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Highly Enantioselective Insertion of Carbenoids into O−H Bonds of Phenols: An Efficient Approach to Chiral α-Aryloxycarboxylic Esters

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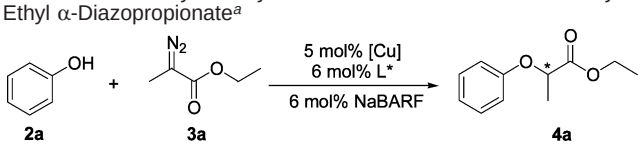
As a proven efficient means of constructing complex chemical structures from simple, readily available precursors, the catalytic insertion of α-diazocarbonyl compounds into X−H (X = C, N, O, S, etc.) bonds has been widely used in organic synthesis.[1] Remarkable advances have been made in the methodology for catalytic asymmetric diazo insertion into C−H bonds,[2] but only limited success has been achieved for asymmetric insertions into heteroatom−hydrogen bonds.[3] The O−H insertion was an efficient method for preparing α-alkoxy or α-aryloxy ketones and esters, and oxygen-containing heterocyclic compounds.[4] However, only recently Fu et al.[5] have made a breakthrough in asymmetric O−H insertion. With a Cu complex of chiral biazaferrocene as a catalyst, they realized the first highly enantioselective insertion of α-diazocarbonyl compounds into O−H bonds of alcohols. Under the optimal reaction conditions, various alcohols reacted with methyl α-diazo-α-phenylacetate, producing the corresponding α-alkoxy esters in high enantioselectivities. Unfortunately, when the Cu/biazaferrocene catalyst was applied to phenol substrates, the enantioselectivity markedly decreased (11% ee). Thus, the catalytic asymmetric insertion reaction of α-diazocarbonyl compounds with phenols remains a challenge. In a previous paper, we accomplished the highly enantioselective insertion of α-diazoesters into N−H bonds by using the copper complexes of chiral spiro bisoxazolines.[6] In this communication, we report the first efficient chiral catalyst for enantioselective insertion of carbenoids into O−H bond of phenols, yielding α-aryloxycarboxylic esters in high yields with enantioselectivities of up to 99.6% ee.

The insertion reaction of ethyl α-diazopropionate (**3a**) and phenol (**2a**) was first carried out in the presence of copper catalyst generated in situ from 5 mol % CuCl, 6 mol % bisoxazoline ligands, and 6 mol % NaBARF[7] additive in dichloromethane at 25 °C. As shown in Table 1, bisoxazoline ligands (*S*,*S*)-Ph-Box, (*S*,*S*)-^{i}Pr-Pybox, (S_a,*S*,*S*)-Ph-Binabox, and (R_a,*S*,*S*)-Ph-Binabox (Scheme 1) afforded O−H insertion products in moderate yields with very low enantioselectivities (Table 1, entries 1−4). In sharp contrast, the ligand Spirobox (S_a,*S*,*S*)-**1a**, containing a chiral spirobiindane backbone, has an excellent enantioselectivity (99% ee) (entry 5). The fact that the ligand (R_a,*S*,*S*)-**1a** gave a racemic product (entry 6) showed that the matched combination of the chiralities of backbone and oxazoline rings in the ligands **1a** played a crucial role in the enantiocontrol. The NaBARF additive is also essential for the reaction. Without NaBARF, no O−H insertion took place under the same reaction conditions. To improve the yield of the reaction, molecular sieves (MS) were added, with the addition of 600 mg of 5 Å MS giving the highest yield (entry 8). Uses of 5 equiv of phenol and 5 mol % catalyst are necessary for obtaining high yields. Reducing both the amount of phenol to 2 equiv and the catalyst loading to 2 mol % resulted in lower yields (entries 10 and 11). In addition to dichloromethane, chloroform, 1,2-dichloroethane, toluene, and hexane can serve as solvents in the insertion of ethyl α-diazopropionate into the O−H bond of phenol; however, the enantioselectivities were slightly lower, especially for the reaction in hexane (entries 12−15). In addition to CuCl, $Cu(OTf)_2$ and $Cu(PF_6)$ were also good catalyst precursors, affording excellent enantioselectivities in the reaction (entries 16 and 17). We examined the effect of the substituents of the oxazoline rings of spiro ligands **1** on the enantioselectivity of the O−H insertion reaction. The ligand

Table 1. Cu-Catalyzed Asymmetric O−H Insertion of Phenol by Ethyl α-Diazopropionate[a]

