Asymmetric Catalysis

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Highly Enantioselective Insertion of Carbenoids into N–H Bonds Catalyzed by Copper(I) Complexes of Binol Derivatives**

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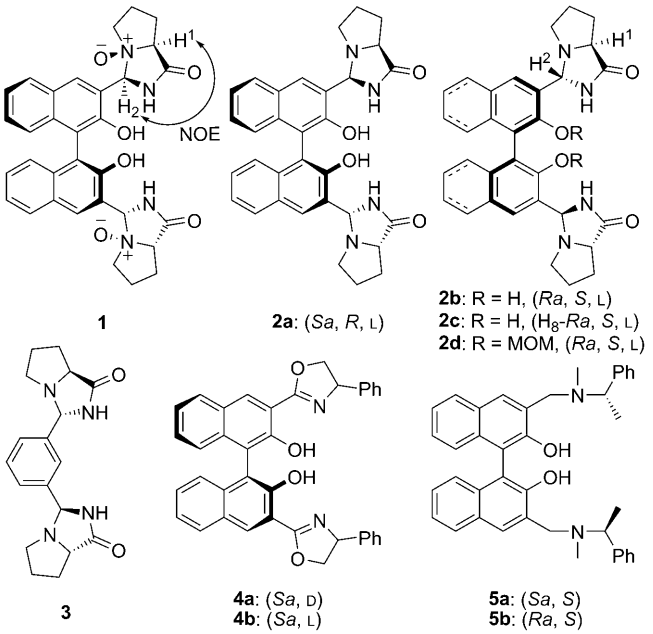
The catalytic asymmetric insertion reaction of α-diazocarbonyl compounds into X–H bonds (X = C, N, P, O, S, etc.) has attracted much attention because it provides an efficient way to construct versatile and useful building blocks.[1] In contrast to the extensive and fruitful studies on asymmetric C–H insertion,[2] the investigation of enantioselective insertion of α-diazocarbonyl compounds into heteroatom–hydrogen bonds (X–H) is still limited.[3] This may result from the presence of the highly reactive polar X–H bonds, which form the ylide intermediates upon attack of the electrophilic metal carbene to the lone pair of electrons on the heteroatom, thus leading to a more intricate complexion.[4] Moreover, the Lewis basic nitrogen atoms in the starting amine and in the products tend to strongly coordinate to the central metal atom in the catalyst, which may result in the deactivation of the catalyst.[5] Among the insertion reactions, metal-catalyzed carbenoid N–H insertions are of great importance, because they lead to the formation of various bioactive molecules such as α-amino ketones, α-amino acid derivatives, and pharmaceutically useful compounds.[6] In a pioneering study, Jørgensen and co-workers reported the first asymmetric intermolecular N–H insertion reactions by means of chiral copper(I)/silver(I) bisoxazoline complexes. Although only low to moderate yields and *ee* values were obtained, this study has actually opened the doors to asymmetric versions of N–H insertion reactions.[7] No further breakthrough was made until Zhou and co-workers reported excellent *ee* values (98%) and yields (94%) using a catalytic system consisting of a spirobisoxazoline ligand, CuCl, and NaBARF (BARF = $[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$).[8] Later, Lee and Fu disclosed another highly enantioselective N–H insertion reaction with α-aryl diazoesters and carbamates (Boc-NH_2 and Cbz-NH_2; Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl) as substrates, which leads to useful arylglycine derivatives with excellent *ee* values (up to 94%).[9] Despite these achievements, in view of the great utility of this N–H insertion reaction, the exploration of alternative efficient catalytic systems is still highly desirable. Herein, we describe a novel and readily available copper(I) catalyst generated from the (*R*)-binol derivative **2b** and CuCl, from which a series of enantioenriched substituted α-amino acetates were prepared in excellent yields and *ee* values.

Recently, our research group reported a novel axially chiral *N*,*N*′-dioxide **1**, which was demonstrated to be a highly efficient organocatalyst for the enantioselective Strecker reaction of *N*-Ts-protected ketimines (Ts = 4-toluenesulfonyl; Scheme 1).[10] To find further uses for this compound,



Scheme 1. Ligands used in this study.

we employed it as a chiral ligand in N–H insertion reactions. However, almost racemic product was obtained in moderate yield for the reaction of aniline (**6a**) with three equivalents of the diazo compound **7a** using the complex of **1** with CuCl in CH_2Cl_2 (Table 1, entry 1).

