

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