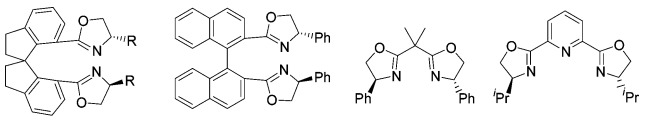


2a **3a** **4a**

entry	ligand	[Cu]/additive[b]	solvent	yield (%)[c]	ee (%)[d]
1	(*S*,*S*)-Ph-Box	CuCl	CH_2Cl_2	51	32
2	(*S*,*S*)-^{i}Pr-Pybox	CuCl	CH_2Cl_2	65	12
3	(S_a,*S*,*S*)-Ph-Binabox	CuCl	CH_2Cl_2	67	0
4	(R_a,*S*,*S*)-Ph-Binabox	CuCl	CH_2Cl_2	31	11
5	(S_a,*S*,*S*)-**1a**	CuCl	CH_2Cl_2	52	99
6	(R_a,*S*,*S*)-**1a**	CuCl	CH_2Cl_2	59	3
7	(S_a,*S*,*S*)-**1a**	CuCl/4 Å MS	CH_2Cl_2	79	99
8	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	CH_2Cl_2	87	99
9[e]	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	CH_2Cl_2	70	99
10[f]	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	CH_2Cl_2	79	99
11[g]	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	CH_2Cl_2	60	96
12	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	$CHCl_3$	78	97
13	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	DCE	65	94
14	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	toluene	70	96
15	(S_a,*S*,*S*)-**1a**	CuCl/5 Å MS	hexane	65	82
16	(S_a,*S*,*S*)-**1a**	$Cu(OTf)_2$/5 Å MS	CH_2Cl_2	67	98
17	(S_a,*S*,*S*)-**1a**	$CuPF_6$/5 Å MS	CH_2Cl_2	63	99
18	(S_a,*S*,*S*)-**1b**	CuCl/5 Å MS	CH_2Cl_2	81	92
19	(S_a,*S*,*S*)-**1c**	CuCl/5 Å MS	CH_2Cl_2	86	99
20	(S_a,*S*,*S*)-**1d**	CuCl/5 Å MS	CH_2Cl_2	79	88

[a] Reaction conditions: [Cu] (0.02 mmol), ligand (0.024 mmol), NaBARF (0.024 mmol), and solvent (4 mL) were stirred under argon at 25 °C for 2 h; then phenol (2.0 mmol) and ethyl α-diazopropionate (0.4 mmol) were introduced, and the reaction mixture was stirred for another 3 h. [b] 600 mg of MS was added unless otherwise noted. [c] Isolated yield. [d] Determined by chiral HPLC using a Chiralcel OD-H column. [e] 300 mg of 5 Å MS was added. [f] With 2 equiv of phenol. [g] With 2 mol % catalyst.

Scheme 1



Spirobox
(S_a,*S*,*S*)-**1a:** R = Ph
(R_a,*S*,*S*)-**1a:** R = Ph
(S_a,*S*,*S*)-**1b:** R = Bn
(S_a,*S*,*S*)-**1c:** R = ^{i}Pr
(S_a,*S*,*S*)-**1d:** R = ^{t}Bu

(S_a,*S*,*S*)-Ph-Binabox
(R_a,*S*,*S*)-Ph-Binabox

(*S*,*S*)-Ph-Box

(*S*,*S*)-^{i}Pr-Pybox

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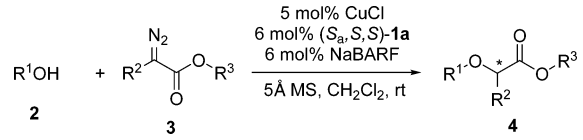
Table 2. Asymmetric Catalytic Carbenoid Insertion into O−H Bonds of Phenols[a]



