Synthetic Methods

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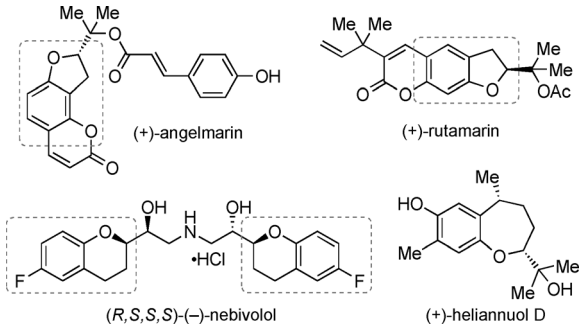
Enantioselective Copper-Catalyzed Intramolecular Phenolic O–H Bond Insertion: Synthesis of Chiral 2-Carboxy Dihydrobenzofurans, Dihydrobenzopyrans, and Tetrahydrobenzooxepines**

*Xiao-Guang Song, Shou-Fei Zhu, Xiu-Lan Xie, and Qi-Lin Zhou**

The construction of carbon–heteroatom bonds (C–X, where X = N, O, S, etc.) is one of the most widely used methods in organic synthesis. In particular, catalytic asymmetric formation of C–X bonds provides a direct method for the synthesis of chiral compounds containing heteroatoms,[1] and remarkable progress on the intramolecular asymmetric formation of such bonds has been made.[2] However, the known methods for the synthesis of chiral heterocyclic compounds by means of intramolecular enantioselective C–X formation are generally substrate dependent, which limits their utility in organic synthesis. For instance, chiral 2-carboxy dihydrobenzofuran, dihydrobenzopyran, and tetrahydrobenzo[*b*]oxepine, which are the core structures of numerous natural products and pharmaceuticals such as (+)-angelmarin,[3] (+)-rutamarin,[4] (*R*,*S*,*S*,*S*)-(−)-nebivolol,[5] and (+)-heliannuol D[6] (Scheme 1), have not been accessed by means of catalytic enantioselective intramolecular C–O bond formation reactions. Recently, we developed a highly efficient transition-metal-catalyzed asymmetric O–H bond insertion reaction that provides a powerful method for the enantioselective construction of C–O bonds.[7] Herein, we report a copper-catalyzed enantioselective intramolecular insertion of carbenoids into phenolic O–H bonds as a novel strategy for the synthesis of chiral 2-carboxy dihydrobenzofurans, dihydrobenzopyrans, and tetrahydrobenzo[*b*]-oxepines. The method affords high yields (86–99%) and excellent enantioselectivities (94–99% *ee*), proceeds under mild and neutral conditions, and affords cyclic ethers with 5- to 7-membered rings.[8]



Scheme 1. Representative biologically active compounds derived from chiral 2-carboxy dihydrobenzofuran, dihydrobenzopyran, and tetrahydrobenzo[*b*]oxepine.

We began our study with intramolecular insertion into the phenolic O–H bond of methyl 2-diazo-3-(2-hydroxyphenyl)-propanoate (**2a**) catalyzed by a chiral copper catalyst prepared in situ from copper chloride, ligand (S_a,*S*,*S*)-**1a**, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) (Table 1, entry 1). The reaction was complete within 5 min and afforded 2-methoxycarbonyl 2,3-dihydrobenzofuran (**3a**) in 69% yield with 70% *ee*. To improve the catalyst reactivity and enantioselectivity, we evaluated a variety of copper salts as catalyst precursors (Table 1, entries 1–7). All the tested catalysts promoted the reaction of **2a** to afford desired product **3a**, with $[Cu(MeCN)_4]PF_6$ giving the highest enantioselectivity (97% *ee*, entry 4). The corresponding chiral iron complex, an efficient catalyst for the enantioselective intermolecular O–H bond insertion of alcohols and water,[7d] can also promote the present reaction albeit with medium yield and enantioselectivity (45% and 78% *ee*, Table 1, entry 8). Various spiro bisoxazoline ligands were then compared. The use of ligand (R_a,*S*,*S*)-**1a** substantially reduced the reaction rate and enantioselectivity (compare entries 9 and 4 in Table 1), thereby implying that the combination of its chiral components was mismatched. Ligands (S_a,*S*,*S*)-**1b**–**1d** exhibited essentially the same yields and enantioselectivities (91–97% and 96% ee; Table 1, entries 10–12) as (S_a,*S*,*S*)-**1a**; only ligand (S_a,*S*,*S*)-**1e**, with its bulky *tert*-butyl groups, showed substantially low yield and enantioselectivity. These results indicate that the substituents on the oxazoline rings of the ligand had a negligible influence on the reactivity and enantioselectivity of the catalyst. To verify this conclusion, we tested unsubstituted ligand (S_a)-**1f** and found that it afforded **3a** in 98% yield with 98% *ee* (Table 1, entry 14), which demonstrates that the spiro backbone of the ligand was crucial for chiral induction. We next evaluated the effects of various solvents on the reaction. Dichloromethane, chloroform, 1,2-dichloroethane, and toluene were all suitable (Table 1, entries 15–17), whereas the polar, coordinating solvent acetonitrile markedly slowed the reaction and eliminated the enantioselectivity (entry 18). The catalyst was so