Interestingly, when **2a** (the precursor of **1**) was used both the yield and the *ee* value were slightly improved, thus suggesting that the *N*-oxide moieties in **1** were not necessary for the present reaction (Table 1, entry 2). From the observation that several chiral elements co-existed in ligand **2a**, it was

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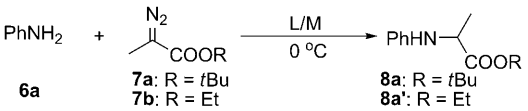
Table 1: Catalytic asymmetric insertion of diazopropionate into the N–H bond of aniline.



6a

7a: R = *t*Bu
7b: R = Et

8a: R = *t*Bu
8a': R = Et

Entry[a]	L/M	Solvent	Additive (M.S.)	Yield [%][b]	*ee* [%][c]
1	**1**/CuCl	CH_2Cl_2		62	−8
2	**2a**/CuCl	CH_2Cl_2		85	−17
3	**2b**/CuCl	CH_2Cl_2		96	85
4	**2c**/CuCl	CH_2Cl_2		99	67
5	**2d**/CuCl	CH_2Cl_2		trace	0
6	**3**/CuCl	CH_2Cl_2		86	8
7	**4a**/CuCl	CH_2Cl_2		12	0
8	**4b**/CuCl	CH_2Cl_2		trace	−6
9	binol/CuCl	CH_2Cl_2		90	−5
10	**5a**/CuCl	CH_2Cl_2		trace	3
11	**5b**/CuCl	CH_2Cl_2		22	8
12	**2b**/$CuCl_2$	CH_2Cl_2		NR	–
13	**2b**/$CuClO_4$	CH_2Cl_2		NR	–
14	**2b**/CuCl	$CHCl_3$		76	38
15	**2b**/CuCl	toluene		trace	0
16	**2b**/CuCl	THF		trace	−28
17	**2b**/CuCl	CH_3CN		trace	66
18	**2b**/CuCl	CH_2Cl_2	3 Å	92	86
19	**2b**/CuCl	CH_2Cl_2	4 Å	98	88
20	**2b**/CuCl	CH_2Cl_2	5 Å	93	87
21[d]	**2b**/CuCl	CH_2Cl_2	4 Å	96	86 (*S*)
22[e]	**2b**/CuCl	CH_2Cl_2	4 Å	99	93
23[e,f]	**2b**/CuCl	CH_2Cl_2	4 Å	88	85
24[e,g]	**2b**/CuCl	CH_2Cl_2	4 Å	99	91

[a] All the reactions were carried out with **6a** (0.2 mmol), **7a** (3 equiv) in 2 mL solution with 10 mol% of catalyst at 0°C in a dry test tube under an inert atmosphere and reactions were stirred for 8 hours unless otherwise specified. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] **7b** was used instead of **7a**. [e] For details, see the Experimental Section. [f] 2 mol% of catalyst was used. [g] 20 mol% of catalyst was used.

reasonable to speculate that the chirally matched properties might have a significant impact on the reaction outcome. As expected, when the configuration of the binaphthyl unit was switched from *S* (**2a**) to *R* (**2b**) while other structural moieties were kept constant, a high yield (96%) and a greatly enhanced enantioselectivity (85% *ee*) were observed (Table 1, entry 3). It should be noted that to the newly formed chiral center in ligand **1** (or **2a**) derived from (*S*)-binol and L-proliamide was assigned the *R* configuration based on the observation of a strong NOE interaction between H_1 and H_2.[10] However, for the ligand **2b** derived from (*R*)-binol and L-proliamide, nearly no NOE interaction was observed, thus suggesting that the corresponding H_1 and H_2 are in the *anti* positions. This assumption was further confirmed by the single-crystal X-ray analysis of **2b**, and the configuration of the new stereogenic center was assigned as *S* (Figure 1).[11] Based on the above findings, it was concluded that the configuration of the new chiral center was predominantly controlled by the axial chirality of the binol ligand rather than by L-proliamide.

