Asymmetric Catalysis

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Catalytic Asymmetric Amination of Enecarbamates**

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Asymmetric electrophilic amination reactions have recently received much attention.[1] In particular, the asymmetric amination of carbonyl compounds has been developed to obtain biologically important α-amino acids and their derivatives. A number of compounds, such as sulfonyl azides,[2] 1-chloro-1-nitroso reagents,[3] and nitroso benzenes,[4] are known to act as electrophilic nitrogen sources, but perhaps the most prominent are azodicarboxylates. A catalytic asymmetric α-amination of carbonyl compounds using azodicarboxylates was pioneered by Evans and Nelson, who used a chiral magnesium bis(sulfonamide) complex as a catalyst.[5] Subsequently, Evans's group[6] and our group[7] reported the catalytic asymmetric amination using silicon enolates. List and Jørgensen and co-workers reported asymmetric proline-catalyzed amination of linear aldehydes using azodicarboxylates,[8] and furthermore Jørgensen and co-workers examined the direct use of ketones in proline-catalyzed amination of azodicarboxylates.[9] Direct α-amination of 2-ketoesters and β-ketoesters in the presence of a chiral bisoxazoline-Cu^{II} complex[10] and direct organocatalytic amination of α-substituted α-cyanoacetates[11] are also alternative methods for the synthesis of enantioenriched α-amino carbonyl compounds. Whereas those methods gave excellent enantioselectivities (in general over 90% *ee*), relatively high catalyst loadings (in almost all cases, not less than 5 mol%) were necessary to obtain high enantioselectivies and substrates are limited in many reactions.[12] Herein, we report the first catalytic asymmetric amination of enecarbamates catalyzed by a chiral diamine-Cu^{II} complex using azodicarboxylates. Yields and enantioselectivities are generally high for various kinds of enecarbamates derived from aromatic and aliphatic ketones, and aldehydes, and lower levels of catalyst loadings have been attained (in some cases, 0.2 mol% of the catalyst was sufficient). We also describe the facile synthesis of optically active *trans*-1,2-diamine compounds by using this method.

We first investigated the amination of propiophenone-derived enecarbamate **2a** (Table 1).[13] When $AgClO_4$-binap

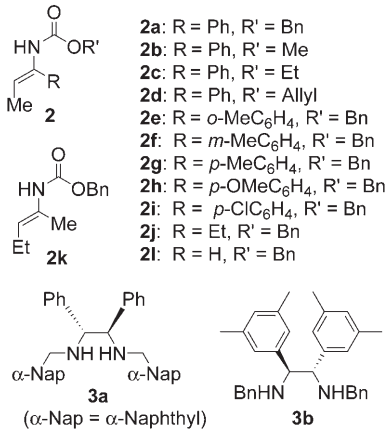
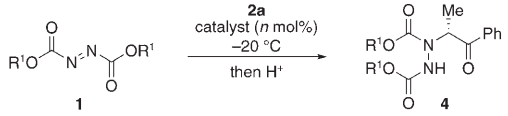


Table 1: Optimization of reaction conditions.[a]



Entry	R^1	Catalyst	*n* [mol%]	**2a**	Solvent	*t* [h]	Yield [%]	*ee* [%]
1[b]	Bn	$AgClO_4$ + (*S*)-binap	10	*Z*	THF	72	77	36
2[b]	Bn	$Zn(OTf)_2$ + **3a**	10	*Z*	CH_2Cl_2	144	51	32[c]
3[b]	Bn	$Cu(OTf)_2$ + **3a**	10	*Z*	CH_2Cl_2	30	96	66[c]
4[b]	Bn	$Cu(OTf)_2$ + **3a**	10	*E*	CH_2Cl_2	1.5	98	70[c]
5[d]	Bn	$Cu(OTf)_2$ + **3b**	10	*E*	toluene	6	99	85
6[d]	Bn	$Cu(BF_4)_2 \cdot x H_2O$ + **3b**	10	*E*	toluene	7	100	87
7[d]	*i*Pr	$Cu(BF_4)_2 \cdot x H_2O$ + **3b**	10	*E*	toluene	4	100	93
8[d]	*i*Pr	$Cu(BF_4)_2 \cdot x H_2O$ + **3b**	1	*E*	toluene	52	34	88
9	*i*Pr	$Cu(BF_4)_2 \cdot x H_2O$ + **3b**	1	*E*	toluene	36	97	89
10	*i*Pr	$Cu(OTf)_2$ + **3b**	1	*E*	toluene	6	94	95

