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Facile synthesis of chiral [2,3]-fused hydrobenzofuran *via* asymmetric Cu(I)-catalyzed dearomative 1,3-dipolar cycloaddition†

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Intermolecular asymmetric dearomative 1,3-dipolar cycloaddition of 2-nitrobenzofurans with azomethine ylides was enabled by using a chiral Cu(I)/(S,S_p)-^{i}Pr-Phosferrox catalyst. As a result, a series of highly stereoselective chiral [2,3]-fused hydrobenzofurans possessing four contiguous stereogenic centers were obtained with good to high yields, diastereoselectivities and enantioselectivities. The reaction has broad substrate scope tolerating various functional groups.

The fused polycyclic hydrobenzofurans are naturally prevalent molecules, some of which exhibit a broad range of biological activities.[1] For example (Fig. 1), rocaglamide is a naturally occurring complex molecule that possesses a tricyclic hydrobenzofuran scaffold and exhibits potent anticancer, anti-inflammatory and neuroprotective activities.[2] (+)-Gynunone isolated from the roots of *Gynura elliptica* possesses anti-platelet aggregation activity.[3] As a member of the [2,3]-fused hydrobenzofurans, CID755673, which was found in a marine sponge, contains a benzofuro[2,3-*c*]azepin core and is a highly selective protein kinase inhibitor.[4] Moreover, azonazine, a novel dipeptide from *Aspergillus insulicola*, exhibits anti-inflammatory activity by inhibiting NF-kB luciferase and nitrite production.[5] In this context, the exploration of an efficient synthesis route for constructing this type of scaffold can be highly valuable.

The catalytic asymmetric dearomatization (CADA) reactions have emerged as a powerful tool for the rapid assembly of enantio-enriched three-dimensional polycyclic molecules from readily available aromatic substrates.[6] The dearomatization of electron-rich arenes (naphthol, indole, pyrrole, *etc.*) has been successfully developed based on their inherent nucleophilicity.[7]

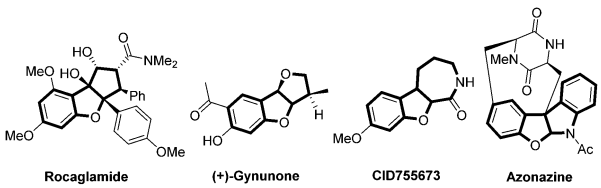

Fig. 1 Representative examples of natural products containing fused polycyclic hydrobenzofuran scaffolds.

On the contrary, studies on the dearomatization of electron-deficient arenes as electrophiles remain relatively scarce.[8,9] Recently, several dearomatization reactions based on the electrophilicity of nitro-substituted arenes were reported. In 2017, You and co-workers[9a] developed a method for the straightforward construction of chiral tetrahydrofurobenzofurans *via* palladium-catalyzed dearomative [3+2] cycloaddition of nitrobenzofurans with epoxybutene. Later, Yuan and co-workers[9b] reported the CADA reaction of nitrobenzofurans with 3-isothiocyanato oxindoles by using bis(oxazoline)/Zn(OTf)$_2$ as a catalyst (Scheme 1A). Despite this elegant progress, the one-step construction of chiral hydrobenzofuran molecules containing multiple chiral centers and functional groups remains a challenging task. In recent years, catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with electron deficient C=C bonds has provided a direct route to highly substituted pyrrolidines with multiple stereogenic centers.[10] However, the merging of CADA reaction with cycloaddition of azomethine ylides to construct chiral-fused polycyclic compounds is rare.[8h] Herein, we report the straightforward construction of new chiral core structures of hydrobenzofuran enabled by copper-catalyzed asymmetric dearomative 1,3-dipolar cycloaddition of 2-nitrobenzofurans with azomethine ylides (Scheme 1B).

Initially, we investigated the 1,3-dipolar reaction of 2-nitrobenzofuran **1a** with *N*-benzylidene glycine methyl ester **2a** by using Cs_2CO_3 as the base in MTBE and Cu(MeCN)$_4$ClO$_4$/*rac*-BINAP-**L1** complex as the catalyst at 0 °C. Gratifyingly, the reaction proceeded well, delivering the desired racemic dearomatized