Next, the dihedral angle of the binaphthyl unit was investigated. However, the ligand **2c** derived from H_8-binol

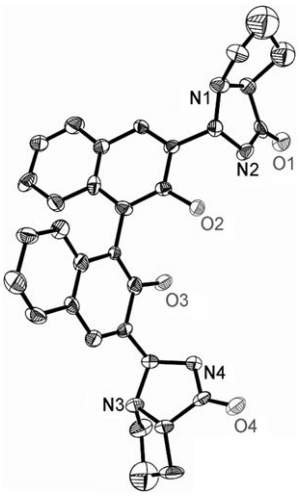


Figure 1. ORTEP plot of **2b** with ellipsoids drawn at 30% probability.

led to a lower *ee* value (Table 1, entry 4), thus indicating that a suitable dihedral angle was crucial in the chiral induction step of the catalytic process. When two hydroxy groups of **2b** were replaced by two methoxymethoxy groups (**2d**), traces of racemic product were obtained, which showed that the hydroxy groups in ligand **2b** were essential to the formation of a complex with Cu^I (Table 1, entry 5). When the axially chiral binaphthyl skeleton was replaced by an achiral benzene ring to afford ligand **3**, the enantioselectivity was drastically decreased (Table 1, entry 6). Moreover, binol-derived bisoxazolines **4a** and **4b** were also synthesized for ligand screening. However, nearly no enantiodiscrimination, and very low yields were given under identical reaction conditions (Table 1, entries 7 and 8). Other ligands such as (*S*)-binol and binol-derived tertiary amines **5a** and **5b** were also examined. However, only very poor results were obtained (Table 1, entries 9–11).

With **2b** as the optimal ligand, other copper sources including $CuCl_2$ and $CuClO_4$ were tested. However, nearly no reaction was observed (Table 1, entries 12 and 13). Besides CH_2Cl_2, other solvents were investigated. When $CHCl_3$ was used, low *ee* values and moderate yields were obtained (Table 1, entry 14) while use of toluene, led to the formation of the product in a trace amount (Table 1, entry 15). Other coordinating solvents such as THF and CH_3CN were also tested, however, the reactions were very slow and the *ee* values were dramatically decreased (Table 1, entries 16 and 17). Additive screening showed that molecular sieves (M.S.) have a slight positive effect on the enantioselectivity (Table 1, entries 18–20). Among the tested molecular sieves, 4 Å M.S. gave the best *ee* value (Table 1, entry 19). However, when the R group in the diazopropionate **7** was changed from *tert*-butyl to ethyl, a lower *ee* value (86%) was obtained with a yield of 96% (Table 1, entry 21).

To further improve the outcome of our reaction, different kinds of operational procedures were tried and compared. Intriguingly, it was found that better results could be achieved by allowing the reaction mixture to stay without continuous stirring after the full addition of the reactants to the solution

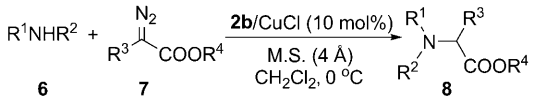
containing the catalyst. However, the reaction mixture should be kept homodisperse by shaking the reaction tube for several seconds every 2 hours during the initial 6 hours of the reaction at the reaction temperature. We reasoned that under such conditions, the reaction rate was effectively lowered. As a result, the non-enantioselective background reaction was to some extent suppressed and more products were formed through the desired enantioselective route (Table 1, entry 22). Some other catalyst loadings (such as 2 mol% and 20 mol%) were also tried, but improved results were not achieved (Table 1, entries 23 and 24).

Under the optimized reaction conditions, a broad range of substituted anilines were examined with *tert*-butyl 2-diazopropionate (**7a**). As shown in Table 2, regardless of the position and the nature of the substituents, various substituted anilines could be smoothly converted into the corresponding products in high yields (92–99%) with excellent *ee* values (87–98%; Table 2, entries 1–18). In addition, 1-naphthyl amine was also treated with **7a** to afford α-amino ester in 93% *ee* with 90% yield (Table 2, entry 19).

