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Organocatalytic asymmetric biomimetic transamination of α-keto acetals to chiral α-amino acetals†

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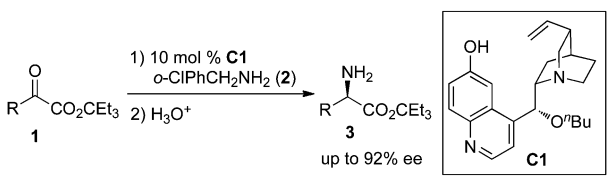
This paper describes a chiral base-catalyzed asymmetric biomimetic transamination of α-keto acetals. A wide variety of α-amino acetals containing various functional groups can be synthesized in 50–85% yield and 82–86% ee.

Chiral amines are important functional moieties present in many natural products and pharmaceuticals, and are useful building blocks in organic synthesis. Various effective methods have been developed for synthesis of optically active amines.[1–3] Asymmetric transamination of ketones presents a straightforward approach to chiral amines. Great success has been achieved in biocatalytic transamination.[4] Asymmetric biomimetic transamination has also received considerable attention.[5–12] Thus far, the substrates are generally limited to α-keto esters and α-trifluoromethyl ketimines. The isomerization of ketimine to aldimine is greatly facilitated by the ester and trifluoromethyl groups. Asymmetric transamination of ketones with less activating groups is highly desirable but still presents a formidable challenge.[12]



Scheme 1 Chiral base-catalyzed biomimetic transamination.

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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/c3ra42906g

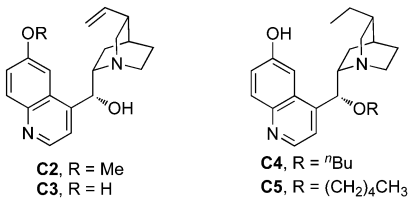
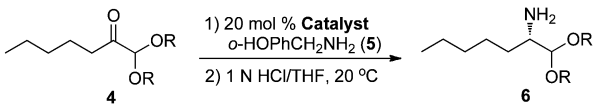


Fig. 1 Selected examples of catalyst examined.

Earlier, we reported an efficient chiral base-catalyzed biomimetic transamination of α-keto esters to α-amino esters with *o*-$ClPhCH_2NH_2$ in high ee's (Scheme 1).[8a] Recently, we have

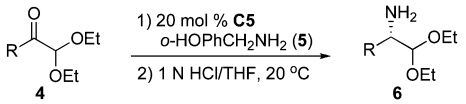
Table 1 Studies on catalysts, solvents and acetal groups[a]



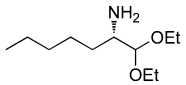
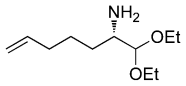
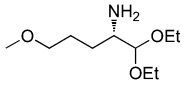
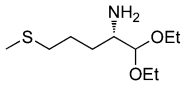
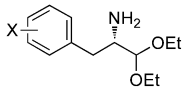
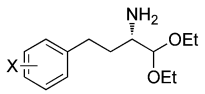
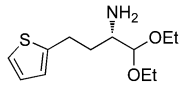
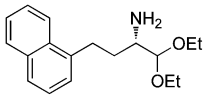
Entry	Catalyst	4	Solvent	Yield[b] (%)	ee[c] (%)
1	**C1**	**4a**, R = Et	Toluene	59	85
2	**C2**	**4a**, R = Et	Toluene	13	14
3	**C3**	**4a**, R = Et	Toluene	35	75
4	**C4**	**4a**, R = Et	Toluene	60	85
5	**C5**	**4a**, R = Et	Toluene	65	85
6	**C5**	**4a**, R = Et	Benzene	47	85
7	**C5**	**4a**, R = Et	Cyclohexane	35	85
8	**C5**	**4a**, R = Et	$ClCH_2CH_2Cl$	12	55
9	**C5**	**4a**, R = Et	MeCN	26	82
10	**C5**	**4b**, R = Me	Toluene	69	82
11	**C5**	**4c**, R = ^{n}Bu	Toluene	38	76
12	**C5**	**4d**, R = ^{i}Bu	Toluene	46	77

[a] All reactions were carried out with α-keto acetals **4** (0.50 mmol), *o*-$HOPhCH_2NH_2$ (**5**) (0.75 mmol), and catalyst (0.10 mmol) in solvent (2.5 mL) at reflux for 72 h. [b] Isolated yield based on α-keto acetals **4**. [c] The ee's were determined by chiral HPLC (Chiralpak AD-H column) after the amino acetals were converted into their *N*-benzoyl derivatives.

