JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Well-Defined Binuclear Chiral Spiro Copper Catalysts for Enantioselective N−H Insertion

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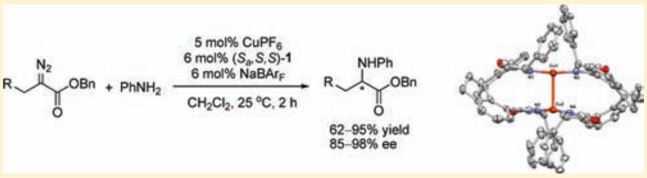
Supporting Information



ABSTRACT: An asymmetric N−H insertion of α-diazoesters with anilines catalyzed by well-defined copper complexes of chiral spiro bisoxazoline ligands was studied in detail. The copper-catalyzed asymmetric N−H insertion of a wide range of α-alkyl-α-diazoacetates with anilines was accomplished with excellent enantioselectivity (up to 98% ee) and provided an efficient method for the preparation of optically active α-amino acid derivatives. A correlation study of the electronic properties of the substrates with the enantioselectivity of the N−H insertion reaction supports a stepwise insertion mechanism, and the significant first-order kinetic isotope effect proves that the proton transfer is most likely the rate-limiting step. A binuclear chiral spiro copper catalyst having 14-electron copper centers, a trans coordination model, a perfect C_2-symmetric chiral pocket, and significant Cu−Cu interaction was isolated and extensively studied. The novel structure of the binuclear chiral spiro copper catalyst leads to unique reactivity as well as enantioselectivity in the N−H insertion reaction.

INTRODUCTION

The development of efficient methodologies for preparing chiral α-amino acids, the basic building blocks of proteins, is an enduring challenge in organic synthesis.[1] Transition-metal-catalyzed insertion of metal carbenes or carbenoids generated in situ from α-diazoesters into N−H bonds is an efficient approach to the preparation of α-amino acid derivatives and has received considerable attention.[2] Although N−H insertion has been known for decades,[3] progress toward the development of asymmetric versions of this important transformation has been limited.[4] In 1996, McKervey and co-workers[5] reported the first asymmetric intramolecular N−H bond insertion reaction, which was catalyzed by chiral rhodium(II) carboxylates and afforded pipecolic acid derivatives with enantiomeric excesses (ee's) of up to 45%. In 2002, Moody and co-workers[6] reported an intermolecular N−H insertion reaction between methyl α-diazophenylacetate or dimethyl α-diazobenzylphosphonate and benzyl carbamate in the presence of chiral dirhodium(II) catalysts; the products were obtained in good yield but with only 9% ee. Recently, Saito et al.[7] reported asymmetric N−H insertion reactions between α-diazo-α-arylacetates and anilines cooperatively catalyzed by dirhodium(II) carboxylates and cinchona alkaloids. The cooperative catalysts exhibited excellent activity for the N−H insertion reaction, but the enantioselectivity was only modest (up to 71% ee). Although copper catalysts were the first catalysts to be used for N−H insertion reactions,[3] it was not until 2004 that Jørgensen and co-workers[8] reported the first copper-catalyzed asymmetric N−H insertion: the reaction between α-diazoesters and anilines affords the insertion products with up to 28% ee. In 2007, we[9] reported highly enantioselective N−H insertion reactions between α-diazopropionates and anilines in the presence of copper catalysts bearing a chiral spiro bisoxazoline ligand (SpiroBOX, **1**); the reactions afford high yields (86−96%) and excellent enantioselectivities (85−98% ee). Later, two other chiral copper catalysts for asymmetric N−H insertion reactions were developed independently by Lee and Fu[10] and Feng and co-workers.[11] The former used bispyridine (−)-**2** as a ligand for N−H insertion reactions between α-diazophenylacetates and carbamates, and the latter used binaphthol-derived chiral ligand **3** for N−H insertion reactions between α-diazopropionates and anilines. Both catalysts exhibit excellent enantioselectivities (Scheme 1).[12]