Moreover, besides primary amines, the secondary amine *N*-methylaniline was also examined under the same reaction conditions. The desired product was obtained in high yield although with only 25% *ee* (Table 2, entry 20). When methyl and ethyl α-diazophenylacetate were treated with *N*-methylaniline, improved *ee* values were observed (Table 2, entries 21 and 22). To our knowledge, these are the best results for the reaction of α-diazoester with secondary amines.

In summary, a novel and readily available binol-derivative copper(I) catalyst was developed for the highly enantioselective catalytic insertion reaction of α-diazoesters into N–H bonds of the amines under mild reaction conditions. In addition to the excellent *ee* values and yields observed for primary amines, the reaction with secondary amine also led to moderate to good results. A variety of useful chiral α-amino esters with different N-substituted groups could be facilely prepared in excellent yields and enantiomeric excesses. Further studies on the efficient catalytic N–H insertion of secondary amine with diazoesters as well as mechanistic studies are in progress.

Table 2: copper(I)-catalyzed asymmetric insertion of diazoesters into the N–H bond of amine.



6 **7** **8**

Entry[a]	Aniline **6**		Diazo **7**		Product	Yield [%][b]	*ee* [%][c]
	R^1	R^2	R^3	R^4			
1	Ph	H	Me	*t*Bu	**8a**	99	93
2	2-FC_6H_4	H	Me	*t*Bu	**8b**	99	94
3	3-FC_6H_4	H	Me	*t*Bu	**8c**	98	97
4	4-FC_6H_4	H	Me	*t*Bu	**8d**	99	93
5	2-ClC_6H_4	H	Me	*t*Bu	**8e**	99	96
6	3-ClC_6H_4	H	Me	*t*Bu	**8f**	99	98
7	4-ClC_6H_4	H	Me	*t*Bu	**8g**	99	96
8	2-BrC_6H_4	H	Me	*t*Bu	**8h**	97	94
9	3-BrC_6H_4	H	Me	*t*Bu	**8i**	98	95
10	4-BrC_6H_4	H	Me	*t*Bu	**8j**	98	96
11	3-MeC_6H_4	H	Me	*t*Bu	**8k**	92	90
12	3-$NO_2C_6H_4$	H	Me	*t*Bu	**8l**	95	94
13	2-$CF_3C_6H_4$	H	Me	*t*Bu	**8m**	92	87
14	3-$CF_3C_6H_4$	H	Me	*t*Bu	**8n**	93	95
15	4-$CF_3C_6H_4$	H	Me	*t*Bu	**8o**	98	93
16	2-$CF_3OC_6H_4$	H	Me	*t*Bu	**8p**	92	90
17	3-$CF_3OC_6H_4$	H	Me	*t*Bu	**8q**	99	97
18	4-$CF_3OC_6H_4$	H	Me	*t*Bu	**8r**	98	95
19	1-naphthyl	H	Me	*t*Bu	**8s**	90	93
20	Ph	Me	Me	*t*Bu	**8t**	98	25
21	Ph	Me	Ph	Me	**8u**	82	67
22	Ph	Me	Ph	Et	**8v**	88	70

[a] All the reactions were carried out with **6** (0.2 mmol), **7** (3 equiv) in 2 mL CH_2Cl_2 with 10 mol% catalyst and M.S. (4 Å, 50 mg) at 0°C in a dry test tube under an inert atmosphere for 18 h. [b] yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

Experimental Section

Typical procedure for the N–H insertion reaction: CH_2Cl_2 (2.0 mL) was added under an inert atmosphere to a dry test tube charged with **2b** (0.02 mmol), CuCl (0.02 mmol), and M.S.(4 Å, 50 mg). The tube was well sealed with a septum and the mixture was stirred at 30°C for 1 h. After cooling to 0°C, amine (0.2 mmol) and α-diazoester (0.6 mmol) were introduced successively by syringes. Subsequently, the reaction mixture was carefully shaken for several seconds. During the next 6 h, the mixture was shaken for several seconds every 2 h to ensure homodispersity and then allowed to stay without stirring for further 12 h at 0°C. The reaction mixture was directly upload onto a column of silica gel and eluted with petroleum ether/ethyl acetate = 10:1.

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[11] CCDC 765587 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

