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Copper-Catalyzed Asymmetric Annulation Reactions of Carbenes with 2-Iminyl- or 2-Acyl-Substituted Phenols: Convenient Access to Enantioenriched 2,3-Dihydrobenzofurans

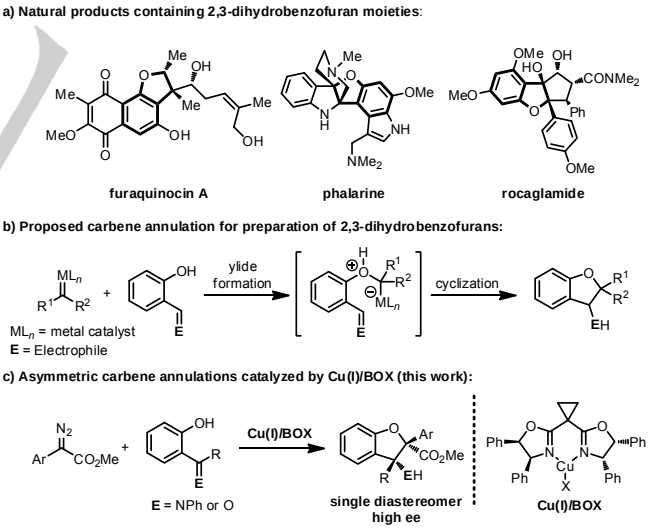
Xin-Shen Liang, Rui-Dong Li, and Xiao-Chen Wang*

Dedicated to the 100th anniversary of Nankai University

Abstract: We have developed a method for highly diastereo- and enantioselective construction of 2,3-dihydrobenzofurans bearing tetrasubstituted carbon stereocenters by means of annulation reactions between carbenes and 2-iminyl- or 2-acyl-substituted phenols with catalysis by readily accessible copper(I)/bisoxazoline catalysts under mild conditions. These reactions feature a unique mechanism in which the copper catalyst serves a dual function: first it reacts with the diazo compound to generate a metal carbene, and second, upon formation of an oxonium ylide, it acts as a Lewis acid to activate the imine or ketone for diastereo- and enantioselective cyclization.

2,3-Dihydrobenzofuran motifs are present in a number of natural products and bioactive compounds,[1] many of which bear a tetrasubstituted carbon stereocenter or two contiguous tetrasubstituted carbon stereocenters (e.g., furaquinocin A,[2] phalarine,[3] and rocaglamide;[4] Scheme 1a). Therefore, the development of methods for diastereo- and enantioselective synthesis of these motifs is of great importance. There are several known methods for asymmetric synthesis of 2,3-dihydrobenzofurans, including [4+1] cycloaddition reactions of quinone methides with a one-carbon synthon,[5] catalytic asymmetric dearomatization reactions of benzofurans,[6] intramolecular carbene C–H insertion reactions of alkylated phenols,[7] and intramolecular Heck reactions of allyl phenyl ethers.[8] However, the synthesis of molecules with tetrasubstituted carbons remains challenging because their steric bulk decreases their reactivity and enantiocontrol is difficult.

Given the versatility of metal carbenes,[9] we envisioned that carbene annulation reactions of phenols bearing an *ortho* electrophile might effectively provide access to 2,3-dihydrobenzofurans (Scheme 1b). In particular, we speculated that reaction of a phenol with a metal carbene would generate an oxonium ylide, which would then intramolecularly attack the electrophile to give a cyclized product, rather than undergoing proton migration to give an O–H insertion product.[9,10] Furthermore, we expected that the use of a chiral catalyst would provide enantioenriched 2,3-dihydrobenzofurans. Although addition of ylides (generated in situ from diazo compounds) to electrophiles has been studied extensively, especially by the Hu group,[11,12] this reaction has never been used for phenol-derived oxonium ylides, probably because of the challenges presented by the competing reaction pathways, such as O–H insertion[10] and electrophilic substitution[13]. Furthermore, most of the asymmetric ylide addition reactions reported to date rely on a Rh(II)/chiral phosphoric acid (or chiral Lewis acid) cooperative catalytic system: Rh(II) effects the formation of the metal carbene, and the chiral acid activates the electrophile and is responsible for the enantiocontrol.[11,12] There have been only a few cases in which enantiocontrol was achieved with a single catalyst.[14,15] Although Cu catalysts have long been known to induce carbene formation and to function as Lewis acids to activate electrophiles, it was only recently that Waser and co-workers achieved the first Cu-catalyzed enantioselective ylide addition to an electrophile, via an oxy-alkynylation reaction of diazo compounds.[15] Herein, we disclose that readily available Cu(I)/bisoxazoline (BOX) complexes can catalyze annulation reactions between aryldiazoacetates and 2-iminyl- or 2-acyl-substituted phenols to give 2,3-dihydrobenzofurans bearing tetrasubstituted carbon stereocenters with excellent diastereomeric ratios and high enantiomeric excesses (Scheme 1c).