entry	R^1	R^2	R^3	product	yield (%)	ee (%)
1	Ph	Me	Et	**4a**	87	99 (*R*)
2	*o*-MePh	Me	Et	**4b**	71	98
3	*o*-MeOPh	Me	Et	**4c**	68	95
4	*o*-PhPh	Me	Et	**4d**	83	99.2
5	*m*-MePh	Me	Et	**4e**	79	99.3
6	*m*-MeOPh	Me	Et	**4f**	71	99
7	*m*-BrPh	Me	Et	**4g**	78	99
8	*m*-PhPh	Me	Et	**4h**	82	99
9	*p*-MePh	Me	Et	**4i**	88	99
10	*p*-MeOPh	Me	Et	**4j**	78	99
11	*p*-^{t}BuPh	Me	Et	**4k**	70	98
12	*p*-ClPh	Me	Et	**4l**	83	99.1 (*R*)
13	*p*-BrPh	Me	Et	**4m**	85	99.6
14	*p*-MeO_2CPh	Me	Et	**4n**	62	99
15	2,4-diMePh	Me	Et	**4o**	80	99
16	3,5-diPhPh	Me	Et	**4p**	84	99
17	1-naphthyl	Me	Et	**4q**	77	99.1 (*R*)
18	2-naphthyl	Me	Et	**4r**	83	98 (*R*)
19	$Ph(CH_2)_3$	Me	Et	**4s**	63	59
20	$PhCH{=}CHCH_2$	Me	Et	**4t**	85	61 (*R*)
21	Ph	Ph	Me	**4u**	71	10 (*R*)
22	Ph	Me	Me	**4v**	70	98 (*R*)
23	Ph	Me	^{t}Bu	**4w**	80	99

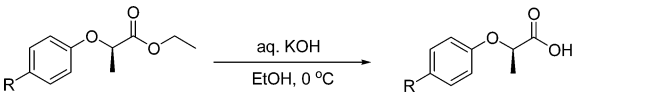
[a] Reaction conditions were the same as those in Table 1, entry 8. All reactions were completed within 3 h. For the characterization and analysis of ee values of insertion products, see Supporting Information.

(S_a,*S*,*S*)-**1c**, having an ^{i}Pr unit, gave the insertion product in 99% ee (entry 19), identical to that obtained with ligand (S_a,*S*,*S*)-**1a**. The ligands (S_a,*S*,*S*)-**1b** and (S_a,*S*,*S*)-**1d**, containing benzyl and *tert*-butyl groups, respectively, showed lower enantioselectivities (entries 18 and 20).

Under the optimized reaction conditions, a variety of substituted phenols were examined in the copper/Spirobox-catalyzed asymmetric O−H insertion of ethyl α-diazopropionates (Table 2). All substituted phenols including naphthols completed the insertion reaction in 3 h to produce the corresponding α-aryloxypropionates in good yields and extremely high enantioselectivities (≥95% ee) regardless of the nature and the position of the substituents (entries 1−18). In addition to phenols, aliphatic alcohols such as 3-phenylpropanol and cinnamic alcohol also underwent O−H insertion reaction under the same reaction conditions, although the enantioselectivities were not as high as those in the reactions with phenols (entries 19 and 20). The methyl of the R^1 group in the α-diazoester is vital for the reaction. When the methyl was changed to phenyl, the O−H insertion product was obtained in a negligible ee value (entry 21). In the reaction of benzyl α-diazobutyrate (R^2 = Et), only the *β*-elimination product of carbenoid, benzyl 2-butenoic ester (81%) was isolated. The reactions with methyl and *tert*-butyl α-diazopropionates gave O−H insertion products in good yields and with excellent enantiomeric excess (entries 22 and 23), showing that the size of R^3 group in the α-diazoester has almost no influence on the enantioselectivity and reactivity in the O−H insertion reaction.

The α-aryloxypropionic acids are biologically important compounds and have been widely utilized as crop protection reagents and as key intermediates in the preparation of chiral drugs.[8] They can be easily prepared from our O−H insertion products. For example, the hydrolysis of α-aryloxypropionates **4a** and **4l** with aqueous KOH at 0 °C afforded the acids (*R*)-**5a** and (*R*)-**5l** in quantitative yields (Scheme 2). Thus, the copper/(S_a,*S*,*S*)-**1a**-catalyzed asymmetric insertion of the O−H bond of phenols by α-diazoesters provided a new efficient access to the synthesis of optically pure α-aryloxypropionic acids from simple substrates in two steps.

Scheme 2



In summary, the first highly enantioselective insertion of carbenoids into O−H bonds of phenols has been realized. By using copper complexes of chiral spiro bisoxazolines as catalysts, the optically active α-aryloxypropionates and the related acids were synthesized conveniently. The successful use of spiro bisoxazolines in the asymmetric insertion of O−H bonds of phenols indicates the potential of these novel nitrogen ligands in asymmetric insertion reactions of heteroatom−hydrogen bond (X−H) of a wide range of substrates.

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

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