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Highly Enantioselective Insertion of Carbenoids into N−H Bonds Catalyzed by Copper Complexes of Chiral Spiro Bisoxazolines

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The catalytic insertion of α-diazocarbonyl compounds, which are easily prepared from readily accessible precursors and have a long history of useful applications in organic synthesis, into X−H (X = C, N, O, S) bonds is a very powerful organic transformation for preparing highly versatile building blocks.[1] Among these reactions, the insertion of N−H bonds was proven to be an efficient method for preparing α-amino ketones, α-amino esters, and nitrogen-containing heterocycles and has received considerable attention.[2] The concept of metal−carbenoid insertions into N−H bonds has been known for more than three decades, but surprisingly, only two catalytic asymmetric versions of this topic have been documented, and the enantioselectivities were very low.[3] In 1996, McKervey and co-workers[4] reported the first asymmetric intramolecular N−H bond insertion reaction catalyzed by chiral rhodium(II) carboxylates leading to pipecolic acid derivatives with up to 45% ee. Very recently, Jørgensen et al.[5] disclosed the copper- and silver-catalyzed asymmetric intermolecular insertion of α-diazoesters into N−H bonds in the presence of chiral nitrogen ligands, including Evans bisoxazoline, resulting in α-amino acid derivatives with up to 48% ee. The highly enantioselective catalytic N−H insertion reaction remains a great challenge to organic chemists. Recently, we have developed a new class of chiral bisoxazoline ligands (SpiroBOX, **1**) based on the spirobiindane scaffold (Scheme 1) and proved they were efficient for copper-catalyzed asymmetric cyclopropanation and allylic oxidation.[6] Here we report a copper-catalyzed asymmetric insertion of α-diazoesters into N−H bonds of aromatic amines in the presence of chiral spiro bisoxazoline ligands **1**, providing α-amino acid derivatives in high yields with excellent enantioselectivities (up to 98% ee).

In our study, the insertion of ethyl 2-diazopropionate (**2a**) into the N−H bond of aniline (**3a**) was initially performed in dichloromethane at 25 °C with the catalyst generated in situ from 5 mol % of $CuPF_6(MeCN)_4$ and 6 mol % of (S_a,*S*,*S*)-**1a**. The insertion product, ethyl α-phenylaminopropionate, was obtained in 78% yield with 43% ee (Table 1, entry 1). Comparison of the two diastereomers of ligand **1a** clearly revealed that the (S_a,*S*,*S*)-**1a** has a matched combination of chiralities in terms of enantioselectivity (entries 1 and 2). Various copper catalyst precursors, including CuOTf and CuCl, were tested in the reaction with ligand (S_a,*S*,*S*)-**1a**. The nature of the counterions of the catalysts significantly influenced the enantioselectivity and reactivity of the catalyst. The CuOTf gave the insertion product in only 5% ee, which showed that the smaller and stronger coordinating OTf^- ion is evidently inferior to the PF_6^- ion in the enantiocontrol of the reaction (entries 1 and 3). The use of the neutral copper catalyst precursor CuCl gave an extremely low yield and no asymmetric induction (entry 4). To improve the enantioselectivity of the reaction, we further investigated a copper catalyst with the larger and non-coordinating ion $BARF^-$,[7] which has been successfully applied in a range of catalytic asymmetric transformations for modifying the reactivity and enantioselectivity of catalysts.[8] The catalyst [Cu((S_a,*S*,*S*)-**1a**)]$^+BARF^-$ was prepared by mixing CuCl, ligand (S_a,*S*,*S*)-**1a**, and NaBARF. As we expected, the catalyst [Cu((S_a,*S*,*S*)-**1a**)]$^+BARF^-$ dramatically increased the ee value of the insertion products **4a** to 98% and afforded a high yield (entry 5). The catalyst with the $BARF^-$ anion also has a high activity, which permitted reduction of catalyst loading to 1 mol % (entry 6). Besides CuCl, $CuCl_2$ could be used as a catalyst precursor, although the enantioselectivity was slightly lower than that obtained by using CuCl. In addition to CH_2Cl_2, $CHCl_3$ and C_6H_6 are suitable solvents for the insertion reaction with good to excellent enantioselectivities (entries 8 and 9). However, the reaction became very slow and non-enantioselective in the polar coordinating solvent MeCN (entry 10). In contrast to the ligand (S_a,*S*,*S*)-**1a**, other spiro bisoxazolines containing different aliphatic substituents on the oxazoline rings gave lower enantioselectivities (entries 11−13). The Evans ligand (*S*,*S*)-Ph-Box was

