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Transition-Metal-Catalyzed Enantioselective Heteroatom–Hydrogen Bond Insertion Reactions

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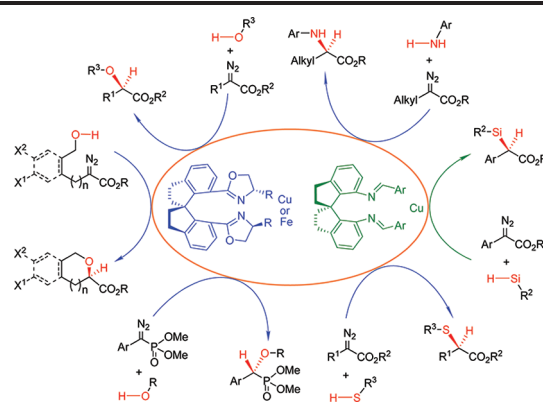
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CONSPECTUS

Carbon–heteroatom bonds (C–X) are ubiquitous and are among the most reactive components of organic compounds. Therefore investigations of the construction of C–X bonds are fundamental and vibrant fields in organic chemistry. Transition-metal-catalyzed heteroatom–hydrogen bond (X–H) insertions via a metal carbene or carbenoid intermediate represent one of the most efficient approaches to form C–X bonds. Because of the availability of substrates, neutral and mild reaction conditions, and high reactivity of these transformations, researchers have widely applied transition-metal-catalyzed X–H insertions in organic synthesis. Researchers have developed a variety of rhodium-catalyzed asymmetric C–H insertion reactions with high to excellent enantioselectivities for a wide range of substrates. However, at the time that we launched our research, very few highly enantioselective X–H insertions had been documented primarily because of a lack of efficient chiral catalysts and indistinct insertion mechanisms.

In this Account, we describe our recent studies of copper- and iron-catalyzed asymmetric X–H insertion reactions by using chiral *spiro*-bisoxazoline and diimine ligands. The copper complexes of chiral *spiro*-bisoxazoline ligands proved to be highly enantioselective catalysts for N–H insertions of α -diazoesters into anilines, O–H insertions of α -diazoesters into phenols and water, O–H insertions of α -diazophosphonates into alcohols, and S–H insertions of α -diazoesters into mercaptans. The iron complexes of chiral *spiro*-bisoxazoline ligands afforded the O–H insertion of α -diazoesters into alcohols and water with unprecedented enantioselectivities. The copper complexes of chiral *spiro*-diimine ligands exhibited excellent reactivity and enantioselectivity in the Si–H insertion of α -diazoacetates into a wide range of silanes. These transition-metal-catalyzed X–H insertions have many potential applications in organic synthesis because the insertion products, including chiral α -aminoesters, α -hydroxyesters, α -hydroxyphosphonates, α -mercaptoesters, and α -silyl esters, are important building blocks for the synthesis of biologically active compounds.

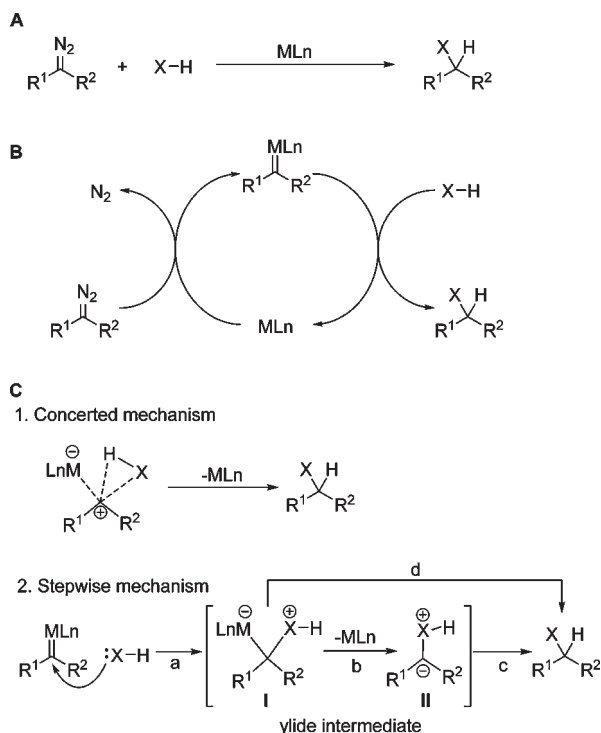
The electronic properties of α -diazoesters and anilines markedly affected the enantioselectivity of N–H insertion reaction, which supports a stepwise ylide insertion mechanism. A novel binuclear *spiro* copper complex was isolated and fully characterized using X-ray diffraction analysis and ESI-MS analysis. The positive nonlinear effect indicated that binuclear copper complexes were the catalytically active species. The 14-electron copper centers, trans coordination model, perfect C_2 -symmetric chiral pocket, and Cu–Cu interaction facilitate the performance of the chiral *spiro* catalysts in X–H insertion reactions.



1. Introduction

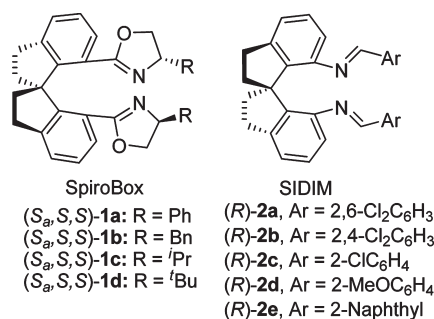
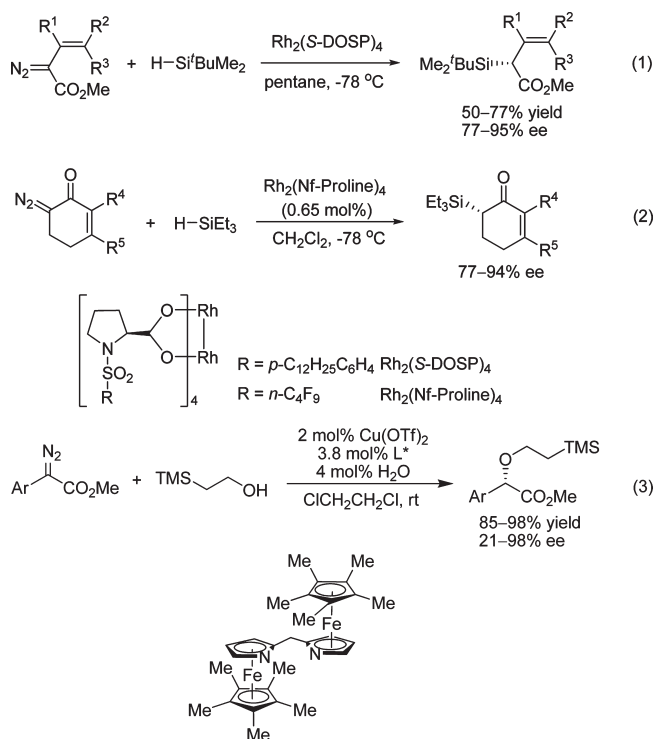
Since carbon–heteroatom (C–X) bonds are ubiquitous and generally are one of the most active parts of organic compounds, the research on construction of C–X bonds is an essential task in organic chemistry.¹ Transition-metal-catalyzed insertion of carbenes or carbenoids, in situ generated

from diazo compounds, into the heteroatom–hydrogen (X–H, X = N, O, S, Si, etc.) bonds are one of the most efficient tools for the construction of C–X bonds (Scheme 1A).² The history of transition-metal-catalyzed X–H insertions can be traced back to 1950s.³ The copper salts were the first catalysts used, while rhodium(II) acetate derivatives