Although recent progress on copper-catalyzed asymmetric N−H insertion reactions has been remarkable, many challenges continue to limit the application of this important reaction. For instance, the reaction is highly substrate-dependent. Only two types of α-diazo compounds (α-diazopropionates and α-diazophenylacetates) give good yields and high enantioselectivities (Scheme 1). As a consequence, only α-aminopropionates and phenylglycine derivatives can be prepared by the asymmetric N−H insertion reactions reported to date.[13] Furthermore, unlike the well-established C−H insertion reaction,[14] the N−H insertion reaction has not been studied extensively, and useful information for understanding the reaction, such as catalyst structures and reaction mechanisms, is lacking. In this paper, we report the results of our detailed investigations of Cu−(S_a,S,S)-**1**-catalyzed asymmetric N−H insertion reactions, including substrate scope, insertion mechanism, and catalyst structure.

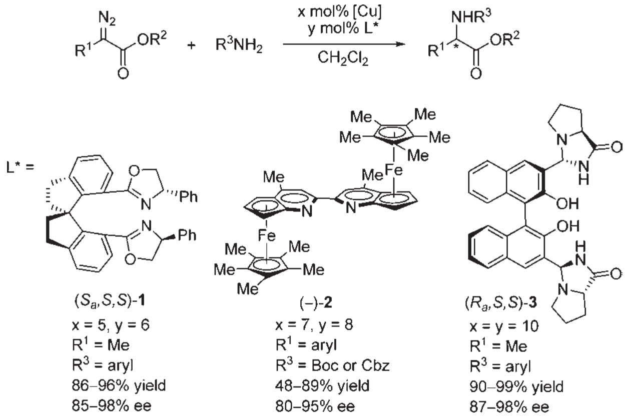
Received: September 7, 2011
Published: November 08, 2011

dx.doi.org/10.1021/ja2084493 | *J. Am. Chem. Soc.* 2012, 134, 436–442

RESULTS AND DISCUSSION

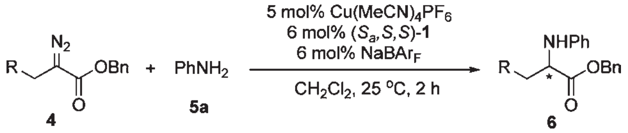
1. Copper-Catalyzed Asymmetric N−H Insertion Reactions of α-Alkyl-α-diazoacetates. Variability in α-substitution is essential for any general method for the synthesis of chiral α-amino acids. In a previous communication,[9] we reported that ethyl α-diazopropionates showed high yields (86−96%) and excellent enantioselectivities (85−98% ee) in Cu−(S_a,S,S)-**1**-catalyzed asymmetric N−H insertion reactions with aniline. When ethyl α-diazobutanoate was used, the N−H insertion product was obtained in 51% yield and 94% ee. We attributed the low yield mainly to competitive β-H elimination from the copper carbene intermediate.[15] To our delight, in the current study we found that when $Cu(MeCN)_4PF_6$ instead of CuCl was used as the catalyst precursor,[16] β-H elimination was suppressed. For example, the reaction of benzyl α-diazobutanoate (**4a**) with aniline afforded the N−H insertion product **6a** in 83% yield and 98% ee, accompanied by the β-H elimination byproduct benzyl but-2-enoate in 12% yield with Z/E = 1:1.

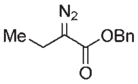
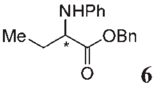
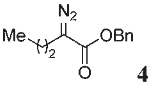
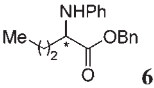
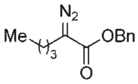
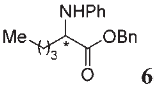
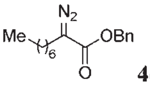
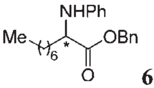
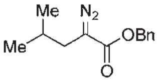
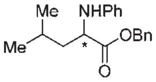
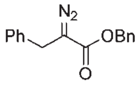
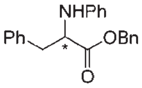
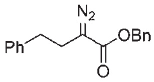
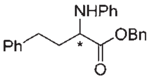
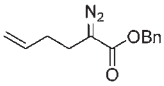
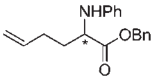
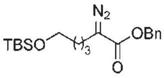
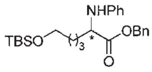
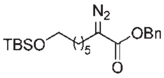
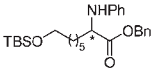
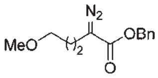
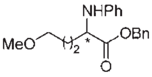
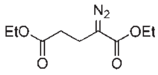
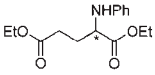
Scheme 1. Copper-Catalyzed Asymmetric N−H Insertion Reactions