Scheme 1

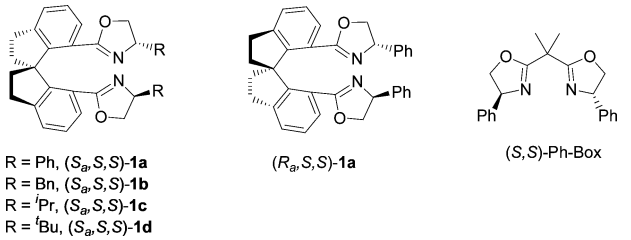
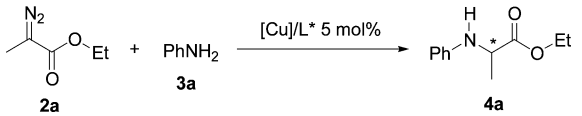


Table 1. Cu-Catalyzed Asymmetric Insertion of Ethyl 2-Diazopropionate into the N−H Bond of Aniline[a]



entry	ligand	[Cu]	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	(S_a,*S*,*S*)-**1a**	$CuPF_6(MeCN)_4$	CH_2Cl_2	2	78	43
2	(R_a,*S*,*S*)-**1a**	$CuPF_6(MeCN)_4$	CH_2Cl_2	2	95	5
3	(S_a,*S*,*S*)-**1a**	$CuOTf(Tol)_{1/2}$	CH_2Cl_2	2	83	5
4	(S_a,*S*,*S*)-**1a**	CuCl	CH_2Cl_2	24	15	rac
5	(S_a,*S*,*S*)-**1a**	CuCl/NaBARF	CH_2Cl_2	2	94	98
6[d]	(S_a,*S*,*S*)-**1a**	CuCl/NaBARF	CH_2Cl_2	2	90	95
7	(S_a,*S*,*S*)-**1a**	$CuCl_2$/NaBARF	CH_2Cl_2	2	80	85
8	(S_a,*S*,*S*)-**1a**	CuCl/NaBARF	$CHCl_3$	2	89	98
9	(S_a,*S*,*S*)-**1a**	CuCl/NaBARF	C_6H_6	6	80	85
10	(S_a,*S*,*S*)-**1a**	CuCl/NaBARF	MeCN	72	45	rac
11	(S_a,*S*,*S*)-**1b**	CuCl/NaBARF	CH_2Cl_2	2	83	61
12	(S_a,*S*,*S*)-**1c**	CuCl/NaBARF	CH_2Cl_2	2	90	79
13	(S_a,*S*,*S*)-**1d**	CuCl/NaBARF	CH_2Cl_2	2	75	85
14	(*S*,*S*)-Ph-Box	CuCl/NaBARF	CH_2Cl_2	2	66	5

[a] Reaction conditions: [Cu] (0.01 mmol), ligand (0.012 mmol), and NaBARF (0.012 mmol) (entries 5−14) were mixed in solvent (2 mL) for 2 h at 25 °C, then aniline (0.2 mmol) and ethyl 2-diazopropionate (0.2 mmol) were introduced and stirred at 25 °C. [b] Isolated yield. [c] Determined by chiral HPLC using a Chiralpak AS column. [d] With 1 mol % of catalyst, refluxing.