[*] X.-G. Song, Prof. S.-F. Zhu, X.-L. Xie, Prof. Q.-L. Zhou
State Key Laboratory and Institute of Elemento-organic Chemistry
Nankai University
Tianjin 300071 (China)
E-mail: qlzhou@nankai.edu.cn
Homepage: http://zhou.nankai.edu.cn

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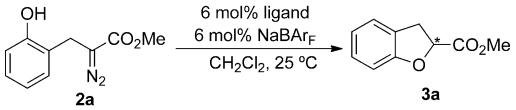
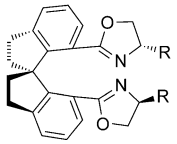
Table 1: Copper-catalyzed asymmetric intramolecular phenolic O–H insertion of **2a**: Optimization of reaction conditions.[a]





(S_a,*S*,*S*)-**1a**: R = Ph
(S_a,*S*,*S*)-**1b**: R = Me
(S_a,*S*,*S*)-**1c**: R = Bn
(S_a,*S*,*S*)-**1d**: R = *i*Pr
(S_a,*S*,*S*)-**1e**: R = *t*Bu
(S_a)-**1f**: R = H

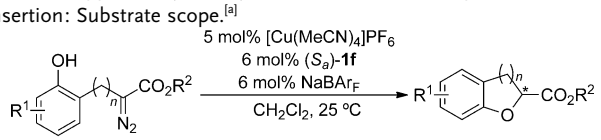
Entry	[Cu]	Ligand	Solvent	*t*	Yield [%][b]	*ee* [%][c]
1	CuCl	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	5 min	69	70
2	CuCN	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	10 h	80	36
3	CuOTf·$^1/_2$ toluene	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	5 min	92	95
4	[Cu(MeCN)$_4$]PF$_6$	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	5 min	84	97
5	$CuCl_2$	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	3 h	80	91
6	Cu(OTf)$_2$	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	1 min	74	92
7	$CuSO_4$	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	6 h	79	36
8	$FeCl_2$	(S_a,*S*,*S*)-**1a**	CH_2Cl_2	24 h	45	78
9	[Cu(MeCN)$_4$]PF$_6$	(R_a,*S*,*S*)-**1a**	CH_2Cl_2	30 min	94	49
10	[Cu(MeCN)$_4$]PF$_6$	(S_a,*S*,*S*)-**1b**	CH_2Cl_2	5 min	97	96
11	[Cu(MeCN)$_4$]PF$_6$	(S_a,*S*,*S*)-**1c**	CH_2Cl_2	20 min	91	96
12	[Cu(MeCN)$_4$]PF$_6$	(S_a,*S*,*S*)-**1d**	CH_2Cl_2	15 min	93	96
13	[Cu(MeCN)$_4$]PF$_6$	(S_a,*S*,*S*)-**1e**	CH_2Cl_2	36 h	80	61
14	[Cu(MeCN)$_4$]PF$_6$	(S_a)-**1f**	CH_2Cl_2	5 min	98	98
15	[Cu(MeCN)$_4$]PF$_6$	(S_a)-**1f**	$CHCl_3$	5 min	84	95
16	[Cu(MeCN)$_4$]PF$_6$	(S_a)-**1f**	DCE	5 min	98	95
17	[Cu(MeCN)$_4$]PF$_6$	(S_a)-**1f**	toluene	5 min	76	94
18	[Cu(MeCN)$_4$]PF$_6$	(S_a)-**1f**	MeCN	24 h	53	rac
19[d]	[Cu(MeCN)$_4$]PF$_6$	(S_a)-**1f**	CH_2Cl_2	5 min	95	96

[a] Reaction conditions: [Cu]/ligand/NaBAr$_F$/**2a** = 0.02:0.024:0.024:0.4 mmol, in 4 mL CH_2Cl_2 at 25 °C. DCE = 1,2-dichloroethane. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralcel OD-H column. [d] Using 1 mol% catalyst.

active that the reaction could be carried out at a catalyst loading of 1 mol% without diminishing the yield or enantioselectivity (Table 1, entry 19).