With catalyst $Cu(MeCN)_4PF_6$/(S_a,S,S)-**1**, N−H insertion reactions between various α-alkyl-α-diazoesters[17] and aniline were examined. All of the α-alkyl-α-diazoester substrates gave N−H insertion products in good yields (62−95%) and good to excellent enantioselectivities (85−98% ee) (Table 1). The length of the α-alkyl group had a negligible effect on the yield and ee of the N−H insertion products (entries 1−4). However, a sterically hindered substrate, benzyl α-diazo-4-methylpentanoate (**4e**), exhibited relatively low enantioselectivity (entry 5). The introduction of a phenyl group at the β-position of the diazoester (e.g., **4f**) favored β-H elimination to form conjugated products, and therefore, the yield of the N−H insertion product decreased (entry 6). Various substrate functional groups, such as an olefin, an ether, a silyl ether, and an ester, were tolerated under the reaction conditions (entries 8−12); however, substrates with a methoxy- (**4k**) or ethoxycarbonyl (**4l**) showed lower enantioselectivities (entries 11 and 12).

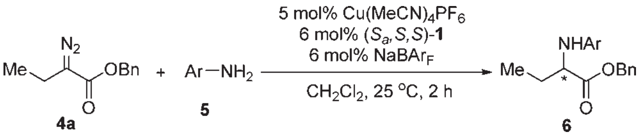
Table 1. N−H Insertion of α-Alkyl-α-diazoesters with Aniline[a]



entry	α-diazoester	product	yield (%)[b]	ee (%)[c]
1	 **4a**	 **6a**	83	98
2	 **4b**	 **6b**	87	98
3	 **4c**	 **6c**	75	98
4	 **4d**	 **6d**	77	97
5	 **4e**	 **6e**	72	91
6	 **4f**	 **6f**	62	96(R)
7	 **4g**	 **6g**	87	96
8	 **4h**	 **6h**	84	95
9	 **4i**	 **6i**	83	98
10	 **4j**	 **6j**	75	98
11	 **4k**	 **6k**	85	85
12	 **4l**	 **6l**	95	88(R)

[a] Reaction conditions: $Cu(MeCN)_4PF_6$/(S_a,S,S)-**1**/$NaBAr_F$/**4**/**5a** = 0.015:0.018:0.018:0.3:0.3 (mmol), 3 mL of CH_2Cl_2, 25 °C, 2 h. [b] Isolated yields. [c] Determined by HPLC or supercritical fluid chromatography (SFC) using a chiral column. The absolute configurations of **6f** and **6l** were assigned by comparison with reported optical rotations.[18]

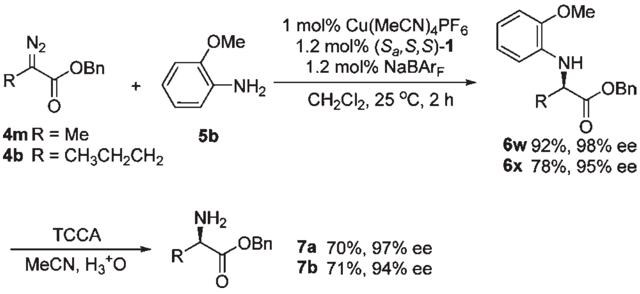
Table 2. N–H Insertion of Benzyl α-Diazobutanoate with Anilines[a]