SCHEME 1. Transition-Metal-Catalyzed X–H Insertion Reactions and Mechanisms

become predominant catalysts after they were launched in 1970s.⁴

Benefiting from mild reaction conditions and high efficiency, transition-metal-catalyzed X–H insertion reactions have been widely utilized in organic synthesis in the past decades. As an example, Merck used a rhodium-catalyzed intramolecular N–H insertion as a key step for the preparation of the antibiotic thienamycin.⁵ The development of the asymmetric version of the transition-metal-catalyzed X–H insertion reaction is a significant topic in organic synthesis. However, compared with remarkable advances achieved in catalytic asymmetric C–H insertion reactions,⁶ transition-metal-catalyzed asymmetric X–H insertion reactions are quite underdeveloped. In earlier years, McKerver⁷ and Moody⁸ tested various chiral dirhodium(II) catalysts in asymmetric intramolecular and intermolecular N–H insertion of carbamates and obtained 45% ee and 9% ee, respectively. Later, Jørgensen et al.⁹ turned to the chiral copper and silver catalysts for N–H insertion of anilines; however, both catalysts exhibited modest enantioselectivities (28% ee and 48% ee, respectively). Landais and co-workers¹⁰ tried the rhodium-catalyzed asymmetric O–H insertion reaction and obtained very low enantioselectivity (8% ee). The attempts at copper- and rhodium-catalyzed asymmetric S–H insertion also gave very low enantioselectivity (not higher than 23% ee).¹¹

SCHEME 2. Early Highly Enantioselective X–H Insertion Reactions^a**FIGURE 1.** Chiral *spiro*-bisoxazoline and -diimine ligands.

The enantioselectivities of early rhodium-catalyzed asymmetric Si–H insertions are only moderate.¹²

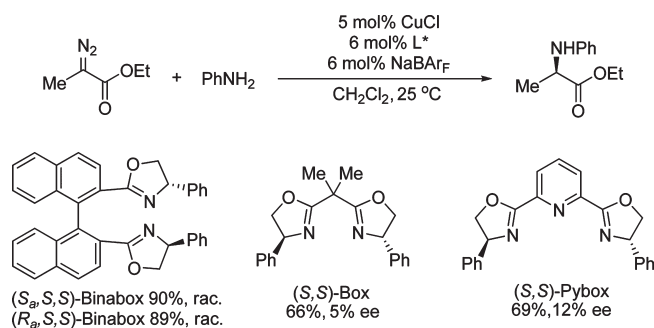
A generally accepted insertion mechanism includes the formation of a metal carbene intermediate via a transition-metal-mediated decomposition of diazo compound and the insertion of the electron-deficient metal carbene into an X–H bond (Scheme 1, B). Two distinct pathways exist in X–H insertion reactions (Scheme 1C). In the concerted mechanism, the metal carbene directly inserts into the X–H bond to form insertion products in one step. In contrast, ylide formation and a subsequent 1,2-proton transfer are involved in the stepwise process. The complicated mechanism

TABLE 1. Copper-Catalyzed Asymmetric N–H Insertion: Anion Effect

Reaction scheme for Table 1: $\text{Me}-\text{C}(\text{N}_2)=\text{C}(\text{OEt})-\text{R} + \text{PhNH}_2 \xrightarrow[\text{CH}_2\text{Cl}_2, 25^\circ\text{C}]{5 \text{ mol\% [Cu]}, 6 \text{ mol\% } (S_a, S_a, S_a)\text{-1}, 6 \text{ mol\% additive}}$ $\text{Me}-\text{CH}(\text{NHPH})-\text{C}(\text{OEt})-\text{R}$

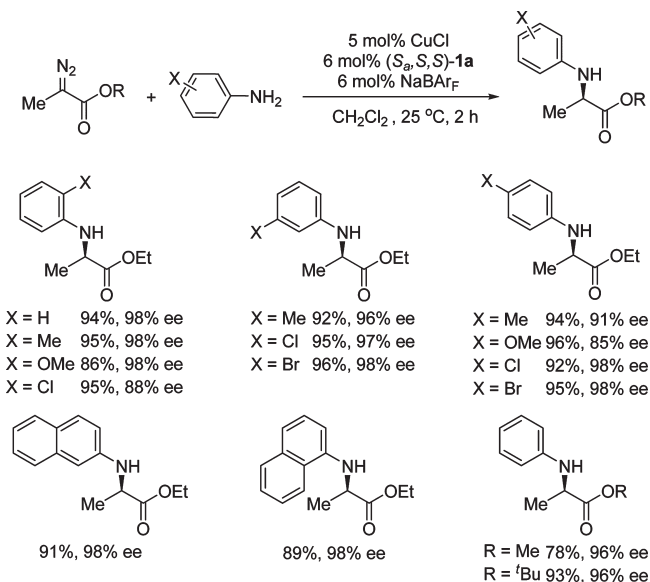
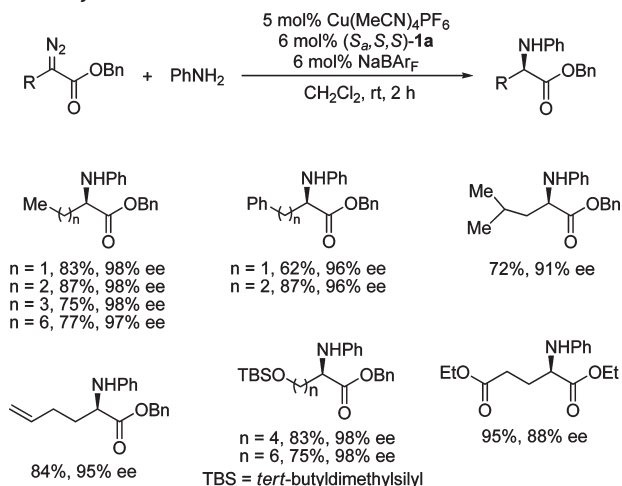
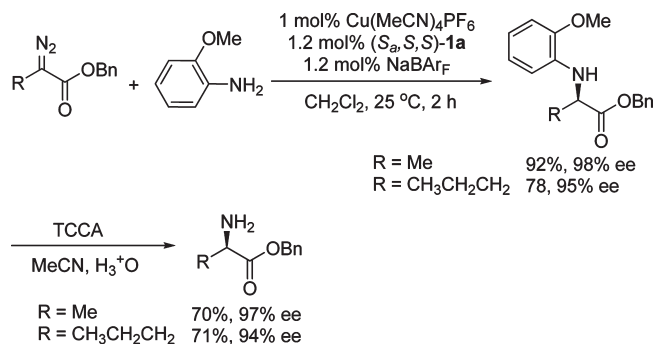
Structure of BARF^- : $\left[\text{B}(\text{C}_6\text{F}_5)_3 \right]^-$

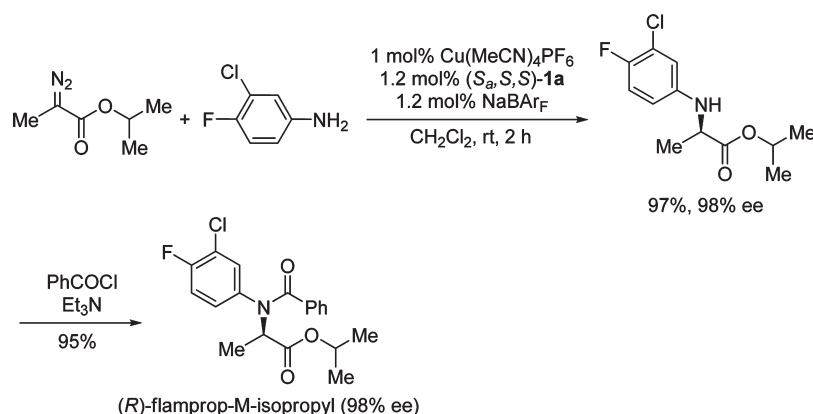
entry	Cu source	ligand	additive	time (h)	yield (%)	ee (%) ^b
1	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	$(S_a, S_a, S_a)\text{-1a}$	none	2	78	43
2	CuOTf	$(S_a, S_a, S_a)\text{-1a}$	none	2	83	5
3	CuCl	$(S_a, S_a, S_a)\text{-1a}$	none	24	15	<i>rac</i>
4	CuCl	$(S_a, S_a, S_a)\text{-1a}$	NaBARF	2	94	98
5	CuCl	$(S_a, S_a, S_a)\text{-1b}$	NaBARF	2	83	61
6	CuCl	$(S_a, S_a, S_a)\text{-1c}$	NaBARF	2	90	79
7	CuCl	$(S_a, S_a, S_a)\text{-1d}$	NaBARF	2	75	85
8 ^a	CuCl	$(S_a, S_a, S_a)\text{-1a}$	NaBARF	2	90	95

^aWith 1 mol % catalyst, refluxing. ^bThe configuration of product is *R*.**SCHEME 3.** Copper-Catalyzed Asymmetric N–H Insertion: Ligand Evaluation

of X–H insertion hampers the development of highly enantioselective X–H insertion reactions.