Scheme 1. Syntheses of 2,3-dihydrobenzofurans

We began by investigating the reaction of phenyldiazoacetate **1a** with 2-iminyl-substituted phenol **2a** under various conditions (Table 1). When a complex generated from $Cu(CH_3CN)_4PF_6$ and phenyl-BOX ligand **L1** was used as the catalyst (5 mol %), the desired annulation reaction occurred to give 2,3-dihydrobenzofuran **3a** as a single diastereomer in 30% yield with 11% ee (entry 1). Considering that the reaction involves a proton-transfer step, we decided to add an organic base (10 mol %) to serve as a proton shuttle. Although the addition of NEt_3 shut down the reaction (entry 2), presumably because of competitive

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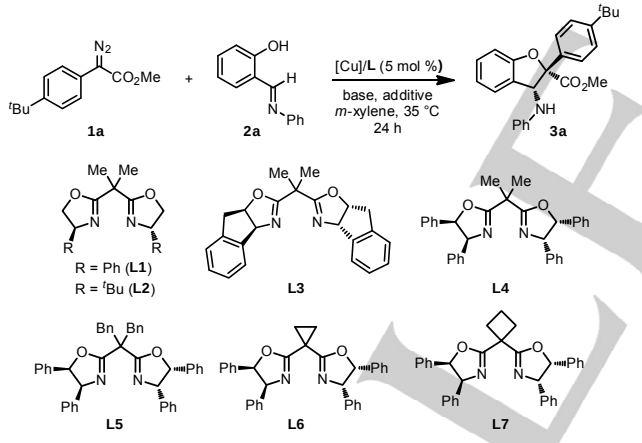
coordination of the base to the Lewis acid catalyst, we were surprised to find that bulkier bases (DIPEA [diisopropylethylamine], DIPA [diisopropylamine], and PMP [1,2,2,6,6-pentamethylpiperidine]) improved both the reactivity and the enantioselectivity (entries 3–5). In fact, when DIPEA was used, the ee reach 75% (entry 3). Next, various BOX ligands were examined in the presence of DIPEA. Although *tert*-butyl-BOX **L2**, indane-BOX **L3**, and diphenyl-BOX ligands **L4** and **L5** failed to further improve the enantioselectivity (entries 6–9), cyclopropane-derived diphenyl-BOX **L6** increased the ee to 86% (entry 10). Cyclobutane-derived analog **L7** was less enantioselective than **L6** (82% ee, entry 11). Gratifyingly, screening of various additives revealed that addition of a catalytic amount of sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate (NaBARF, 6 mol %) markedly improved the yield (to 70%) and the enantioselectivity (to 92% ee) (entry 12). Because NaBARF is very hygroscopic, we added activated 4Å molecular sieves to scavenge water; and we added 15-crown-5 to help solubilize the sodium salt in the organic phase.[16] Finally, evaluation of different Cu sources revealed CuCl to be optimal: under these conditions, **3a** was obtained in 94% yield with 92% ee (entry 15). It is worth mentioning that we separately prepared the product of an O–H insertion reaction between **1a** and **2a** and subjected it to the optimal conditions for the annulation reaction, but no formation of **3a** was observed (See the supporting information). This result rules out the possibility that our reaction occurred via a cascade process involving O–H insertion and a Mannich reaction.

Table 1. Optimization of reaction conditions[a]