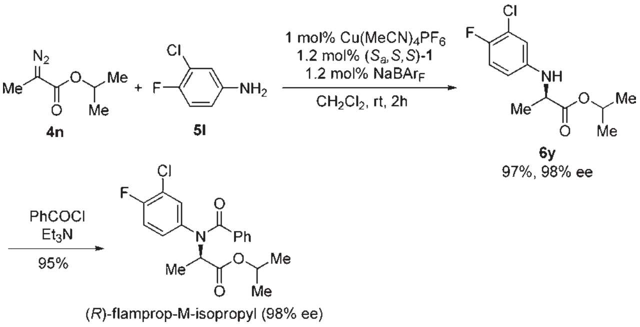
entry	Ar	product	yield (%)	ee (%)
1	2-MeOC$_6$H$_4$ (**5b**)	**6m**	75	96
2	2-MeC$_6$H$_4$ (**5c**)	**6n**	79	97
3	2-ClC$_6$H$_4$ (**5d**)	**6o**	74	83
4	3-MeOC$_6$H$_4$ (**5e**)	**6p**	75	97
5	3-MeC$_6$H$_4$ (**5f**)	**6q**	80	94
6	3-ClC$_6$H$_4$ (**5g**)	**6r**	71	96
7	3-BrC$_6$H$_4$ (**5h**)	**6s**	81	95
8	4-MeOC$_6$H$_4$ (**5i**)	**6t**	77	60
9	4-ClC$_6$H$_4$ (**5j**)	**6u**	70	97
10	4-FC$_6$H$_4$ (**5k**)	**6v**	80	97

[a] Reaction conditions and analysis were the same as in Table 1.

Scheme 2. Synthesis of α-Amino Acid Derivatives

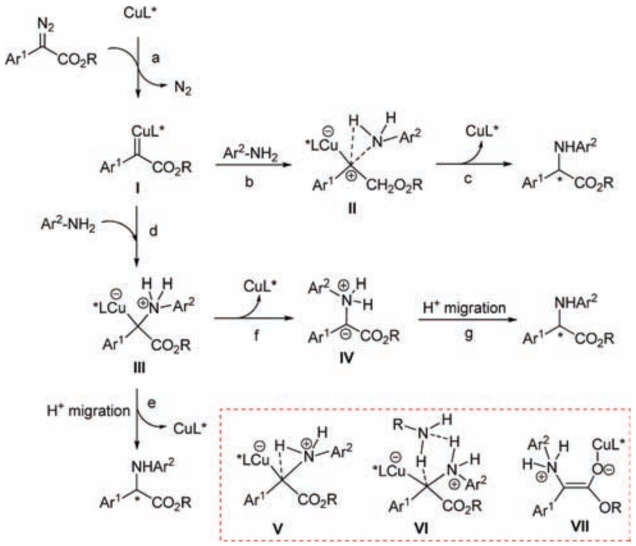


Scheme 3. Preparation of (*R*)-Flamprop-M-isopropyl



The copper-catalyzed asymmetric N–H insertion reactions of benzyl α-diazobutanoate (**4a**) with various substituted anilines were also performed under the standard reaction conditions. As shown in Table 2, all of the reactions took place smoothly and afforded the corresponding insertion products in good yields (70–81%). Except for the anilines having an electron-withdrawing group at the ortho position (**5d**) or an electron-donating group at the para position (**5i**), which afforded lower enantioselectivity (entries 3 and 8), all of the tested anilines exhibited excellent enantioselectivity (94–97% ee).

Scheme 4. Proposed Mechanisms for Copper-Catalyzed N–H Insertion



The Cu–(S_a,S,S)-**1**-catalyzed reactions of benzyl α-diazopropionate and benzyl α-diazopentanoate with *o*-methoxyaniline afforded the corresponding N–H insertion products **6w** and **6x** in high yields with excellent enantioselectivities (Scheme 2). The *o*-methoxyphenyl groups in **6w** and **6x** could be easily removed by oxidation with trichloroisocyanuric acid[19] to produce α-amino acid esters **7a** and **7b**, respectively. In view of the high yields, excellent enantioselectivities, and wide range of substrates, the present copper-catalyzed asymmetric N–H insertion reaction provides a concise method for the preparation of optically active α-amino acid derivatives.