Before we started our research on transition-metal-catalyzed asymmetric X–H insertion reactions, only two examples of rhodium-catalyzed asymmetric Si–H insertion reactions were reported by Davies and Corey, respectively, with greater than 90% ee (Scheme 2, eqs 1 and 2).¹³ A more recent example of a highly enantioselective copper-catalyzed insertion of α -aryl- α -diazoacetates into O–H bonds of alcohols was accomplished by Fu and co-workers by using a chiral bisazaferrocene ligand (Scheme 2, eq 3).¹⁴ In this Account, we describe our recent efforts on the development of copper- and iron-catalyzed asymmetric X–H insertion reactions. Taking into account the advantages of chiral *spiro*-bisoxazoline ligands **1** and -diimine ligands **2** (Figure 1),¹⁵

SCHEME 4. Copper-Catalyzed Asymmetric N–H Insertion of α -Diazoacetates**SCHEME 5.** Copper-Catalyzed Asymmetric N–H Insertion of Aniline with α -Alkyl- α -diazoacetates**SCHEME 6**

SCHEME 7. Preparation of (*R*)-flamprop-M-isopropyl

the insertions of various X–H bonds, such as N–H, O–H, S–H, and Si–H bonds, were accomplished with high yields as well as excellent enantioselectivities.

2. N–H Bond Insertions

The insertion of N–H bonds was proven to be an efficient method for preparing α -amino esters, α -amino ketones, and nitrogen-containing heterocycles and attracted intensive attention. We first studied the copper-catalyzed asymmetric N–H insertion of ethyl α -diazopropionate with aniline.¹⁶ The enantioselectivity of the N–H insertion directly related to the anion of the copper precursor: the smaller and stronger coordinating anions are evidently inferior to the larger and weaker coordinating anion in chiral induction (Table 1, entries 1–3). Based on this information, a copper catalyst with a bulky and noncoordinating anion, BAR_F^- {tetrakis[3,5-bis(trifluoromethyl)phenyl]borate}, was prepared by means of anion exchange; it greatly improved the enantioselectivity to 98% ee (Table 1, entry 4). Other *spiro*-bisoxazoline ligands containing alkyl groups on the oxazoline rings gave lower enantioselectivities (Table 1, entries 4–7). The catalyst $\text{Cu}-(S_a,S,S)-\mathbf{1a}$ was highly active, and 1 mol % catalyst loading was sufficient for obtaining satisfactory result (Table 1, entry 8).

The chiral bisoxazoline ligands with other backbones, such as Box, Pybox, and Binabox exhibited very low enantioselectivity (0–12% ee) (Scheme 3). These results clearly demonstrate that the chiral *spiro*biindane structure of bisoxazoline ligands **1** is essential for obtaining high enantioselectivity in Cu-catalyzed asymmetric N–H insertion reaction.

A broad range of primary aniline derivatives were suitable substrates for the N–H insertion reaction and gave high yields (78–96%) with good to excellent enantioselectivities (85–98% ee) (Scheme 4). An electron-withdrawing group at

the *ortho*-position (X = 2-Cl) and electron-donating groups at the *para*-position (X = 4-Me or 4-MeO) of the anilines slightly decreased the enantioselectivity (88% ee, 91% ee, and 85% ee, respectively).

Besides α -diazopropionate, other α -alkyl- α -diazoacetates also underwent the insertion reaction smoothly with good yields (62–95%) and high enantioselectivities (88–98% ee) (Scheme 5).¹⁷ The functional groups, such as olefins, esters, and ethers, were tolerated under the reaction conditions. It is noteworthy that the competitive 1,2-hydride migration² can be markedly suppressed in the presence of the chiral *spiro* copper catalysts.

The N–H insertion of *ortho*-methoxyaniline exhibited excellent reactivity as well as enantioselectivity and the corresponding insertion products were easily converted to α -amino acid derivatives with retained ee values by oxidation with trichloroisocyanuric acid (TCCA) (Scheme 6). In view of its high reactivity, excellent enantioselectivity, and broad substrate scope, the present copper-catalyzed asymmetric N–H insertion reaction shows a high potential for wide applications in the preparation of optically active α -amino acid derivatives.

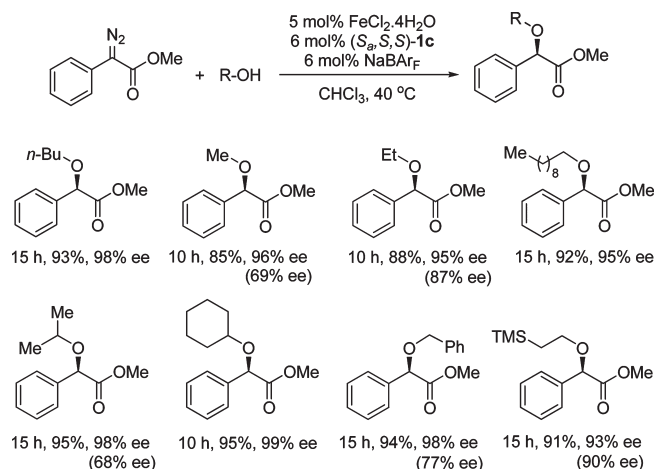
With the copper-catalyzed asymmetric N–H insertion as a key step, a chiral arylalanine herbicide (*R*)-flamprop-M-isopropyl was concisely prepared from available material (Scheme 7). The corresponding N–H insertion was accomplished in 97% yield with 98% ee in the presence of 1 mol % of chiral *spiro* copper catalyst.

3. O–H Bond Insertions

The O–H insertion is an efficient method for preparing α -alkoxy, α -aryloxy, or α -hydroxy esters and oxygen-containing heterocyclic compounds. We investigated copper- and iron-catalyzed asymmetric O–H insertions of α -diazoesters

