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Copper-catalyzed enantioselective carbenoid insertion into S–H bonds†‡

Yong-Zhen Zhang, Shou-Fei Zhu, Yan Cai, Hong-Xiang Mao and Qi-Lin Zhou*

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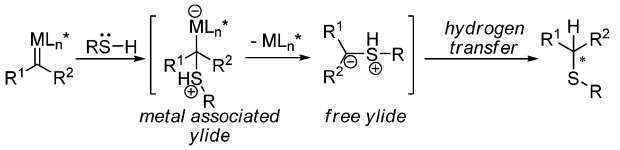
An asymmetric carbenoid insertion into S–H bonds catalyzed by copper–chiral spiro bisoxazoline complexes has been developed, in which a series of α-mercaptoesters were produced in high yields with moderate to good enantioselectivities (up to 85% ee); this result represents the best enantioselectivity in the catalytic asymmetric carbenoid S–H bond insertion reaction.

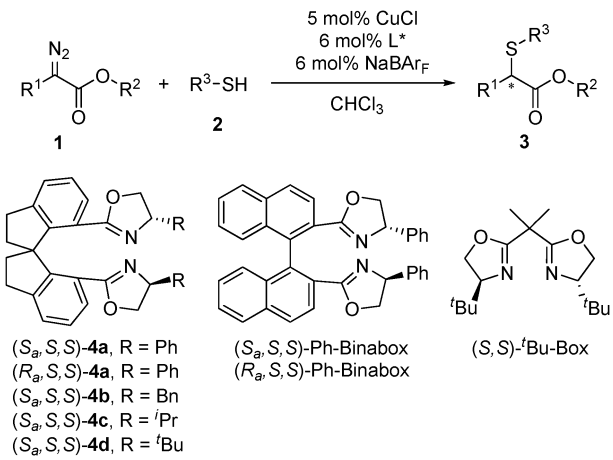
The catalytic asymmetric insertion of metal carbenoids into X–H (X = C, Si, N, O, S, *etc.*) bonds is a very powerful organic transformation for preparing highly versatile building blocks and has drawn considerable attention.[1] Various chiral dirhodium catalysts have been developed for highly enantioselective C–H bond insertion[2] with quite a broad substrate scope. Very recently, breakthroughs in asymmetric Si–H,[3] O–H[4] and N–H[5] bond insertion reactions have also been achieved by using chiral copper or dirhodium catalysts. Chiral α-mercaptocarbonyl compounds are ubiquitous structural subunits in biologically active compounds[6] and the catalytic asymmetric S–H bond insertion reaction provides an efficient approach for their construction. However, a highly enantioselective catalyst for the asymmetric carbenoid insertion into S–H bonds has not been developed yet.[7] The first catalytic asymmetric S–H bond insertion reaction was reported by Brunner *et al.*[8] using a chiral copper–Schiff base catalyst, albeit with enantioselectivities only up to 13.8% ee. Simonneaux and co-workers[9] investigated the S–H bond insertion reaction of ethyl α-diazopropionate and thiophenols by using a chiral porphyrin–ruthenium(II) complex as the catalyst, and obtained an enantioselectivity of 8% ee. After screening numerous chiral copper and rhodium catalysts, Wang *et al.*[10] archived 23% ee in the asymmetric S–H bond insertion reaction of α-diazophenylacetate and thiophenols catalyzed by Rh_2(*S*-DOSP)$_4$. This is, to the best of our knowledge, the highest enantioselectivity ever reported in the catalytic asymmetric S–H bond insertion reaction. The low level of enantiocontrol observed in S–H bond insertion reactions 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 the sulfonium ylide may increase the trend of degeneration of the metal-associated ylide to free ylide, which lowers the efficiency of chiral induction (Scheme 1).[11] In fact, the catalytic asymmetric S–H bond insertion reaction remains a great challenge nowadays.



Scheme 1

We have recently developed highly enantioselective copper–chiral spiro bisoxazoline complexes as efficient catalysts for O–H[4b,c] and N–H[5a] bond insertion reactions. We found that the chiral spiro bisoxazoline ligands with a rigid spirobiindane backbone enhanced the stability of the copper catalysts and performed an efficient chiral induction in the copper carbenoid insertion reactions. The unique characteristics of the spiro bisoxazoline ligands provide a good opportunity for developing a highly enantioselective S–H insertion reaction. In this communication, we report an asymmetric S–H bond insertion reaction catalyzed by copper complexes of chiral spiro bisoxazolines. Under mild reaction conditions, the copper-catalyzed S–H bond insertion of carbenoids generated *in situ* from α-diazoesters with mercaptans and thiophenols works smoothly to yield α-mercaptocarbonyl compounds in high yields with unprecedentedly high enantioselectivities (up to 85% ee).