As a further demonstration of its synthetic utility, we used the copper-catalyzed asymmetric N–H insertion reaction to prepare the chiral arylalanine herbicide (*R*)-flamprop-M-isopropyl.[20] The reaction of isopropyl α-diazopropionate (**4n**) with 3-chloro-4-fluoroaniline (**5l**) catalyzed by 1 mol % Cu–(S_a,S,S)-**1** afforded insertion product **6y** in 97% yield with 98% ee. Treatment of **6y** with benzoyl chloride gave the target herbicide in 95% yield and retained ee value (Scheme 3). This highly enantioselective two-step synthesis indicates the potential for wide application of Cu–(S_a,S,S)-**1**-catalyzed asymmetric N–H insertion reactions.

2. Mechanism Considerations. Possible mechanisms for the copper-catalyzed N–H insertion reaction, which involves the formation of an electron-deficient carbene and its insertion into the N–H bond, are illustrated in Scheme 4. Two distinct pathways have been reported: a concerted mechanism (a → b → c) and a stepwise mechanism (a → d → e or a → d → f → g).[2] It is generally accepted that insertions into X–H bonds bearing lone-pair electrons on the X atom most likely proceed by a stepwise mechanism[21] and that insertions into C–H or Si–H bonds proceed by a concerted mechanism.[14,22]

In the stepwise mechanism shown in Scheme 4, copper-associated ylide **III** is formed by attack of the lone-pair electrons of the aniline N atom on the electron-deficient copper carbene. Ylide **III** may undergo one of two possible processes to generate the N–H insertion product. One process involves simultaneous proton transfer and catalyst dissociation (step e). The alternative

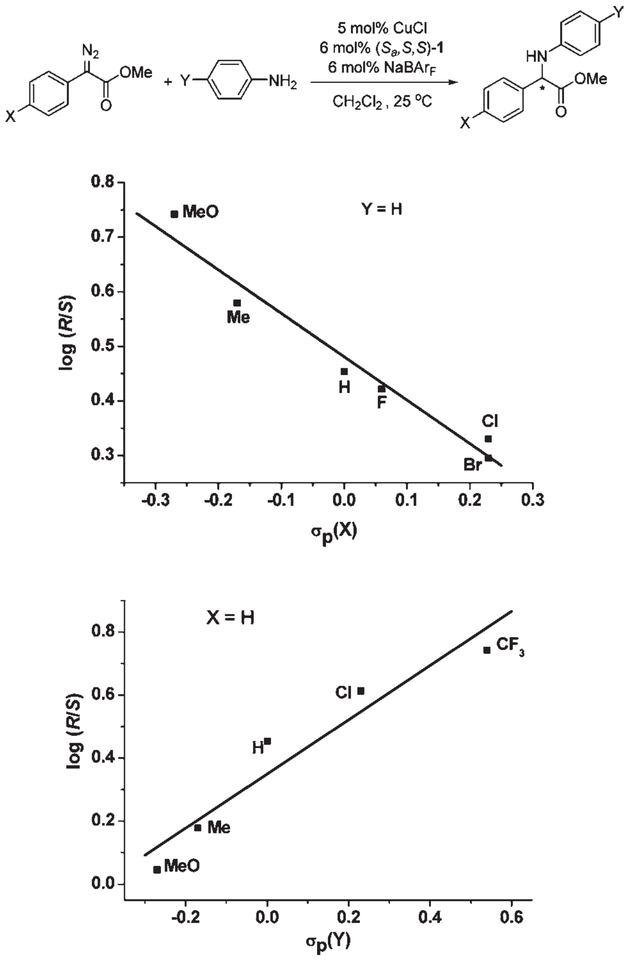
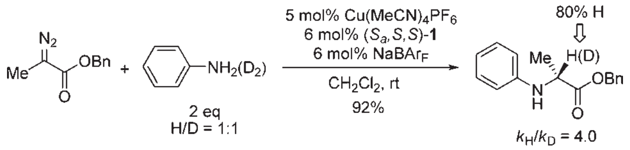


Figure 1. Correlations between the logarithms of the product er values and the Hammett constants (σ) of the para substituents.

Scheme 5. Kinetic Isotope Effect of the N−H Insertion Reaction



process involves dissociation of the copper catalyst to form free ylide **IV** (step f). Because retention of the configuration of the free ylide intermediate **IV** is difficult, the enantioselectivity cannot be assured in the proton transfer step (step g). The high enantioselectivities we obtained in the Cu−(S_a,S,S)-**1**-catalyzed asymmetric N−H insertion reactions indicate that the reactions most likely proceeded by the pathway a → d → e.