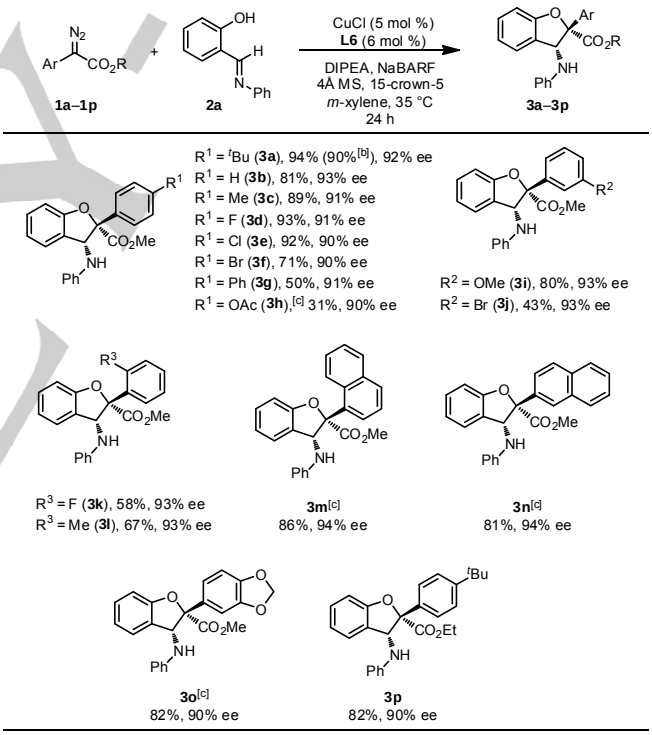


entry	[Cu]	L	base	additive	yield (%)[b]	ee (%)[c]
1	$Cu(CH_3CN)_4PF_6$	**L1**	none	none	30	11
2	$Cu(CH_3CN)_4PF_6$	**L1**	NEt_3	none	trace	n.a.
3	$Cu(CH_3CN)_4PF_6$	**L1**	DIPEA	none	47	75
4	$Cu(CH_3CN)_4PF_6$	**L1**	DIPA	none	45	52
5	$Cu(CH_3CN)_4PF_6$	**L1**	PMP	none	52	53
6	$Cu(CH_3CN)_4PF_6$	**L2**	DIPEA	none	20	0
7	$Cu(CH_3CN)_4PF_6$	**L3**	DIPEA	none	17	13
8	$Cu(CH_3CN)_4PF_6$	**L4**	DIPEA	none	27	74
9	$Cu(CH_3CN)_4PF_6$	**L5**	DIPEA	none	32	50
10	$Cu(CH_3CN)_4PF_6$	**L6**	DIPEA	none	37	86
11	$Cu(CH_3CN)_4PF_6$	**L7**	DIPEA	none	40	82
12[d]	$Cu(CH_3CN)_4PF_6$	**L6**	DIPEA	NaBARF	70	92
13[d]	CuOTf	**L6**	DIPEA	NaBARF	77	90
14[d]	$Cu(OTf)_2$	**L6**	DIPEA	NaBARF	70	92
15[d]	CuCl	**L6**	DIPEA	NaBARF	94	92

[a] Unless otherwise specified, all reactions were performed with 0.15 mmol of **1a**, 0.1 mmol of **2a**, 0.005 mmol of [Cu], 0.006 mmol of **L**, and 0.01 mmol of a base in 1 mL of *m*-xylene. [b] Isolated yields. [c] Determined by HPLC with a Chiralcel OD-H column; n.a., not applicable. [d] NaBARF (6 mol %), 15-crown-5 (6 mol %), and activated 4Å molecular sieves (30 mg) were added.

With the optimal conditions for the annulation reaction in hand, we explored its generality by first carrying out reactions of various aryldiazoacetates with 2-iminyl-substituted phenol **2a** (Table 2). Phenyldiazoacetates with an electron-donating or electron-withdrawing group at the *para* position of the phenyl ring were tolerated, giving the corresponding products (**3a**–**3h**) in 31–94% yields with 90–92% ee values. *Meta*- and *ortho*-substituted phenyldiazoacetates also afforded the desired products (**3i**–**3l**) with high ee values. Reactions of 1-napthyl- and 2-naphyldiazoacetates and a benzodioxole-derived diazo compound (**3m**–**3o**) proceeded in high yields with high enantioselectivities. Furthermore, the methyl ester could be changed to an ethyl ester (**3p**). Moreover, we performed the gram-scale reaction of **1a** with **2a** (for details, see the supporting information), and product **3a** was obtained in 90% yield and 92% ee. Therefore, this reaction can be scaled up.

Table 2. Scope of the annulation reaction with respect to the diazo compound[a]



[a] Unless otherwise specified, all reactions were performed with 0.15 mmol of the diazo compound, 0.1 mmol of **2a**, 5 mol % of CuCl, 6 mol % of **L6**, 10 mol % of DIPEA, 6 mol % of NaBARF, 6 mol % of 15-crown-5, and 30 mg of activated 4Å molecular sieves in 1 mL of *m*-xylene. [b] Performed at gram-scale. [c] Performed at 20 °C.