The insertion reaction of benzyl α-diazopropionate (**1a**) and benzyl mercaptan (**2a**) was first performed in chloroform at 60 °C with a copper catalyst generated *in situ* from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBAr$_F$[12] (Scheme 2). Various chiral bisoxazoline ligands with spirobiindane backbones developed by us were compared. As shown in Table 1, spiro



Scheme 2

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China.
E-mail: qlzhou@nankai.edu.cn; Fax: +86 22-23506177;
Tel: +86 22-23500011

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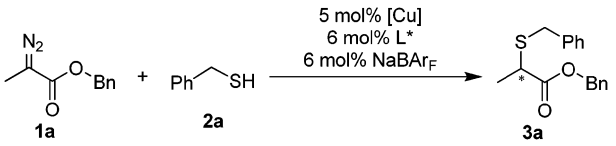
‡ Electronic supplementary information (ESI) available: Experimental details and data for new compounds. See DOI: 10.1039/b911670b

Table 1 Cu-catalyzed asymmetric S–H bond insertion of benzyl α-diazopropionate with benzyl mercaptan: optimization of the reaction conditions[a]



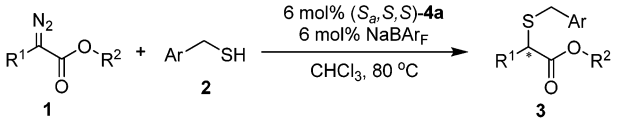
Entry	[Cu]	Ligand	Solvent	Temp./ °C	Time/ h	Yield (%)[b]	ee (%)[c]
1	CuCl	(S_a,S,S)-**4a**	$CHCl_3$	60	1	82	81
2	CuCl	(R_a,S,S)-**4a**	$CHCl_3$	60	12	72	9
3	CuCl	(S_a,S,S)-**4b**	$CHCl_3$	60	12	70	55
4	CuCl	(S_a,S,S)-**4c**	$CHCl_3$	60	12	79	48
5	CuCl	(S_a,S,S)-**4d**	$CHCl_3$	60	48	46	41
6	CuCl	(S_a,S,S)-Ph-Binabox	$CHCl_3$	60	12	46	0
7	CuCl	(R_a,S,S)-Ph-Binabox	$CHCl_3$	60	48	72	0
8	CuCl	(S,S)-^{t}Bu-Box	$CHCl_3$	60	48	58	22
9[d]	CuCl	(S_a,S,S)-**4a**	$CHCl_3$	60	1	80	83
10[e]	CuCl	(S_a,S,S)-**4a**	$CHCl_3$	60	1	79	80
11	$CuPF_6$	(S_a,S,S)-**4a**	$CHCl_3$	60	1	85	79
12	$Cu(OTf)_2$	(S_a,S,S)-**4a**	$CHCl_3$	60	1	85	80
13	$CuBr_2$	(S_a,S,S)-**4a**	$CHCl_3$	60	1	85	80
14	CuCl	(S_a,S,S)-**4a**	CH_2Cl_2	40	3	81	72
15	CuCl	(S_a,S,S)-**4a**	DCE	60	3	81	76
16	CuCl	(S_a,S,S)-**4a**	$CHCl_3$	40	3	78	81
17	CuCl	(S_a,S,S)-**4a**	$CHCl_3$	80	0.5	82	81
18[f]	CuCl	(S_a,S,S)-**4a**	$CHCl_3$	80	1	74	70

[a] Reaction conditions: [Cu] : ligand : $NaBAr_F$: **1a** : **2a** = 0.01 : 0.012 : 0.012 : 0.2 : 0.2 mmol, in 2 mL $CHCl_3$. [b] Isolated yield. [c] Determined by chiral HPLC using a Chiralcel OJ-H column. [d] $AgSbF_6$ instead of $NaBAr_F$ was used. [e] AgOTf instead of $NaBAr_F$ was used. [f] 1 mol% catalyst was used.