The details of the proton transfer process (step e) for N−H insertion reaction are still unclear;[23] however, two possible proton transfer models (V and VI) can be put forward by analogy to O−H insertion.[24] The proton could be transferred directly from nitrogen to carbon in model V, while aniline or insertion-product-assisted proton transfer is included in VI. Alternatively, if III isomerizes to give copper enolate VII, similar to V and VI, two related proton transfer processes with or without assistance of amino components may also exist.

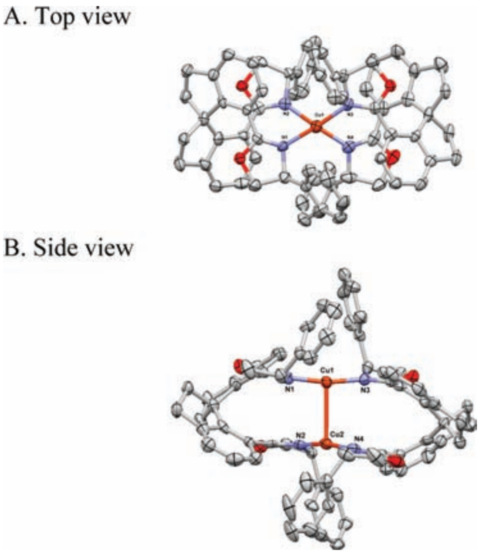


Figure 2. Views of the single-crystal structure of complex **8a**. H atoms and the anion (PF_6^-) have been omitted for clarity. Selected bond distances (Å) and angles (deg): Cu(1)···Cu(2), 2.7828(10); Cu(1)−N(1), 1.874(5); Cu(1)−N(3), 1.867(5); Cu(2)−N(2), 1.860(5); Cu(2)−N(4), 1.851(5); N(3)−Cu(1)−N(1), 169.0(2); N(3)−Cu(1)−Cu(2), 93.85(15); N(1)−Cu(1)−Cu(2), 96.59(15); N(4)−Cu(2)−N(2), 169.5(2); N(4)−Cu(2)−Cu(1), 96.96(16); N(2)−Cu(2)−Cu(1), 92.93(15).

It is reasonable to hypothesize that electron-withdrawing substituents on Ar[1] or electron-donating substituents on Ar[2] would likely stabilize free ylide **IV** and thus favor the free-ylide process (Scheme 4, a → d → f → g), which would lead to lower enantioselectivity. On the basis of this hypothesis, we investigated the relationship between the electronic properties of the substrates and the enantioselectivities of the reactions between para-substituted α-aryl-α-diazoacetates and para-substituted anilines. The correlations between the log(er) values of the products and the Hammett constants (σ)[25] of the para substituents (Figure 1) clearly indicated that electron-withdrawing groups (X) at the para position of Ar[1] (upper part) and electron-donating groups (Y) at the para position of Ar[2] (bottom part) lowered the enantioselectivity. These results strongly suggest that the highly enantioselective Cu−(S_a,S,S)-**1**-catalyzed N−H insertion proceeds via the pathway a → d → e.

We also observed a significant first-order kinetic isotope effect (k_H/k_D = 4.0; Scheme 5), which implies that a proton transfer is involved in the rate-limiting step.[26]

3. Catalyst Structure. Crystals of Cu(I)−(S_a,S,S)-**1** with various anions (**8a**, PF_6^-; **8b**, ClO_4^-; **8c**, BAr_F^-) were grown and subjected to X-ray diffraction analysis. All of the complexes had an unexpected binuclear copper structure, as shown for **8a** in Figure 2. In **8a**, each of the two copper(I) atoms is coordinated by two nitrogen atoms from the two spiro bisoxazoline ligands. The N1−Cu1−N3 and N2−Cu2−N4 angles are 169.0(2) and 169.5(2)°, respectively, which means that the two nitrogen atoms coordinate to a copper(I) atom in a trans orientation. The phenyl groups of the oxazoline ligands form a perfect C_2-symmetric chiral pocket around the copper center. The copper atoms in this complex have a 14-electron structure. The distance between the two copper centers is 2.7828(10) Å, which implies an interaction between the two copper atoms.[27]