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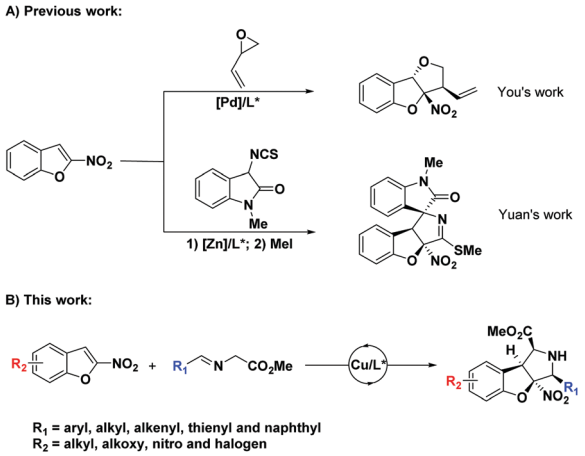
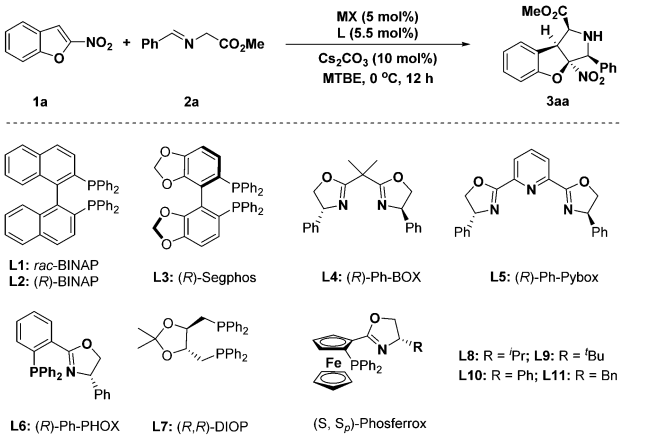


Scheme 1 Different synthetic routes to chiral [2,3]-fused hydrobenzofuran compounds.

Table 1 Optimization of reaction conditions[a]



Entry	MX	L	Yield[b] (%)	dr[c]	ee[d] (%)
1	$Cu(MeCN)_4ClO_4$	**L1**	73	8 : 1	
2	$Cu(MeCN)_4ClO_4$	**L2**	75	8 : 1	23
3	$Cu(MeCN)_4ClO_4$	**L3**	69	10 : 1	45
4	$Cu(MeCN)_4ClO_4$	**L4**	63	9 : 1	5
5	$Cu(MeCN)_4ClO_4$	**L5**	55	8 : 1	3
6	$Cu(MeCN)_4ClO_4$	**L6**	80	9 : 1	53
7	$Cu(MeCN)_4ClO_4$	**L7**	63	7 : 1	56
8	$Cu(MeCN)_4ClO_4$	**L8**	83	9 : 1	98
9	$Cu(MeCN)_4ClO_4$	**L9**	76	8 : 1	83
10	$Cu(MeCN)_4ClO_4$	**L10**	80	9 : 1	89
11	$Cu(MeCN)_4ClO_4$	**L11**	81	7 : 1	78
12	CuCl	**L8**	65	6 : 1	93
13	$Cu(OTf)_2$	**L8**	77	7 : 1	91
14	$AgCO_2CF_3$	**L8**	21	1 : 3	92

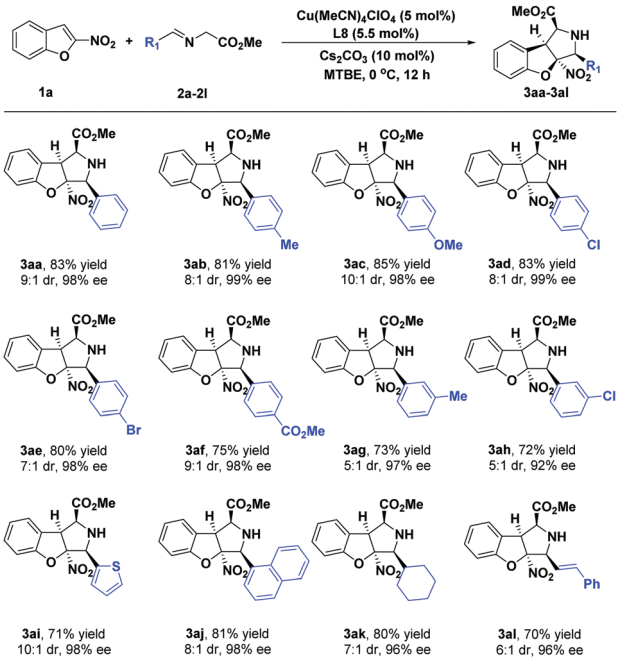
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Cu(MeCN)_4ClO_4$ (5 mol%), **L** (5.5 mol%) and Cs_2CO_3 (10 mol%) in MTBE (2.0 mL), 0 °C, N_2, 12 h. [b] Yields of isolated product. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis.

product **3aa** with a moderate yield (Table 1, entry 1). With such an effective method for synthesizing racemic products, we then turned our attention to chiral ligands (entries 2–11). The axially chiral bidentate phosphine ligands including (*R*)-BINAP-**L2** and (*R*)-segphos-**L3** were first examined. The cycloaddition proceeded well, resulting in **3aa** as a major product with good yield, however, with poor-to-moderate enantioselectivities (Table 1, entries 2 and 3). The enantioselectivity of this reaction was further improved by screening different types of commercially available chiral ligands, such as (*R*)-Ph-BOX-**L4**, (*R*)-Ph-pybox-**L5**, (*R*)-Ph-PHOX-**L6**, (*R*,*R*)-DIOP-**L7** and a series of phosferrox ligands **L8–L11** (entries 4–13). As shown in Table 1, **L4–L5** led to poor enantioselectivities (entries 4 and 5). When (*R*)-Ph-PHOX-**L6** and (*R*,*R*)-DIOP-**L7** were used as ligands, the chiral cycloaddition product was obtained with moderate results (entries 6 and 7). We further focused on the screening of phosferrox ligands with different substituents, among which, the (S,S_p)-^{i}Pr-phosferrox-**L8** was the most promising ligand, generating the desired product **3aa** with 82% yield, 98% ee and 9 : 1 dr (entries 8–11). In the presence of (S,S_p)-^{i}Pr-phosferrox-**L8**, the catalyst $Cu(MeCN)_4ClO_4$ was changed to CuCl, $Cu(OTf)_2$ and $AgCO_2CF_3$. These central metals failed to further improve the enantioselectivity or diastereoselectivity under identical reaction conditions (entries 12–14). Furthermore, the screening of other solvents and bases also did not show better results (see Table S1, ESI†).