Next we evaluated the scope of the reaction with respect to the phenol (Table 3). First, we explored the effect of the substituent on the phenolic ring. Electron-donating and electron-withdrawing groups were tolerated at the *para* position (**4b**–**4g**) and the *meta* position (**4h**–**4j**); yields were moderate to high, and ee values ranged from 88% to 96%. Reactions of substrates with electron-rich heteroaromatic substituents (3-furyl [**4k**] and 2-thienyl [**4l**]) proceeded via the same pathway despite the possibility of side

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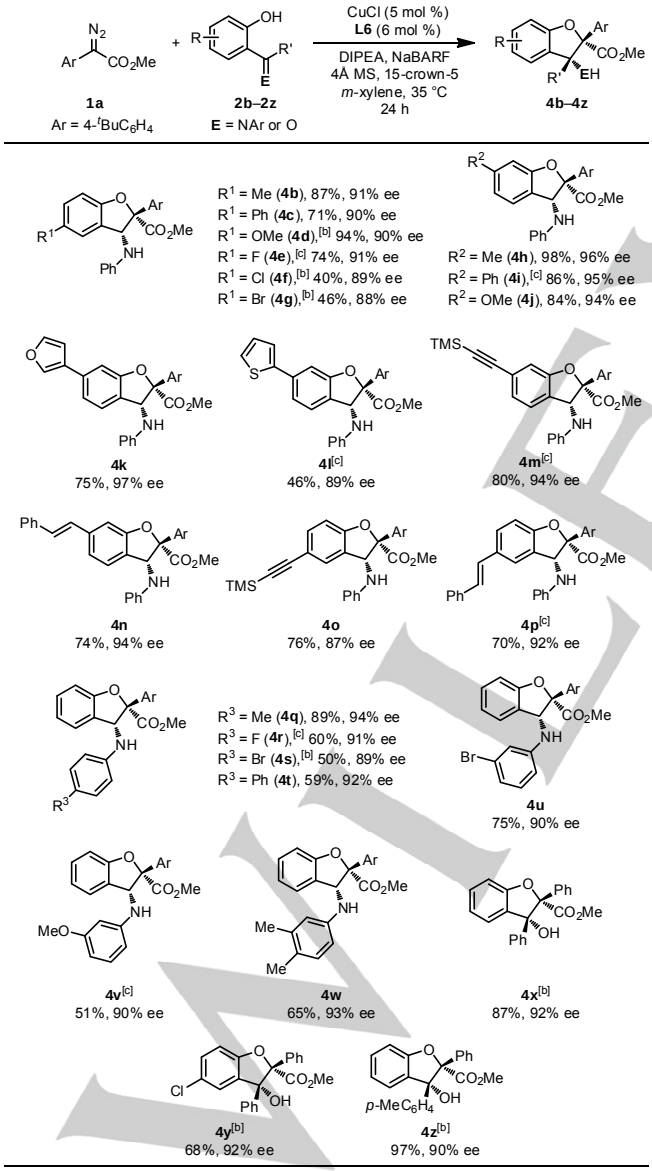
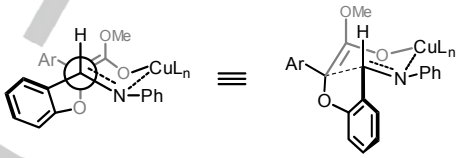
reactions between the heteroarene and the diazo compound, such as Friedel–Crafts or cyclopropanation reactions. Furthermore, alkene or alkyne substituents on the phenolic ring (**4m**–**4p**) did not undergo cyclopropanation or cyclopropenation reactions. The tolerance for these functional groups clearly indicates that this annulation protocol offers opportunities for preparing compounds that can be elaborated further. Iminyl substituents were subsequently examined. Again, electron-donating and electron-withdrawing groups on the *N*-phenyl ring were compatible with the reaction conditions, providing products **4q**–**4w** with high enantioselectivities. Notably, this process was not limited to 2-iminyl phenols. Ketones could also be used as electrophiles; these reactions produced highly enantioenriched 3-hydroxy-substituted 2,3-dihydrobenzofurans (**4x**–**4z**) bearing two contiguous tetrasubstituted carbon stereocenters. The absolute configurations of products **4d** and **4y** were determined to be (2*S*,3*R*) by X-ray analysis of single crystals.[17]

Table 3. Scope of the annulation reaction with respect to the phenol[a]