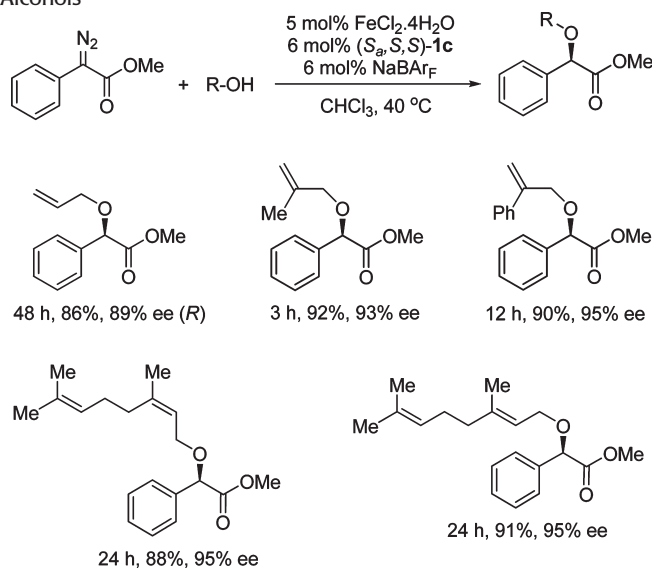
TABLE 2. Catalytic Asymmetric O–H Insertion: Comparison of Catalyst Precursors

entry	M source	ligand	time (h)	yield (%)	ee (%)
1	FeCl ₂ ·4H ₂ O	(S _a ,S,S)- 1a	15	87	86
2	FeCl ₂ ·4H ₂ O	(S _a ,S,S)- 1b	24	86	88
3	FeCl ₂ ·4H ₂ O	(S _a ,S,S)- 1c	15	93	98
4	FeCl ₂ ·4H ₂ O	(S _a ,S,S)- 1d	30	63	50
5	CuCl	(S _a ,S,S)- 1c	1	90	80
6	CoCl ₂	(S _a ,S,S)- 1c	48	23	82
7	NiCl ₂	(S _a ,S,S)- 1c	48	3	81
8	AuCl	(S _a ,S,S)- 1c	48	<i>a</i>	
9	AgOTf	(S _a ,S,S)- 1c	4	63	42
10	[RhCl(CO) ₂] ₂	(S _a ,S,S)- 1c	2	27	15
11	[RuCl ₂ C ₆ H ₆] ₂	(S _a ,S,S)- 1c	2	45	67

^aNo reaction.**SCHEME 8.** Iron-Catalyzed Asymmetric O–H Insertions of Saturated Alcohols

and α -diazophosphonates with various O–H bond donors by using chiral *spiro*-bisoxazoline ligands **1**.

3.1. Intermolecular O–H Bond Insertions. **3.1.1. Insertion of O–H Bond of Alcohols.** It was discovered that the iron catalysts prepared in situ from FeCl₂·4H₂O and chiral *spiro*-bisoxazoline ligand **1** exhibited excellent enantioselectivity, as well as reactivity, for the insertion of O–H bonds of alcohols.¹⁸ When the ligand (S_a,S,S)-**1c**, which has isopropyl moieties on the oxazoline rings, was used, the iron-catalyzed O–H insertion of methyl α -diazophenylacetate with 1-butanol proceeded smoothly at 40 °C and afforded the (*R*)-methyl 2-butoxy-2-phenylacetate in good yield (93%) with high enantioselectivity (98% ee) (Table 2, entry 3). Other transition metals including copper, cobalt, nickel, gold, silver, rhodium, and ruthenium gave markedly lower enantioselectivity under

SCHEME 9. Iron-Catalyzed Asymmetric O–H Insertion of Allylic Alcohols**TABLE 3.** Copper-Catalyzed Asymmetric Insertion of Dimethyl Diazo(phenyl)methylphosphonate into O–H Bonds of Alcohols

Reaction scheme showing the O-H insertion of dimethyl diazo(phenyl)methylphosphonate with an alcohol (R-OH) under the following conditions:

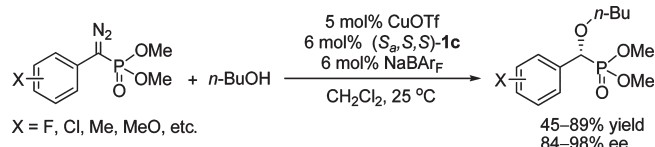
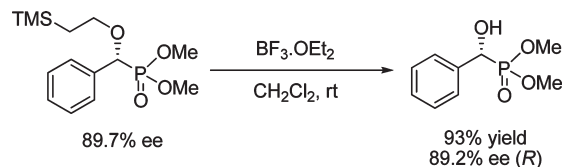
- 5 mol% CuOTf
- 6 mol% (S_S,S_S,S_S)-**1c**
- 6 mol% NaBAR_F
- CH₂Cl₂, 25 °C

The product is a chiral phosphonate where the phenyl group is attached to a carbon atom bonded to an OR group and a dimethylphosphonyl group.

entry	R	time (h)	yield (%)	ee (%)
1	<i>n</i> -Bu	1	89	91
2	Me	1	87	84
3	Et	1	82	91
4	<i>n</i> -C ₈ H ₁₇	1	82	87
5	<i>n</i> -C ₁₀ H ₂₁	1	84	88
6	TMSCH ₂ CH ₂	1	87	90
7	<i>i</i> -Bu	1	74	92
8	<i>i</i> -Arm	1	83	92
9	<i>i</i> -Pr	1	19	89
10	CH=CHCH ₂	12	81	38
11	CH=C(CH ₃)CH ₂	3	70	85
12	Bn	3	69	87

the identical reaction conditions (Table 2, entries 5–11). Since the previously reported iron-catalyzed asymmetric reactions are less enantioselective than other metal-catalyzed reactions with the exception of a few special substrates, the unambiguous superiority of chiral *spiro* iron catalysts on the enantioselectivity in the O–H insertion was significant for encouraging the use of environmentally benign iron catalysts in the development of catalytic asymmetric synthesis.

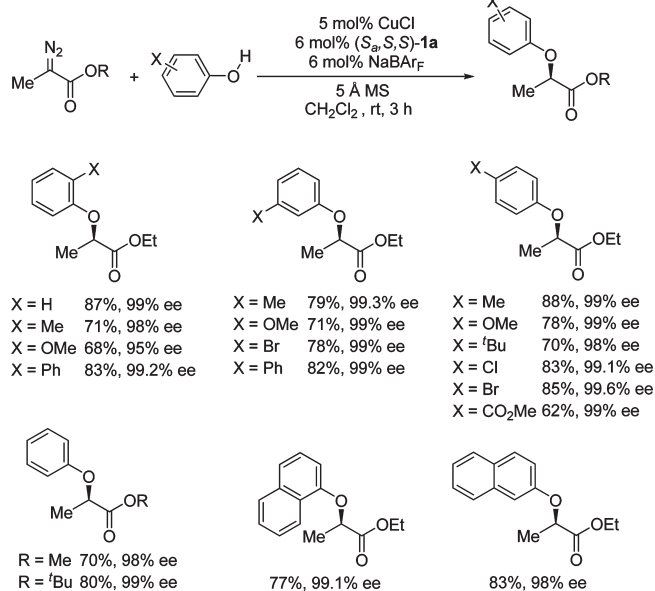
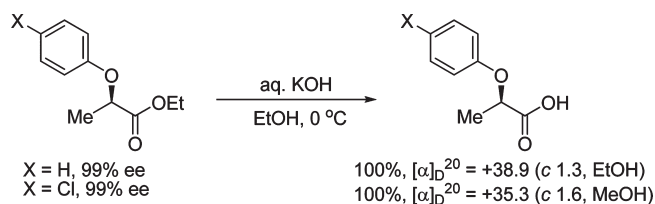
The iron-catalyzed O–H insertion has an unprecedented wide substrate scope. As shown in Scheme 8, all the tested saturated alcohols underwent the O–H insertion reaction to

SCHEME 10. Copper-Catalyzed Asymmetric Insertions of Diazo Phosphonates into the O–H Bond of 1-Butanol**SCHEME 11.** Deprotection of Dimethyl Phenyl[2-(trimethylsilyl)ethoxy]methylphosphonate

afford the corresponding α -alkoxy esters with high yields and excellent enantioselectivities (93–99% ee). All the enantioselectivities of the iron-catalyzed O–H insertion reactions remarkably surpassed the previous records of this reaction (see the data in parentheses).¹⁴