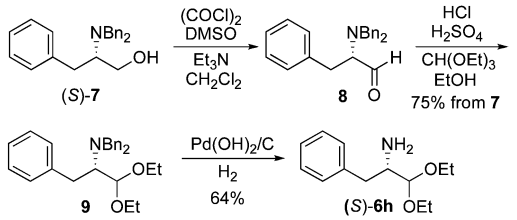
Table 2 Catalytic asymmetric transamination of α-keto acetals[a]



4 6

Entry	α-Amino acetal[b] (6)	Yield[c] (%)	ee[d] (%)
1	 **6a**	65	85
2	 **6e**	85	84
3	 **6f**	61	83
4	 **6g**	81	84
5	 **6h**, X = H	59	83
6	**6i**, X = *m*-Cl	50	82
7	**6j**, X = *m*-Me	54	84
8	**6k**, X = *p*-Me	72	86
9	 **6l**, X = H	79	84
10	**6m**, X = *o*-F	66	84
11	**6n**, X = *m*-Cl	60	83
12	**6o**, X = *p*-Cl	70	85
13	 **6p**	73	82
14	 **6q**	66	82

[a] All reactions were carried out with α-keto acetals **4** (0.50 mmol), *o*-$HOPhCH_2NH_2$ (**5**) (0.75 mmol), and catalyst **C5** (0.10 mmol) in refluxing toluene (2.5 mL) for 72 h. [b] For entry 5, the absolute configuration (*S*) was determined by comparing the optical rotation with the corresponding amino acetal derived from commercially available **(*S*)-7** (Scheme 2). The absolute configurations of remaining amino acetals were tentatively proposed by analogy. [c] Isolated yield based on α-keto acetal **4**. [d] The ee's were determined by chiral HPLC (Chiralpak AD-H column) after the amino acetals were converted into their *N*-benzoyl derivatives.

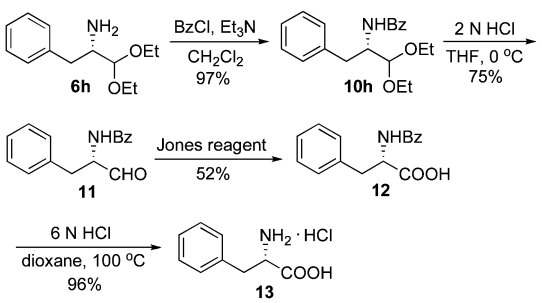


Scheme 2

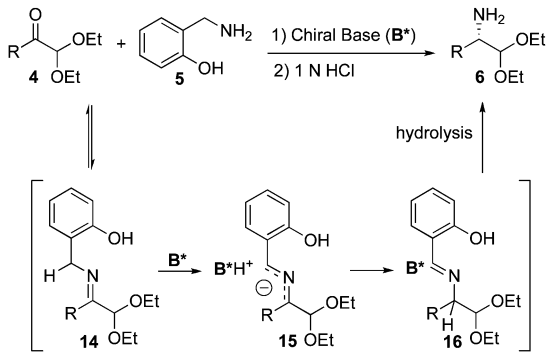
shown that less activated aromatic ketones can be transaminated with *o*-$HOPhCH_2NH_2$ to form chiral amines with up to 85% ee.[13] In efforts to further expand the substrate scope, we have explored transamination of α-keto acetals to form optically active α-amino acetals, which are synthetically useful compounds.[14,15] Herein, we wish to report our preliminary results on this subject.

Initial studies were carried out with 1,1-diethoxy-heptan-2-one (**4a**) as substrate, *o*-$HOPhCH_2NH_2$ (**5**) as nitrogen donor, and quinine derivatives (**C1–C5**) (Fig. 1) as catalysts in refluxing toluene (Table 1, entries 1–5). Catalyst **C5** gave the best result overall (65% yield and 85% ee) (Table 1, entry 5). Among the solvents examined (Table 1, entries 5–9), toluene was found to be optimal. The acetal group has some impact on the enantioselectivity (Table 1, entires 5, 10, 11, and 12). The ethyl acetal gave higher ee than the methyl, *n*-butyl, and *i*-butyl acetals.

The asymmetric transamination process can be extended to a wide variety of α-keto acetals, giving the corresponding α-amino acetals in 50–85% yield and 82–86% ee (Table 2). The side chains of amino acetals can contain saturated (Table 2, entry 1) or unsaturated aliphatic group (Table 2, entry 2), heteroatoms like O and S (Table 2, entries 3 and 4), and various aromatic groups (Table 2, entries 5–14). The absolute configuration of **6h** was determined by comparing the optical rotation with the corresponding compound prepared from commercially available **(*S*)-7** by Swern oxidation,[16] the acetal formation,[16] and debenzylation (Scheme 2).[17] Alternatively, the absolute configuration of (*S*)-phenylalaninal diethylacetal (**6h**) was determined by converting it into (*S*)-phenylalanine hydrochloride (**13**) *via* benzoyl protection, deprotection of ethoxy,[18] Jones oxidation,[19] and deprotection of benzoyl[8c,20] as outlined in Scheme 3. A possible transamination mechanism of α-keto acetals to α-amino acetals is proposed in Scheme 4.[8,11f,13]



Scheme 3



Scheme 4

In summary, we have shown that α-keto acetals can be efficiently transaminated to α-amino acetals in 50–85% yield and 82–86% ee with *o*-$HOPhCH_2NH_2$ as nitrogen donor and hydroquinine derivative **C5** as catalyst. Optically active α-amino acetals are synthetically useful compounds. The current studies extend the biomimetic transamination to another class of carbonyl compounds and further demonstrate its potential for the synthesis of chiral amines. The development of more effective catalytic systems and the expansion of other carbonyl compounds are currently underway.

Acknowledgements

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