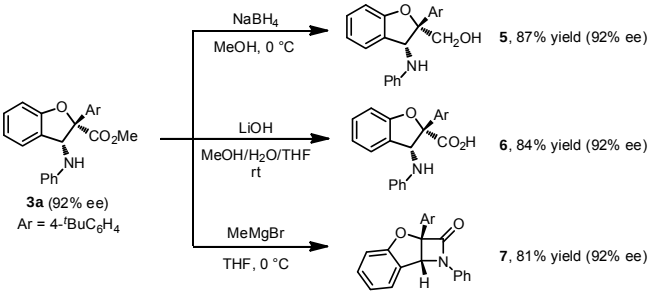
[a] Unless otherwise specified, all reactions were performed with 0.15 mmol of the diazo compound, 0.1 mmol of **2a**, 5 mol % of CuCl, 6 mol % of **L6**, 10 mol % of DIPEA, 6 mol % of NaBARF, 6 mol % of 15-crown-5, and 30 mg of activated 4Å molecular sieves in 1 mL of *m*-xylene. [b] Performed at 20 °C. [c] Performed at 30 °C.

Notably, even though all these reactions formed two stereocenters, they exclusively gave a single diastereomer with the ester and the amine (or the hydroxy group) on the same face of the dihydrobenzofuran ring. To account for the excellent diastereoselectivity of the cyclization step, we propose the transition-state model shown in Scheme 2. Because previous computational studies have demonstrated that Cu(I) catalysts bind to oxonium ylides more strongly than Rh(II) catalysts, thus favoring reactions via a metal-associated ylide rather than via a free ylide,[18] in this model, the Cu catalyst coordinates to both the oxygen atom of the enolate and the nitrogen atom of the imine; and the complex adopts a pseudo chair conformation in which steric repulsion is minimized because all the aryl groups are at equatorial positions. The excellent activity and stereoselectivity showcases the power of the bifunctional Cu/BOX catalyst, which not only reacts with the diazo compound for carbene formation, but also acts as a Lewis acid to activate the electrophile and govern the stereoselectivity.



Scheme 2. Proposed transition state for the cyclization step

To further demonstrate the utility of this annulation method, we carried out several transformations of cyclization product **3a** (Scheme 3). Treatment with $NaBH_4$ reduced the ester group to a hydroxyl group, yielding product **5**. Hydrolysis of the ester with LiOH as the base gave carboxylic acid **6**. Finally, addition of a methyl Grignard reagent as a base delivered azetidinone-fused dihydrobenzofuran **7**. Notably, all these reactions occurred in high yields with retention of the enantiomeric purity.



Scheme 3. Transformations of **3a**.

In conclusion, we have developed a protocol for asymmetric annulation reactions of aryldiazoacetates with *2*-iminyl or 2-acyl-substituted phenols catalyzed by Cu/BOX complexes to afford enantioenriched 2,3-dihydrobenzofurans bearing tetrasubstituted carbon stereocenters. This reaction uses readily available catalysts and mild conditions and shows broad functional group tolerance and excellent diastereo- and enantioselectivities. Furthermore, the bifunctional Cu/BOX catalysts are complementary to the existing cooperative catalytic systems comprising Rh(II) and a chiral phosphoric acid (or a chiral Lewis acid) for asymmetric ylide addition reactions. Currently, we are

investigating new asymmetric ylide transformations with the catalytic system reported herein.

Acknowledgements

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Keywords: carbene • asymmetric catalysis • cyclization • oxonium ylide • dihydrobenzofuran

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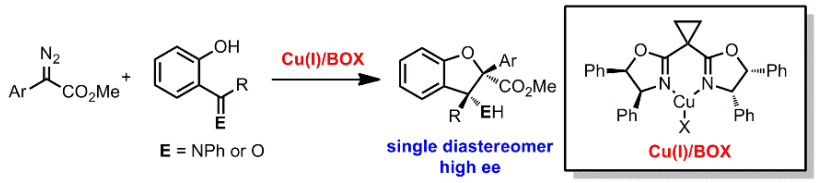

A Cu-catalyzed enantioselective annulation reaction of aryldiazoacetates with 2-iminyl- or 2-acyl-substituted phenols has been developed to prepare enantioenriched 2,3-dihydrobenzofurans. In this reaction, the Cu catalyst first induces carbene formation, and then functions as a Lewis acid to activate the electrophile and control the diastereo- and enantioselectivity.

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