bisoxazoline ligands showed high reactivity and good enantioselectivity in S–H bond insertion reactions. The combination of chiralities in the ligand (S_a,S,S)-**4a** rather than (R_a,S,S)-**4a** is matched in terms of reactivity as well as enantioselectivity (entries 1 and 2). Among the spiro bisoxazoline ligands tested, (S_a,S,S)-**4a** with phenyl substituents on the oxazoline rings gave the highest reactivity and enantioselectivity (82% yield, 81% ee). The bisoxazoline ligands with other scaffolds such as Ph-Binabox and ^{t}Bu-Box were also evaluated in the S–H bond insertion reaction under identical reaction conditions. The reaction became sluggish and very poor enantioselectivities were observed in the presence of those ligands. This result indicated that the chiral spirobiindane structure of the ligands is essential for obtaining high enantioselectivity in the copper-catalyzed carbenoid insertion into S–H bonds. The additive $NaBAr_F$ played an important role in the reaction. No reaction took place under the conditions of entry 1 in the absence of $NaBAr_F$. When $AgSbF_6$ and AgOTf were used instead of $NaBAr_F$, similar yields and enantioselectivities were obtained (entries 9 and 10).

To further improve the enantioselectivity of S–H bond insertion, the reaction conditions were carefully optimized by using ligand (S_a,S,S)-**4a**. A variety of copper salts were tested as catalyst precursors and essentially identical results were obtained (entries 11–13). Besides chloroform, the reaction can also be performed smoothly in boiling CH_2Cl_2 or DCE; however, the enantioselectivity of the reaction became slightly

Table 2 Cu-catalyzed asymmetric S–H bond insertion of α-diazoesters with arylmethylene mercaptans[a]



Entry	R^1	R^2	Ar	Product	Yield (%)	ee (%)
1	Me	Bn	C_6H_5	**3a**	82	81
2	Me	Et	C_6H_5	**3b**	91	73
3	Me	^{t}Bu	C_6H_5	**3c**	62	83
4	Me	Bn	4-$MeOC_6H_4$	**3d**	73	85
5	Me	Bn	4-ClC_6H_4	**3e**	86	83
6	Me	Bn	2-MeC_6H_4	**3f**	87	68
7	Me	Bn	2-ClC_6H_4	**3g**	70	78
8	C_6H_5	Me	C_6H_5	**3h**	59	44
9	2-MeC_6H_4	Me	C_6H_5	**3i**	64	77
10	2-ClC_6H_4	Me	C_6H_5	**3j**	83	73
11	2-$MeOC_6H_4$	Me	C_6H_5	**3k**	88	77
12	3-$MeOC_6H_4$	Me	C_6H_5	**3l**	71	52
13	4-$MeOC_6H_4$	Me	C_6H_5	**3m**	61	61

[a] Reaction conditions were the same as those in Table 1, entry 17. All reactions were completed within 2 h.

lower (entries 14 and 15). The reaction temperature had a negligible effect on the enantioselectivity of the reaction, while a higher reaction temperature apparently increased the reaction rate. For instance, when the reaction was heated to vigorous reflux in a sealed Schlenk tube in an 80 °C oil bath, full conversion was achieved within 30 min without diminishing the enantioselectivity (entry 17). Reducing the catalyst loading to 1 mol%, the reaction could also be finished in 1 h, but with a slightly lower yield and enantioselectivity (entry 18).

We next investigated the substrate scope of the S–H bond insertion reaction. The insertion reactions of various substituted benzyl mercaptans and different α-diazoesters were conducted under the optimal reaction conditions (Table 2). The α-diazopropionate with a less sterically hindered ethyl group gave a higher yield, but a slightly lower ee value (91% yield, 73% ee, entry 2). By increasing the size of R^2 to ^{t}Bu, an enantioselectivity as high as 83% ee was achieved, although the yield was lower (entry 3). The substituted benzyl mercaptans were then examined in the S–H bond insertion reaction (entries 4–7). All the benzyl mercaptans underwent the insertion reaction smoothly and the corresponding insertion products were obtained with good yields. The electronic effect of the benzyl mercaptan substituent on the enantioselectivity was negligible. The reactions of 4-methoxybenzyl mercaptan and 4-chlorobenzyl mercaptan gave similar ee values (85 and 83% ee, respectively; entries 4 and 5). Substitution at the *ortho* position of benzyl mercaptan resulted in a lower enantioselectivity, indicating the existence of a negative steric effect on the mercaptan substrate (entries 6 and 7). The R^1 group of the diazo compounds has a great influence on both reactivity and enantioselectivity in the S–H bond insertion reaction. When benzyl α-diazobutyrate (R^1 = ethyl) was used, only benzyl 2-butenoic ester, the β-elimination product of the carbenoid, was isolated. By changing R^1 from a methyl to a phenyl group, the corresponding α-mercaptoesters were obtained in moderate yields with 44% ee (entry 8). Surprisingly, substitutions at the