Under the optimal reaction conditions, we explored the substrate scope of the intramolecular phenolic O–H bond insertion (Table 2). The variation of the ester groups had a negligible influence on the reactivity and enantioselectivity of the reaction (Table 2, entries 1–3). The steric and electronic properties of the substituents on the benzene ring of diazoesters **2** slightly affected both the reactivity and enantioselectivity of reaction. With diazoesters **2d**–**2l**, the reactions were complete within 5 min and afforded the desired dihydrobenzofuran products in good yields (86–99%) with excellent enantioselectivities (94–99% *ee*, Table 2, entries 4–12). The reaction could be extended to the syntheses of chiral dihydrobenzopyrans and even chiral tetrahydrobenzo[*b*]oxepines; however the Cu-(S_a,*S*,*S*)-**1a** became the catalyst of choice. When using this catalyst, the intramolecular phenolic O–H insertions of diazo compounds **2m**, **2n**, and **2o** were accomplished under mild reaction conditions to afford the chiral dihydrobenzopyrans **3m** and **3n**, and tetrahydrobenzo[*b*]oxepine **3o** in high yields with excellent enantioselectivities (Table 2, entries 13–15). These results demonstrate that

Table 2: Copper-catalyzed asymmetric intramolecular phenolic O–H insertion: Substrate scope.[a]



n = 1, 2, 3

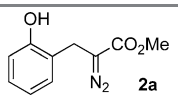
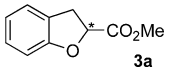
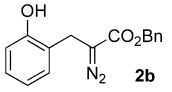
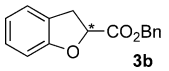
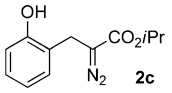
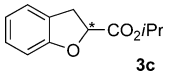
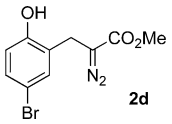
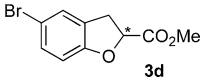
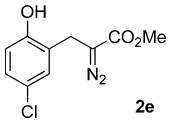
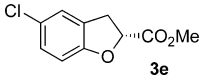
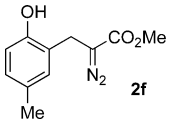
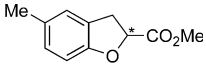
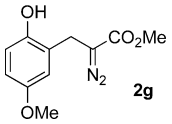
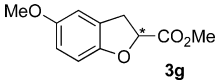
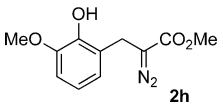
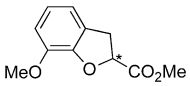
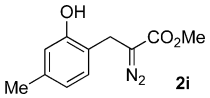
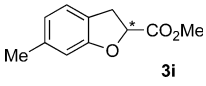
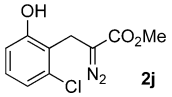
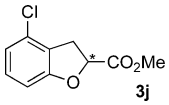
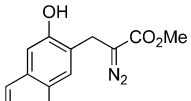
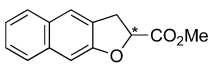
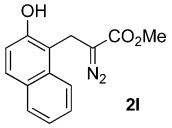
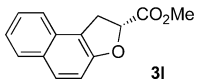
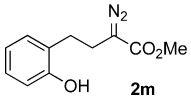
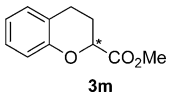
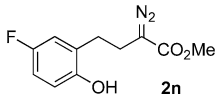
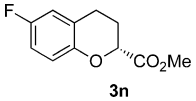
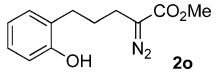
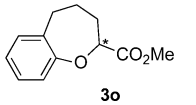
Entry	Diazo compound	Product	Yield [%]	*ee* [%]
1	 **2a**	 **3a**	98	98
2	 **2b**	 **3b**	99	98
3	 **2c**	 **3c**	99	98
4	 **2d**	 **3d**	99	98
5	 **2e**	 **3e**	98	99
6	 **2f**	 **3f**	94	97
7	 **2g**	 **3g**	99	96
8	 **2h**	 **3h**	86	98
9	 **2i**	 **3i**	99	98
10	 **2j**	 **3j**	94	97
11	 **2k**	 **3k**	97	97
12	 **2l**	 **3l**	99	94
13	 **2m**	 **3m**	95 (95)[b]	48 (96)[b]