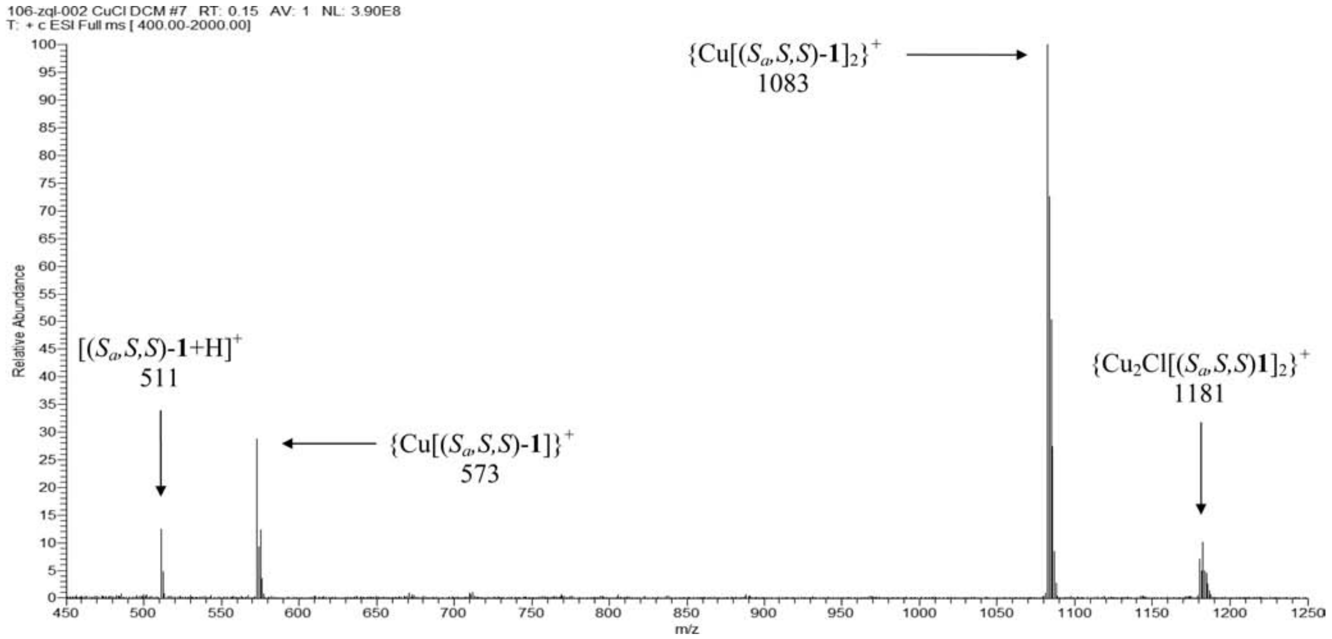


Figure 3. ESI-MS analysis of the solution of Cu−(S_a,S,S)-**1** formed by CuCl and (S_a,S,S)-**1** (1:1 molar ratio) in CH_2Cl_2.

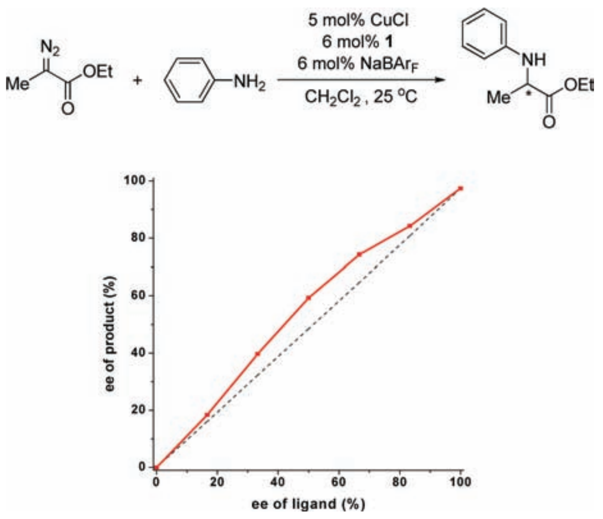


Figure 4. Nonlinear effect experiment.