Because they may undergo undesired [2,3]-sigmatropic rearrangement or cyclopropanation, allylic alcohols are troublesome substrates for the catalytic asymmetric O–H insertion reaction. The carbon–carbon double bond of allylic alcohols, which may coordinate with metal of catalysts, dramatically lowered the reactivity of the O–H insertion reaction.¹⁴ However, the Fe- (S_a,S,S,S) -**1c** can efficiently catalyze the insertion of allylic alcohols with α -diazophenylacetate to produce α -allyloxyphenylacetates in high yields (86–92%) with high enantioselectivities (89–95% ee) (Scheme 9). The present iron-catalyzed asymmetric O–H insertion reaction provides one of the most efficient methods for the preparation of chiral α -allyloxyphenylacetates, very useful building blocks in organic synthesis.¹⁹

The transition-metal-catalyzed asymmetric O–H insertion of α -diazophosphonates affords an efficient access to biologically active phosphorus-containing compounds; however, this methodology had not been previously explored, perhaps due to the high stability of α -diazophosphonates, which impedes their decomposition. We surveyed the copper-catalyzed asymmetric O–H insertion of α -diazophosphonates with alcohols.²⁰ The copper complex of ligand (S_a,S,S,S) -**1c** with isopropyl groups on the oxazoline rings catalyzed the insertion of dimethyl diazo(phenyl)methylphosphonate with 2-(trimethylsilyl)ethanol to provide (*R*)-dimethyl phenyl[2-(trimethylsilyl)ethoxy]methylphosphonate in 87% yield with 90% ee (Table 3, entry 6). Except for

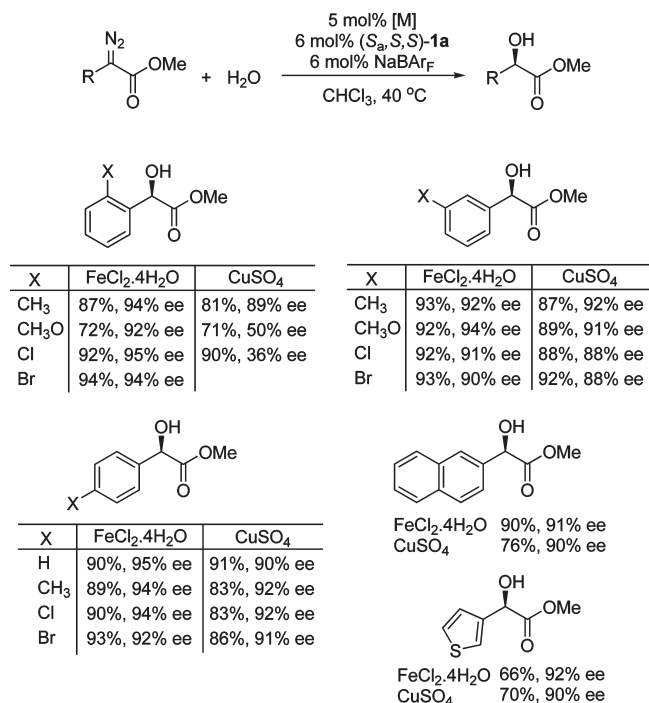
SCHEME 12. Copper-Catalyzed Asymmetric O–H Insertion of Phenols**SCHEME 13.** Hydrolysis of α -Aryloxypropionates

isopropanol and prop-2-en-1-ol (entries 9 and 10), which afforded low yield and low enantioselectivity, respectively, various alcohols underwent the insertion reaction in good yields (69–89%) with high enantioselectivities (84–92% ee).

In addition to dimethyl diazo(phenyl)methylphosphonate, various diazophosphonates with substituted phenyl groups accomplished the O–H insertion of 1-butanol with high enantioselectivity (84–98% ee) (Scheme 10).

The (*R*)- α -alkoxy phosphonate derived from 2-(trimethylsilyl)ethanol could be easily converted to (*R*)- α -hydroxyphosphonate in the presence of boron trifluoride in high yield with retaining ee value (Scheme 11). It means that the present O–H insertion reaction provides an efficient approach not only to α -alkoxy phosphonates but also to the more useful α -hydroxyphosphonates.

3.1.2. Insertion of O–H Bond of Phenols. The α -aryloxy propionates are important biologically active compounds and have wide applications in pharmaceuticals and crop protection. The O–H insertion between α -diazopropionates and phenols provides a direct and efficient method for the preparation of α -aryloxypropionates under neutral and mild

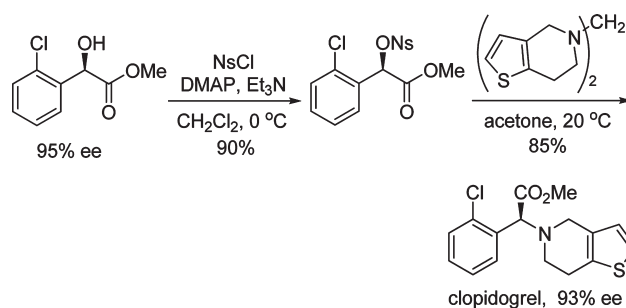
SCHEME 14. Iron- and Copper-Catalyzed Asymmetric O–H Insertion of Water

conditions, which avoids epimerization under harsh conditions. Because phenols have relatively strong coordination ability to transition metals and consequently deactivate catalysts, the O–H insertion of phenols is a challenge.¹⁴

We found that the Cu-(*S_a,S,S*)-**1a** was a highly enantioselective catalyst for the O–H insertion of α -diazopropionates with phenols (Scheme 12).²¹ In the presence of 5 mol % chiral copper catalyst formed in situ from CuCl, (*S_a,S,S*)-**1a**, and NaBAR_F, the O–H insertion of α -diazopropionates occurred smoothly with a wide range of phenols to afford corresponding (*R*)- α -aryloxypropionates in good yields (62–88%) and with excellent enantioselectivities (95–99.6% ee). The steric and electronic properties of the substituents of phenol slightly impacted the enantioselectivity of reaction.

The O–H insertion products can be easily hydrolyzed in an aqueous KOH solution at 0 °C to produce corresponding α -aryloxypropionic acids with ee values maintained (Scheme 13). Thus, the Cu-(*S_a,S,S*)-**1a**-catalyzed asymmetric insertion of α -diazopropionates into the O–H bond of phenols also provided an efficient access to the optically pure α -aryloxypropionic acids.

3.1.3. Insertion of O–H Bond of Water. Water is one of the most abundant, safe, environmentally benign, and cost-efficient resources on the Earth; however, successful catalytic asymmetric transformations using water as reactant are very limited. Transition-metal-catalyzed asymmetric

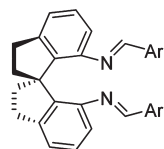
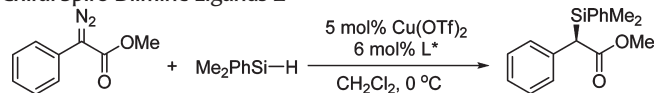
SCHEME 15. Asymmetric Synthesis of Clopidogrel

insertion of α -diazooesters into the O–H bond of water affords an extremely simple approach to chiral α -hydroxyesters, which have been widely used as chiral resolution reagents, ligands, catalysts, and key intermediates for the construction of biologically active molecules. Two previously reported examples of catalytic asymmetric O–H insertions of water have very low enantioselectivities (not more than 15% ee).^{10,14} The challenges of asymmetric O–H insertion of water are mainly attributed to two aspects. First, the active transition metal catalysts are generally sensitive to water. Second, the small molecular structure of water makes chiral discrimination quite difficult.