[a] Reactions conducted with 1.1 equivalents of **1** relative to **2** in the indicated solvent (0.067 M in substrate). Bn = benzyl, OTf = trifluoromethanesulfonate. [b] 0 °C. [c] Opposite enantiomer. [d] 3-Å molecular sieves (M.S.; 100 mg mmol^{-1}) were added.

complex, which gave high enantioselectivity in the reaction of azodicarboxylate with silicon enolates,[7] was used as a catalyst, the ketone product **4** was obtained after hydrolysis with low enantioselectivity (Table 1, entry 1). While the catalytic activity of $Zn(OTf)_2$-diamine **3a** was also found to be low (Table 1, entry 2),[14] $Cu(OTf)_2$-**3a** complex[15] gave higher enantioselectivity (entry 3). Moreover, it was found that changing the enecarbamate geometry from *Z* to *E* resulted in a dramatic improvement of the reactivity (Table 1, entry 4), and that the use of diisopropyl azodicarboxylate in toluene improved enantioselectivity significantly (entries 5–7).[16] The yield was decreased when the catalyst loading was reduced to 1 mol% (Table 1, entry 8), but was improved

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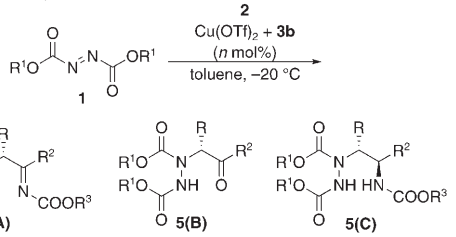
when the reaction was conducted in the absence of 3-Å M.S. (entry 9). Finally, the best result was obtained when $Cu(OTf)_2$ was used as the metal source (Table 1, entry 10). The absolute configuration of the product was determined to be *R* by comparison with literature data by HPLC analysis.

The scope of the catalytic asymmetric amination of enecarbamates was then surveyed under the optimized reaction conditions (Table 2). A wide range of azodicarboxylates and enecarbamates derived from aromatic ketones bearing substituents with various electronic and steric properties, aliphatic ketones, and aldehydes were found to react with azodicarboxylates efficiently to afford the desired products in good yields with high enantioselectivities. The initially formed acylimines **5(A)** were readily converted into ketone products **5(B)** after hydrolysis or 1,2-diamine derivatives **5(C)** after highly stereoselective reduction (see footnote of Table 2). It is of particular note that the amination reaction of enecarbamates followed by $NaBH_4$ reduction can be conducted on a gram scale. The reaction of 3 g enecarbamate (*E*)-**2a** with diisopropyl azodicarboxylate was catalyzed with 0.6 mol% of the catalyst $Cu(OTf)_2$ (24 mg of $Cu(OTf)_2$ as used), followed by reduction with $NaBH_4$ to provide 4.9 g of the 1,2-diamino compound (92% yield; *syn*/*anti* = < 5 : > 95; 96% *ee* for *anti*).

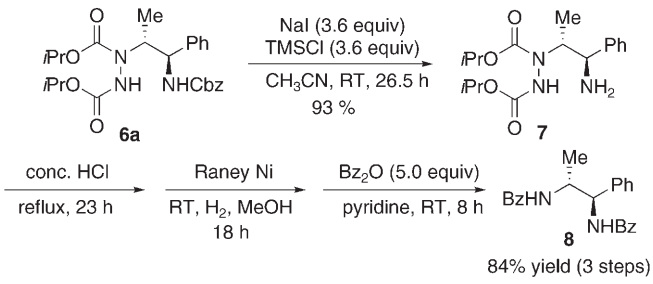
trans-1,2-Diamine derivatives, which are seen in many biologically important compounds as well as in useful chiral ligand skeletons,[18] can be obtained using this new methodology. The product **6a** was efficiently converted into the free amine **7**, whose structure was unambiguously determined by X-ray crystallographic analysis. Deprotection of the carbamate moieties followed by N–N bond cleavage using Raney Ni and benzoylation afforded *trans*-1,2-diamine derivative **8** in high yield (Scheme 1).