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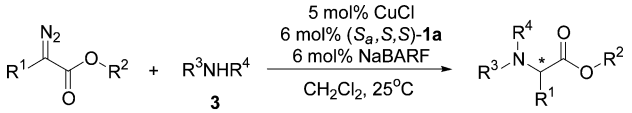
Table 2. Catalytic Asymmetric N−H Insertion of Amines with Diazoesters[a]



entry	R^1	R^2	R^3	R^4	product	yield (%)	ee (%)
1	Me	Et	Ph	H	**4a**	94	98
2	Me	Et	*p*-MePh	H	**4b**	94	91
3	Me	Et	*p*-MeOPh	H	**4c**	96	85
4	Me	Et	*p*-ClPh	H	**4d**	92	98
5	Me	Et	*p*-BrPh	H	**4e**	95	98
6	Me	Et	*m*-MePh	H	**4f**	92	96
7	Me	Et	*m*-ClPh	H	**4g**	95	97
8	Me	Et	*m*-BrPh	H	**4h**	96	98
9	Me	Et	*o*-MePh	H	**4i**	95	98
10	Me	Et	*o*-MeOPh	H	**4j**	86	98
11	Me	Et	*o*-ClPh	H	**4k**	95	88
12	Me	Et	1-naphthyl	H	**4l**	89	98
13	Me	Et	2-naphthyl	H	**4m**	91	98
14	Me	Me	Ph	H	**4n**	78	96
15	Me	^{t}Bu	Ph	H	**4o**	93	96
16[b]	Et	Et	Ph	H	**4p**	51	94
17	Ph	Et	Ph	H	**4q**	85	8
18	Me	Et	Ph	Me	**4r**	93	rac
19[c]	Me	Et	Bz	H	**4s**	55	rac
20	Me	Et	*c*-C_6H_{11}	H		NR[d]	

[a] Reaction conditions were the same as those in Table 1, entry 5. For the characterization and analysis of ee values of insertion products, see Supporting Information. [b] Reaction time: 48 h. [c] Reaction time: 16 h. [d] No reaction.

also compared in the reaction of **2a** and aniline under the identical reaction conditions. The insertion product was obtained in only 5% ee (entry 14), which showed that the chiral spirobiindane structure of ligands is essential for obtaining optimum enantioselectivity in copper-catalyzed insertions of diazoesters into N−H bonds.

A broad range of aniline derivatives was examined in the copper-catalyzed asymmetric insertion reaction with ethyl 2-diazopropionate (**2a**) by using ligand (S_a,*S*,*S*)-**1a** (Table 2). All substituted anilines underwent the insertion reaction with high reactivity, and complete conversions were achieved within 2 h. The corresponding insertion products were obtained in high yields regardless of the nature and the position of the substituents of the aniline derivatives (entries 1−11). For most substrates, the enantioselectivities were excellent (96−98% ee). Introduction of an electron-donating group in the *para* position (entries 2 and 3) or a halogen atom in the *ortho* position (entry 11) of aniline slightly diminished the enantioselectivities to 85−91% ee, but the reason for the negative effect of these substituents is unclear. In addition to aniline and its derivatives, naphthalen-1-amine and naphthalen-2-amine can also react with α-diazoester **2a** to afford the corresponding α-naphthylaminoesters in 98% ee with high yield (entries 12 and 13). In order to demonstrate the scope and potential of the present enantioselective insertion reaction, the influence of the structure of the diazoester on the reactivity and enantioselectivity was examined. The insertion reactions of methyl and *tert*-butyl 2-diazopropionates yielded the corresponding products in 96% ee (entries 14 and 15), showing that the size of the R^2 group of the diazoester has a negligible effect on the enantioselectivity of the reaction. When the R^1 group of the α-diazoester was changed from methyl to ethyl, the insertion reaction with aniline became very slow, and the insertion product was obtained in a moderate yield with 94% ee (entry 16). The reduced yield might be attributed to the steric hindrance of R^1. In the reaction of ethyl α-diazophenylacetate with aniline, the insertion product was formed in high yield; however, the enantioselectivity was only 8% ee (entry 17). Besides aniline and substituted anilines, *N*-methylaniline and benzamide could also react with the diazoester to afford insertion products, but no enantioselectivity was measured (entries 18 and 19). The aliphatic amine, cyclohexylamine, was completely inert under the identical reaction conditions (entry 20).

In summary, we have developed the first highly enantioselective catalytic insertion of α-diazoesters into N−H bonds. By using the copper complexes of chiral spiro bisoxazoline ligands as catalysts, the α-amino acid derivatives were produced in high yields and excellent enantioselectivities (up to 98% ee). Further study on the application of this novel reaction is ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, characterizations of ligands and products, and the analysis of ee values of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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