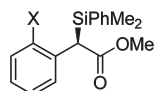
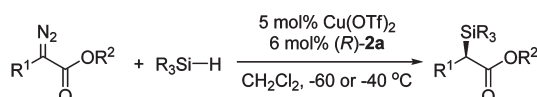
We discovered highly enantioselective O–H insertions of water catalyzed by chiral *spiro* copper and iron catalysts (Scheme 14).^{18,22} Under mild conditions, both copper and iron complexes of (*S_a,S,S*)-**1a** exhibited high enantioselectivity for the O–H insertions of water. Notably, the insertion of α -aryl- α -diazooacetate substrates having a coordinating group at the *ortho* position gave higher enantioselectivity in iron-catalyzed reaction than in copper-catalyzed reaction. For instance, in the insertion reaction of methyl α -diazo-2-chlorophenylacetate with water, the catalyst Fe-(*S_a,S,S*)-**1a** produced methyl (*R*)-*o*-chloromandelate with 95% ee, while the analogous copper catalyst gave the same product with only 36% ee. The activity of the catalyst Fe-(*S_a,S,S*)-**1a** is remarkable for this type of substrate. The catalyst loading can be reduced to 1 mol % without significant diminishment of yield and enantioselectivity.

The facile conversion of methyl (*R*)-*o*-chloromandelate to clopidogrel, a widely used platelet aggregation inhibitor²³ demonstrated that this iron-catalyzed asymmetric insertion with water is an efficient route for the preparation of this important chiral drug (Scheme 15).

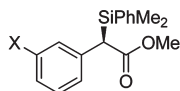
3.2. Intramolecular O–H Bond Insertions. The catalytic intramolecular O–H insertion is a very useful reaction for the construction of cyclic ethers and esters. We realized the copper-catalyzed asymmetric intramolecular O–H insertion

SCHEME 18. Asymmetric Cu-Catalyzed Si–H Bond Insertion Using Chiral Spiro Diimine Ligands **2**

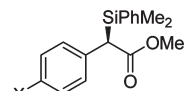
(*R*)-**2a**, Ar = 2,6-Cl₂C₆H₃: 95%, 93% ee
 94%, 98% ee (–60 °C)
 (*R*)-**2b**, Ar = 2,4-Cl₂C₆H₃: 95%, 83% ee
 (*R*)-**2c**, Ar = 2-ClC₆H₄: 93%, 78% ee
 (*R*)-**2d**, Ar = 2-MeOC₆H₄: 93%, 50% ee
 (*R*)-**2e**, Ar = 2-Naphthyl: 92%, 69% ee

SCHEME 19. Cu-(*R*)-**2a**-Catalyzed Asymmetric Si–H Insertion Reaction

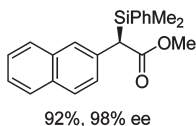
X = H 94%, 98% ee
 X = Me 91%, 96% ee
 X = MeO 89%, 90% ee
 X = Cl 91%, 97% ee



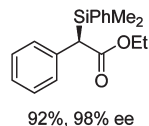
X = Me 95%, 99% ee
 X = MeO 89%, 98% ee
 X = F 85%, 97% ee
 X = Br 87%, 97% ee
 X = Cl 88%, 98% ee
 X = CF₃ 88%, 97% ee



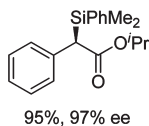
X = Me 97%, 97% ee
 X = Ph 95%, 96% ee
 X = MeO 93%, 95% ee
 X = F 87%, 93% ee
 X = Cl 95%, 99% ee
 X = Br 86%, 98% ee



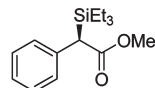
92%, 98% ee



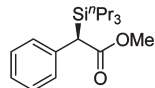
92%, 98% ee



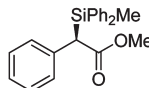
95%, 97% ee



94%, 96% ee



95%, 97% ee



88%, 93% ee

4. S–H Bond Insertion

Transition-metal-catalyzed asymmetric S–H insertion is an important but difficult reaction. Although it has been studied by several groups in the past two decades, the enantioselectivities so far reported for this reaction are very low (<30% ee).¹¹ The low level of enantiocontrol observed in S–H insertion reaction may be partially attributed to two reasons. First, the high coordination ability of the sulfur atom to the transition metal may destroy the active chiral catalyst. Second, the relatively high stability of sulfonium ylide may facilitate the degeneration of metal-associated ylide to free ylide, which lowers the efficiency of chiral induction of catalyst. Therefore, the catalytic asymmetric S–H insertion reaction is a real challenge.

We conducted the S–H insertion of mercaptans with α -diazoesters catalyzed by Cu-(*S*_a,*S*,*S*)-**1a** (Scheme 16).²⁵

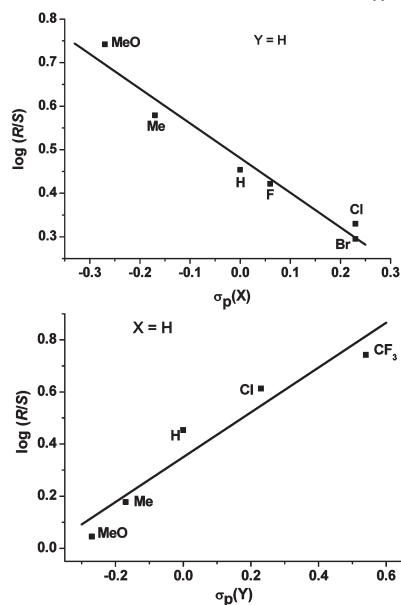
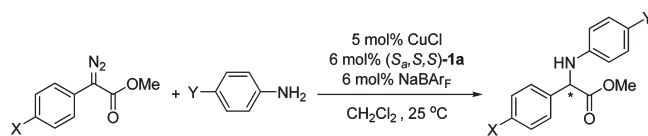
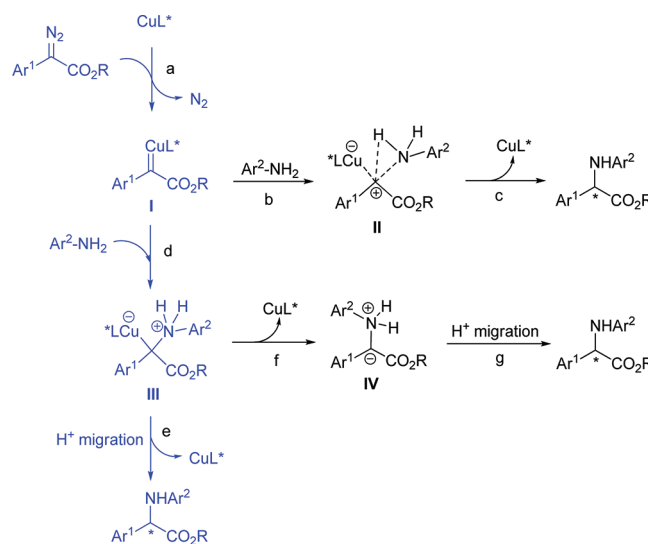
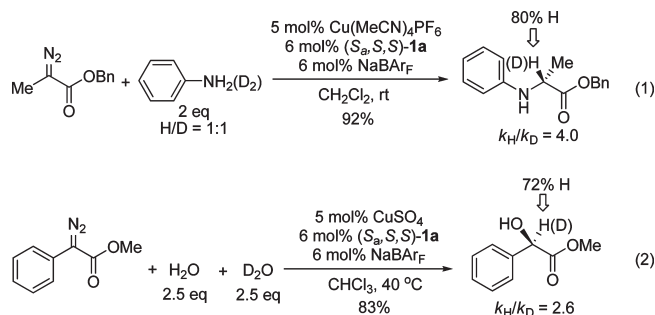


FIGURE 2. The correlations between the log(er) values of the products and the Hammett constants (σ) of the *para* substituents.

SCHEME 20. Proposed Copper-Catalyzed N–H Insertion Mechanisms

The S–H insertion of benzyl α -diazoacetate and benzyl mercaptans occurred smoothly and afforded the corresponding insertion products in good yields (70–87%) with good enantioselectivities (68–85% ee). Changing benzyl α -diazoacetate to methyl α -aryl- α -diazoacetates produced the corresponding α -mercapto esters with moderate enantioselectivities (44–77% ee). The substituents at the *ortho*

SCHEME 21. Kinetic Isotope Effects in N–H and O–H Insertion Reactions

position of α -aryl- α -diazoacetates were beneficial for improving enantioselectivity. In addition to benzyl mercaptans, thiophenols were also suitable S–H donors, affording the S–H insertion products in 76–92% yields with 60–72% ee. There is a clear trend that the bulky mercaptan has higher enantioselectivity in the S–H insertion reaction of aliphatic mercaptans, with trityl thiol being the most enantioselective (77% ee).