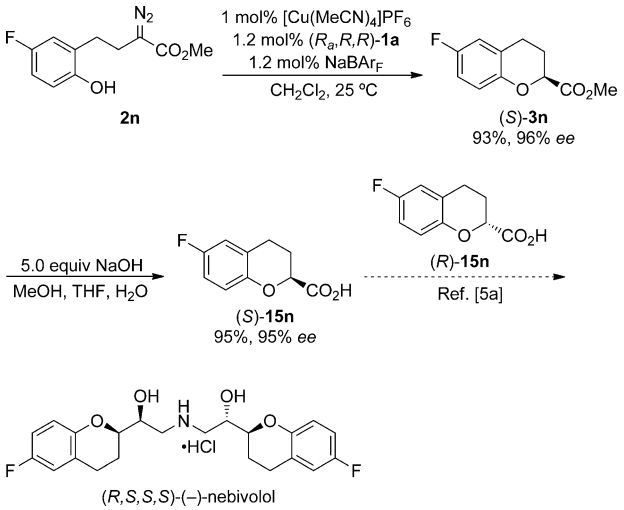
Table 2: (Continued)

Entry	Diazo compound	Product	Yield [%]	*ee* [%]
14	 **2n**	 **3n**	95 (95)[b]	45 (96)[b]
15	 **2o**	 **3o**	95 (99)[b]	98 (99)[b]

[a] The reaction conditions were the same as those in Table 1, entry 14. All the reactions reached full conversion within 5 min. For analyses of products, see the Supporting Information. [b] Using (S_a,*S*,*S*)-**1a**.

the present reaction has a high potential for wide application in the synthesis of chiral benzo hetereocyclic compounds.

To demonstrate the utility of the reaction, we conducted a formal synthesis of (*R*,*S*,*S*,*S*)-(−)-nebivolol, an antihypertensive drug (Scheme 2). We found that two enantiomeric



Scheme 2. Formal synthesis of (*R*,*S*,*S*,*S*)-(−)-nebivolol.

dihydrobenzopyran components could be constructed simply by changing the configuration of the ligand. The intramolecular phenolic O–H bond insertion reaction of diazo compound **2n** catalyzed by (R_a,*R*,*R*)-**1a** or (S_a,*S*,*S*)-**1a** produced chiral dihydrobenzopyran ester (*S*)-**3n** or (*R*)-**3n**, respectively, in excellent yield and enantioselectivity. From (*S*)-**3n** and (*R*)-**3n**, the chiral drug (*R*,*S*,*S*,*S*)-(−)-nebivolol could easily be obtained by using the literature method.

In summary, we have developed a novel, highly enantioselective copper-catalyzed intramolecular phenolic O–H bond insertion reaction, which provides an efficient method for the synthesis of chiral 2-carboxy dihydrobenzofurans, dihydrobenzopyrans, and tetrahydrobenzo[*b*]oxepines. The high reaction rate, high yield, excellent enantioselectivity, and wide substrate scope make this reaction a competitive method for the synthesis of synthetically important chiral benzo heterocycles, and further demonstrate the power of catalytic asymmetric X–H bond insertion reactions in organic synthesis.

Experimental Section

General procedure for intramolecular asymmetric phenolic O–H insertion: $[Cu(MeCN)_4]PF_6$ (7.5 mg, 0.02 mmol, 5 mol%), (S_a)-**1f** (8.6 mg, 0.024 mmol, 6 mol%), and $NaBAr_F$ (22.6 mg, 0.024 mmol, 6 mol%) were combined in an oven-dried Schlenk tube in an argon-filled glovebox. CH_2Cl_2 (3 mL) was injected by using a syringe. After the mixture was stirred at 25 °C for 2 h, diazo compound **2** (0.4 mmol, dissolved in 1 mL of CH_2Cl_2) was added, and the resulting mixture was stirred until **2** was completely consumed, as indicated by TLC. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 8:1), and the *ee* value was determined by HPLC with a chiral column.

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