Table 2: Catalytic asymmetric α-amination of enecarbamates.[a]



Entry	R^1	2	*n* [mol%]	*t* [h]	Yield [%]	*ee* [%]	Product[b]
1[c]	*i*Pr	**2a**	0.2	22	84	98	**C**
2	*i*Pr	**2b**	1	25	90	92	**B**
3	*i*Pr	**2c**	1	24	87	84	**B**
4	*i*Pr	**2d**	1	24	62	83	**B**
5	Me	**2a**	3	24	83	82	**B**
6	Et	**2a**	3	24	91	84	**B**
7[d]	Bn	**2a**	10	6	99	85	**B**
8	*i*Pr	**2e**	5	20	84	96	**A**
9	*i*Pr	**2f**	1	24	93	97	**B**
10	*i*Pr	**2g**	5	10	90	94	**B**
11[c]	*i*Pr	**2h**	3	6	81	90	**C**
12[c]	*i*Pr	**2i**	0.2	24	79	96	**C**
13[e]	*i*Pr	**2j**	2	6	82[f]	82	**C**
14[g]	*i*Pr	**2k**	5	4	70	86	**C**
15[e]	*i*Pr	**2l**	5	26	82	67[h]	**C**

[a] Reactions conducted with 1.1 equivalents of **1** relative to **2** in toluene (0.067 M in substrate). [b] **A**: Acylimine (no treatment); **B**: ketone by hydrolysis; **C**: 1,2-diamino derivative by reduction (*syn*/*anti* = < 5 : > 95). [c] −10 °C. [d] 3-Å M.S. were added (100 mg mmol^{-1}). [e] Ligand **3a** was used instead of **3b**. [f] *syn*/*anti* = 28:72. [g] 3-Å M.S. were added (50 mg mmol^{-1}). [h] See reference [17].



Scheme 1. Synthesis of *trans*-1,2-diamine derivatives **7** and **8**. Cbz = carbobenzyloxy, TMS = trimethylsilyl, Bz = benzoyl.

On the basis of the absolute configuration and the fact that both *E*- and *Z*-enecarbamates gave the same absolute configuration (Table 1, entries 3 and 4),[19] we propose an acyclic concerted transition-state model (Figure 1).[20] We assume that a diamine ligand and azodicarboxylate coordinate to the copper in bidentate fashion, and that the copper adopts a slightly distorted square-planar geometry.[15c] The *Re* face of the azodicarboxylate is shielded by the neighboring benzyl group of the diamine ligand, and an enecarbamate attacks from the *Si* face predominantly (see the Supporting Information). As for the facial selectivity of the enecarbamate, TS-1 and TS-2 in which the enecarbamate reacts with azodicarboxylate through an *antiperiplanar* transition state are reasonable to minimize steric repulsions between the enecarbamate and the copper catalyst or the carbamate group of the azodicarboxylate. TS-1, which gives the *R*-configured product, is more plausible because of the critical steric repulsion between the substituent of the enecarbamate and the copper catalyst in TS-2.

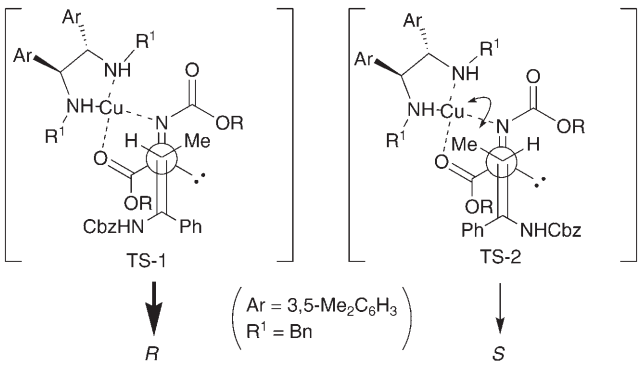


Figure 1. Proposed transition-state model.

In conclusion, we have developed the first catalytic asymmetric amination of enecarbamates using a $Cu(OTf)_2$-diamine complex as catalyst. Yields and enantioselectivities are high in most cases, and catalyst loadings are generally low. This new reaction provides not only α-amino carbonyl

compounds but also α-amino acylimines, which can be readily converted into 1,2-diamine derivatives stereoselectively. We have also shown that this amination reaction can be conducted on a gram scale. Moreover, a transition-state model to explain the absolute configuration observed in this amination reaction of enecarbamates is proposed. Further investigations to apply this new protocol to the synthesis of biologically important compounds are in progress.

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[17] When aldehyde-derived enecarbamate **2l** was used, the initially formed product after Cu-catalyzed reaction was not acylimine but a cyclic product, which was reduced by using triethylsilyl hydride and trimethylsilyl triflate instead of $NaBH_4$. See the Supporting Information for details.
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