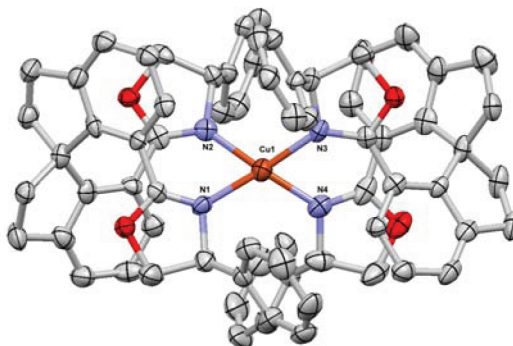
The trityl group of the S–H insertion product was easily removed in the presence of Et_3SiH /trifluoroacetic acid under mild reaction conditions to generate unprotected thiol ester in 81% yield with optical purity retained, which further demonstrated the potential utility of this asymmetric S–H insertion (Scheme 17).

5. Si–H Bond Insertion

The transition-metal-catalyzed carbenoid insertion into the Si–H bond provides a direct and efficient method for the synthesis of silane-containing compounds. As previously mentioned, a few highly enantioselective Si–H insertions have been accomplished using chiral dirhodium catalysts.¹³ The only example of highly enantioselective copper-catalyzed Si–H insertion was reported by Panek, Jacobsen, and co-workers with up to 88% ee.²⁶

The chiral *spiro*-diimine ligand (*R*)-**2a** exhibited much higher activity and enantioselectivity than the *spiro*-bisoxazoline ligand (*R*_a,*S*,*S*)-**1a** in Si–H insertion reaction. The insertion reaction of methyl α -diazophenylacetate with dimethylphenylsilane was completed in 1 h at 0 °C when the catalyst Cu-(*R*)-**2a** was used, and the Si–H insertion product, (*R*)-methyl 2-(dimethyl(phenyl)silyl)-2-phenylacetate, was obtained in 95% yield with 93% ee (Scheme 18).^{15d} Further improvement of enantioselectivity (98% ee) for Si–H insertion was achieved by lowering the reaction temperature to –60 °C. The additive NaBARF is unnecessary in the Si–H insertion if an ionic instead of neutral catalyst precursor is used.

A Top view



B Side view

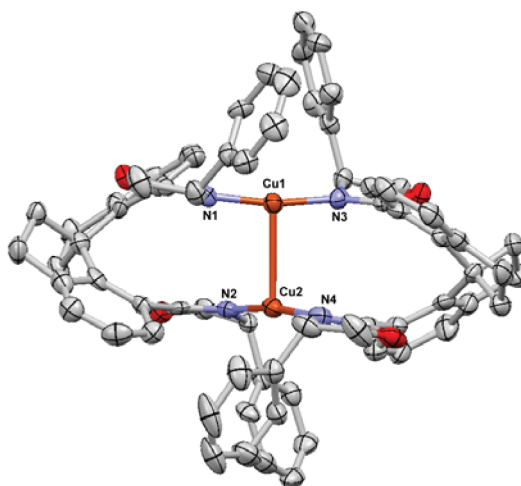


FIGURE 3. Single crystal structure of Cu-(*S*_a,*S*,*S*)-**1a** complex (**3a**). The hydrogen atoms, solvent, and anion (PF_6^-) were omitted for clarity.

A variety of α -diazo- α -phenylacetates conducted the Si–H insertion with dimethylphenylsilane under the optimal reaction conditions in high yields (85–95%) with excellent enantioselectivities (90%–99% ee) (Scheme 19).^{15d} The steric and electronic properties of substituents on the phenyl ring of the diazo esters slightly affected the enantioselectivity of the Si–H insertion reaction. In addition to dimethylphenylsilane, triethylsilane, tripropylsilane, and diphenylmethylsilane were all suitable Si–H bond donors.

6. Mechanism Consideration and Catalyst Structure Studies

6.1. Mechanism Consideration. Compared with the well-defined C–H insertion mechanisms, the detailed X–H insertion mechanisms remain unclear. We preliminarily studied the insertion mechanisms with N–H insertion as a template.¹⁷

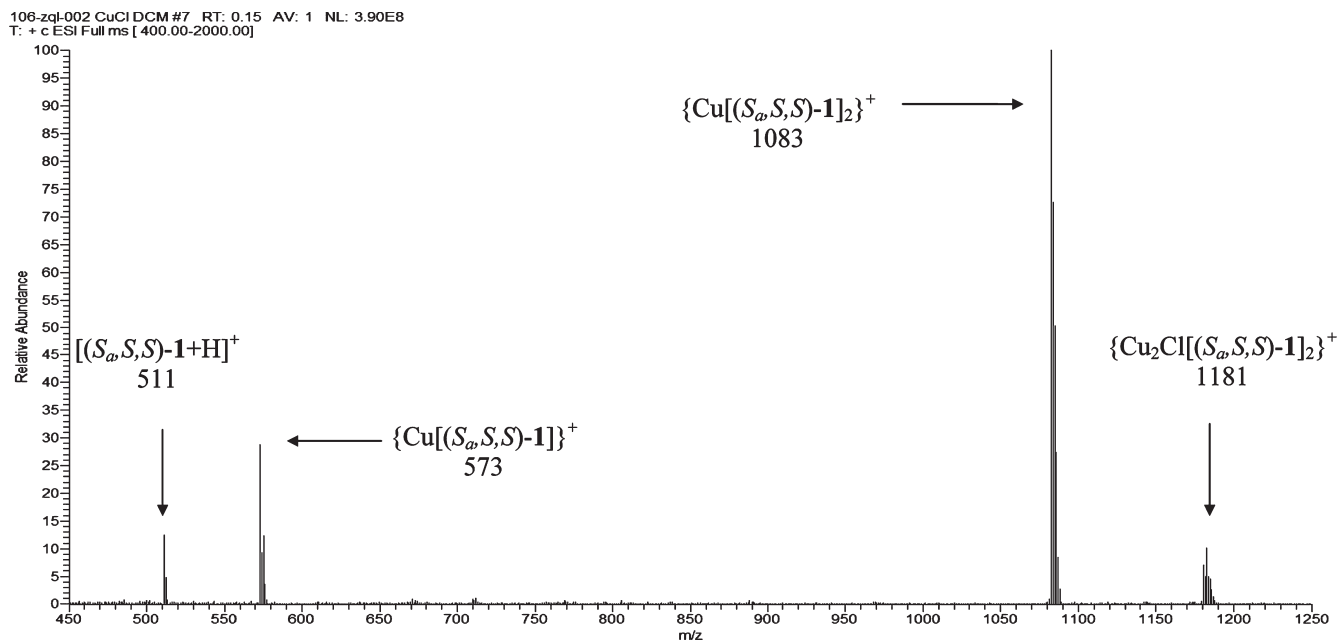


FIGURE 4. ESI-MS analysis of the solution of Cu-(*S_aS_aS_S*)-**1a** formed by CuCl and (*S_aS_aS_S*)-**1a** (1:1 mol) in CH₂Cl₂.