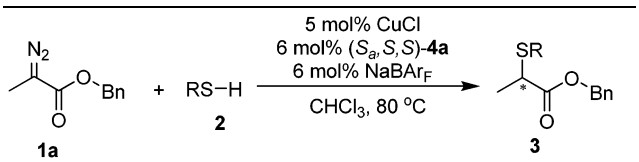
ortho position of 2-aryl-2-diazoacetates, regardless of their electronic and steric properties, significantly enhanced the enantioselectivity (entries 9–11). In contrast, the *meta*- or *para*-substituted aryl diazoacetates only gave modest enantioselectivities under the identical reaction conditions (entries 12 and 13).

In addition to benzyl mercaptans, various thiophenols and aliphatic mercaptans were also examined in the S–H bond insertion reaction with carbenoids derived from benzyl α-diazopropionate (Table 3). All the tested thiophenols underwent the S–H insertion reactions, affording the S–H bond insertion products in high yields (76–92%) with good enatioselectivities (60–72% ee, entries 1–8). Aliphatic mercaptans are also suitable substrates for the S–H bond insertion reaction and the desired products were isolated in high yield, while the enantioselectivities were low (entries 9 and 10). The use of sterically hindered mercaptans greatly improved the enantioselectivity of the reaction. For example, the bulky trityl thiol afforded S–H bond insertion product in 77% ee (entry 12).

To further demonstrate the potential utilities of the copper-catalyzed asymmetric S–H bond insertion reaction, the synthesis of optically active α-unprotected thiol esters was performed. The protecting group of **3y** was removed by using Et_3SiH–TFA[7e] under mild reaction conditions to generate unprotected thiol ester **5** in 81% yield without diminishing the optical purity (Scheme 3).

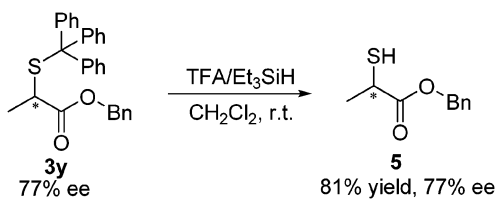
In conclusion, the copper–chiral spiro bisoxazoline complexes were shown to be effective catalysts for asymmetric carbenoid S–H bond insertion reactions. A broad range of mercaptans and thiophenols underwent the insertion reaction with carbenoids generated *in situ* from α-diazoesters to produce α-mercaptoesters in high yields with moderate to good enantioselectivities (up to 85% ee). This provides an efficient and direct approach to the preparation of enantioenriched α-mercaptoester derivatives. The unprecedented enantiocontrol in the catalytic asymmetric S–H bond insertion reaction further demonstrates that the chiral spiro bisoxazoline ligands have great potential applications in metal carbenoid transfer reactions.

Table 3 Cu-catalyzed asymmetric S–H bond insertion of benzyl α-dizaopropionate with thiophenols and aliphatic mercaptans[a]



Entry	RS–H	Product	Yield (%)	ee (%)
1	C_6H_5SH	**3n**	90	69
2	4-$MeOC_6H_4SH$	**3o**	83	72
3	4-ClC_6H_4SH	**3p**	80	62
4	3-$MeOC_6H_4SH$	**3q**	76	62
5	3-ClC_6H_4SH	**3r**	85	60
6	2-$MeOC_6H_4SH$	**3s**	76	60
7	2-ClC_6H_4SH	**3t**	92	60
8	2,6-$Cl_2C_6H_3SH$	**3u**	81	67
9	^{n}BuSH	**3v**	86	17
10	^{i}BuSH	**3w**	84	32
11	^{i}PrSH	**3x**	85	61
12	Ph_3CSH	**3y**	57	77

[a] Reaction conditions were the same as those in Table 1, entry 17. All reactions were completed within 2 h.



Scheme 3

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