Electrospray ionization mass spectrometry (ESI-MS) studies of Cu−(S_a,S,S)-**1** prepared in situ from CuCl and (S_a,S,S)-**1** revealed the presence of a dimeric species in solution (m/z 1181, $\{\mathrm{Cu_2Cl}[(S_a,S,S)\text{-}\mathbf{1}]_2\}^+$; Figure 3). The doubly charged species $\{\mathrm{Cu_2}[(S_a,S,S)\text{-}\mathbf{1}]_2\}^{2+}$ (m/z 573, which is the same as the m/z ratio for $\{\mathrm{Cu}[(S_a,S,S)\text{-}\mathbf{1}]\}^+$) with the typical $\Delta m/z = 0.5$ signal was not detected by ESI-MS. However, a peak with significant intensity was detected for $\{\mathrm{Cu}[(S_a,S,S)\text{-}\mathbf{1}]_2\}^+$ (m/z 1083), a decomposition fragment of the dimer.

We carried out a nonlinear effect experiment to gain further insight into the active catalyst structure. We observed a small but positive nonlinear effect in the Cu−(S_a,S,S)-**1**-catalyzed N−H insertion reaction (Figure 4), which indicates that the active catalyst was a binuclear copper complex or a mononuclear copper complex containing two oxazoline ligands.[28]

On the basis of the catalyst structure and the absolute configuration of the N−H insertion products, we propose the chiral induction model shown in Figure 5. The electron-deficient copper carbene is attacked by aniline (Scheme 4, step d) from the less-hindered *Re* face following a configuration-retaining proton transfer, affording the insertion product with an *R* configuration.

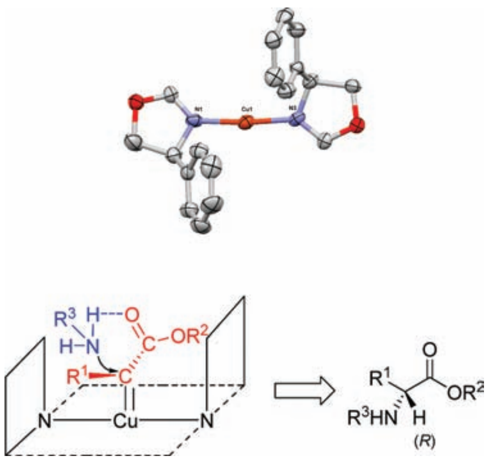


Figure 5. Chiral induction model.

CONCLUSION

We have conducted a detailed study of Cu−(S_a,S,S)-**1**-catalyzed asymmetric N−H insertion reactions between α-alkyl-α-diazoesters and anilines. The chiral spiro copper catalyst Cu−(S_a,S,S)-**1** exhibited excellent activity and enantioselectivity in reactions of various α-alkyl-α-diazoacetates with anilines. The applications of the reaction in the synthesis of an important crop-protection agent and optically active α-amino acid derivatives demonstrated its synthetic utility. A stepwise insertion mechanism involving a proton transfer as the rate-limiting step was supported by correlations between the electronic properties of the substrates and the enantioselectivity of the reaction as well as by the observation of a first-order kinetic isotope effect.

The chiral spiro copper catalysts have a novel binuclear structure, as indicated by single-crystal X-ray diffraction analysis, ESI-MS, and nonlinear effect studies. The 14-electron copper centers, trans coordination model, perfectly C_2-symmetric chiral pocket, and copper−copper interaction in the chiral spiro catalyst allow for efficient chiral induction in the asymmetric N−H insertion reactions. Our results contribute to the understanding of transition-metal-catalyzed asymmetric N−H insertion reactions and can be expected to allow for the design of new, efficient chiral catalysts for other X−H bond insertion reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Crystallographic data for **8a**−**c**, experimental procedures, analytical data for products, NMR spectra for new compounds, and HPLC and SFC charts for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank the National Natural Science Foundation of China and the National Basic Research Program of China (2010CB833300, 2011CB808600) and the "111" Project (B06005) of the Ministry of Education of China for financial support.

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