Two distinct N–H insertion pathways, a concerted mechanism ($a \rightarrow b \rightarrow c$) and a stepwise mechanism ($a \rightarrow d \rightarrow e$ or $a \rightarrow d \rightarrow f \rightarrow g$), are depicted in Scheme 20. 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 and that insertions into C–H or Si–H bonds proceed by a concerted mechanism.² In the stepwise mechanism, copper-associated 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). Because the chiral catalyst is involved in step e, chiral induction can be expected. The alternative process involves a dissociation of copper catalyst from ylide **III** to form free ylide **IV** (step f), which undergoes a proton transfer to yield the insertion product (step g). Because the chiral catalyst does not participate in step g, enantioselectivity cannot be assured. The high enantioselectivities we obtained in the Cu-(*S_aS_aS_S*)-**1a**-catalyzed asymmetric N–H insertion reactions indicate that the reactions most likely proceeded by pathway $a \rightarrow d \rightarrow e$.

It is reasonable to hypothesize that electron-withdrawing substituents on Ar¹ or electron-donating substituents on Ar² would likely stabilize free ylide **IV** and thus favor the free-ylide process (Scheme 20, $a \rightarrow d \rightarrow f \rightarrow g$), which would lead to lower enantioselectivity. The correlations between the log(*er*) values of the products and the Hammett constants (*σ*) of the *para* substituents clearly indicated that electron-withdrawing groups (X) at the *para* position of Ar¹ and electron-

donating groups (Y) at the *para* position of Ar² lowered the enantioselectivity (Figure 2). These results strongly suggest that the highly enantioselective Cu-(*S_aS_aS_S*)-**1a**-catalyzed N–H insertion proceeds via the pathway $a \rightarrow d \rightarrow e$ instead of the pathway $a \rightarrow d \rightarrow f \rightarrow g$.

A significant first-order kinetic isotope effect ($k_H/k_D = 4.0$; Scheme 21, eq 1) was observed in the copper-catalyzed N–H insertion of benzyl α -diazopropionate with aniline, which implies that a proton transfer is involved in the rate-limiting step.¹⁷ The copper-catalyzed O–H insertion of methyl α -diazophenylacetate with water also exhibited first-order kinetic isotope effect ($k_H/k_D = 2.6$, Scheme 21, eq 2).²²

6.2. Catalyst Structure Studies. Crystals of Cu(I)-(*S_aS_aS_S*)-**1a** with various anions (**3a** PF₆[−], **3b** ClO₄[−], and **3c** BARF[−]) had an unexpected binuclear structure, as shown for **3a** in Figure 3.¹⁷ In the structure of **3a**, 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 C₂-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.

Electrospray ionization mass spectrometry (ESI-MS) studies of Cu-(*S_aS_aS_S*)-**1a** prepared in situ from CuCl and (*S_aS_aS_S*)-**1a** revealed the presence of dimeric species in the solution

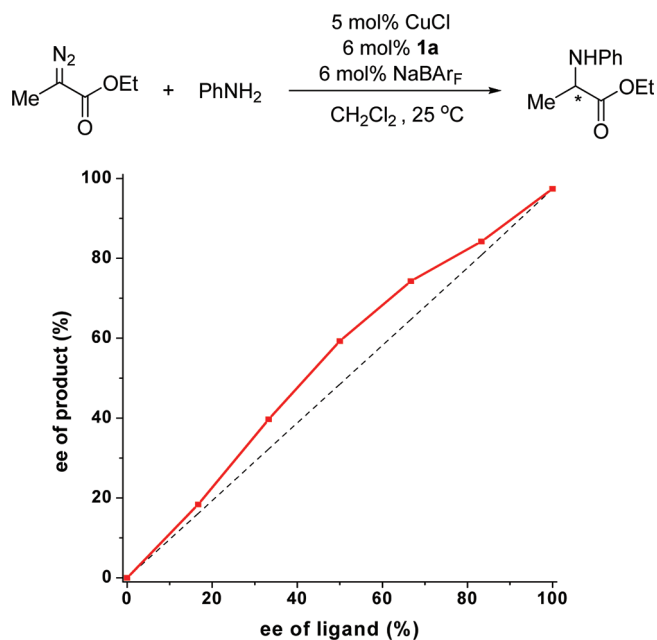


FIGURE 5. Nonlinear effect experiment.

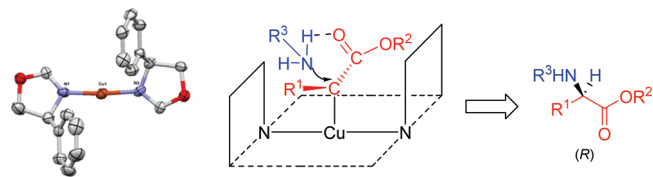


FIGURE 6. Chiral induction model.

($m/z = 1181$, $\{\text{Cu}_2\text{Cl}[(S_a,S,S)-\mathbf{1a}]_2\}^+$; Figure 4). A peak with significant intensity was also detected for $\{\text{Cu}[(S_a,S,S)-\mathbf{1a}]_2\}^+$ ($m/z = 1083$), a decomposition fragment of the dimer.

As shown in Figure 5, a small but clearly positive non-linear effect²⁷ was observed in the copper-catalyzed N–H insertion reaction, which indicates that the dimeric copper complex is most likely the real active catalyst for the N–H insertion reaction.

A chiral induction model was proposed based on the catalyst structure and absolute configuration of the N–H insertion products. As shown in Figure 6, the nitrogen of aniline attacks the electron-deficient carbene from the less hindered *Re* face, affording the insertion product with an *R* configuration, which is consistent with the configuration obtained from the experiments.

7. Conclusion Remarks

The transition-metal-catalyzed asymmetric X–H insertion reactions have become important enantioselective C–X bond-forming approaches. By use of copper or iron complexes with chiral *spiro*-bisoxazoline ligands or -diimine

ligands, the X–H insertions of α -diazo compounds with N–H bonds of anilines, O–H bonds of alcohols, phenols, and even water, S–H bonds of mercaptans, and Si–H bonds of silanes have been accomplished with high to excellent enantioselectivities. Diverse chiral α -amino esters, α -alkoxyl esters, α -aryloxy esters, α -hydroxy esters, α -mercapto esters, α -silyl esters, and α -alkoxyl phosphonates were prepared in high optical purity under neutral and mild conditions. Because C–X bonds commonly exist in natural products and biologically active compounds, the present asymmetric X–H insertions have high potential for wide application in organic synthesis. The preliminary mechanistic studies cast new light into the transition-metal-catalyzed X–H insertions. The catalyst structure studies revealed that the unique rigid and robust dimeric structure of chiral *spiro* catalysts plays a crucial role in the chiral induction.

We believe that the transition metal catalysts based on chiral *spiro*-bisoxazoline and -diimines, along with the catalysts developed by other groups,²⁸ should advance the asymmetric X–H insertion reaction to more mature state.²⁹

We are indebted to co-workers, whose names are cited in the references, for their intellectual and experimental contributions. We thank the National Natural Science Foundation of China and the National Basic Research Program of China (2011CB808600, 2012CB821600), and the “111” project (B06005) of the Ministry of Education of China for financial support.

BIOGRAPHICAL INFORMATION

Shou-Fei Zhu received his Ph.D. degree in chemistry under the supervision of Prof. Qi-Lin Zhou at the Institute of Elemento-Organic Chemistry, Nankai University, in 2005. He then joined the faculty of the same institute and was promoted to associate professor in 2008. His research interests focus on asymmetric synthesis, particularly on the development of chiral ligands and catalysts, as well as new asymmetric reactions.

Qi-Lin Zhou received his Ph.D. degree from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Prof. Yao-Zeng Huang in 1987. After postdoctoral research in Europe and the United States, he joined the faculty of the Institute of Fine Chemicals, East China University of Science and Technology, in 1996. In 1999, he moved to the Institute of Elemento-organic Chemistry, Nankai University, as a Cheung Kong Scholar. He was elected as a member of Chinese Academy of Sciences in 2009. His current research interests include transition-metal-catalyzed reactions, asymmetric catalysis, and synthesis of biologically active compounds.

FOOTNOTES

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