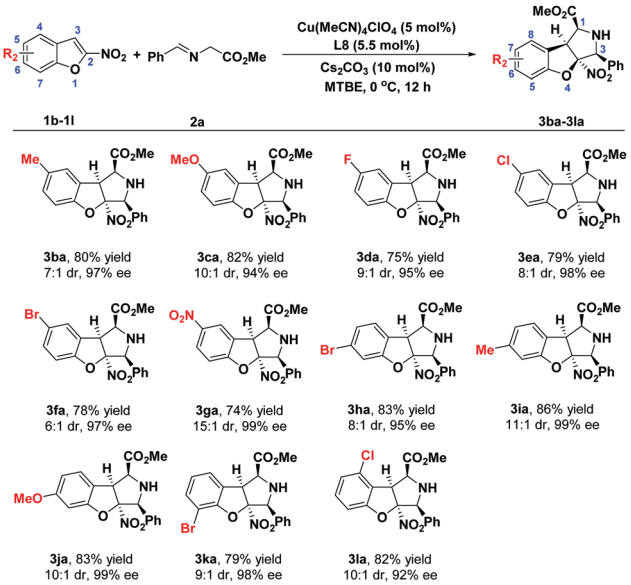
Finally, the optimal reaction conditions were obtained as follows: 5 mol% of $Cu(MeCN)_4ClO_4$, 5.5 mol% of **L8** and 10 mol% of Cs_2CO_3 in MTBE at 0 °C (entry 8).

Under the optimal reaction conditions, various azomethine ylide precursors, α-iminoesters **2a–2l**, were tested by reacting with 2-nitrobenzofuran **1a** using the asymmetric dearomative [3+2] reaction (Scheme 2). The effect of the group at the *para* position of the benzene ring (**3ab–3af**) was firstly investigated. Both the electron-rich and electron-deficient substituents were well tolerated and led to the corresponding adducts with good yields (75–85%) and dr values (up to 10 : 1 dr), and excellent ee values (98–99%). The reaction proceeded smoothly with α-iminoesters containing an aryl ring with *meta* substituents (**2g**, **2h**), generating the desired products with good yields and diastereoselectivities, and excellent enantioselectivities (up to 73% yield, 5 : 1 dr and 97% ee). Moreover, the 2-thienyl- and 2-naphthyl-substituted α-iminoesters (**2i** and **2j**) also delivered the corresponding compounds **3ai** and **3aj** with good results. Delightfully, α-iminoester **2k** derived from an aliphatic aldehyde and α-iminoester **2l** with an alkenyl substituent were also successfully employed under the same reaction conditions, and the targeted chiral [2,3]-fused benzofuranpyrrolidines **3ak** and **3al** were obtained with excellent enantioselectivities (up to 96% ee).

Subsequently, we focused on the groups on the benzofuran ring. A wider variety of nitrobenzofurans were prepared and evaluated (Scheme 3). The reaction proceeded smoothly with *N*-benzylidene glycine methyl ester **2a**, furnishing the respective cycloadducts with excellent results (**3ba–3la**). Substrates bearing various substituents, either with electron-withdrawing or electron-donating groups, at the 5 position (**1b–1g**) led to the corresponding dearomatized products with good yields (74–82%) and diastereoselectivities (6 : 1–15 : 1 dr), and excellent enantioselectivities (94–99% ee). A similar trend was also observed when substituting at the 6 or 7 position (Br, Me, MeO) (**3ha–3ka**). Notably, the highest enantioselectivities were observed in 5-nitro, 6-methyl or 6-methoxy nitrobenzofuran (**1g**, **1i** and **1j**). Furthermore, 4-chloro



Scheme 2 Substrate scope for azomethine ylides. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Cu(MeCN)_4ClO_4$ (5 mol%), **L8** (5.5 mol%) and Cs_2CO_3 (10 mol%) in MTBE (2.0 mL), 0 °C, N_2, 12 h. Yields of isolated product. The dr ratios were determined by ^1H NMR analysis of the crude mixture. The ee values were determined by chiral HPLC analysis.



Scheme 3 Substrate scope for variously functionalized 2-nitrobenzofurans. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Cu(MeCN)_4ClO_4$ (5 mol%), **L8** (5.5 mol%) and Cs_2CO_3 (10 mol%) in MTBE (2.0 mL), 0 °C, N_2, 12 h. Yields of isolated product. The dr ratios were determined by ^1H NMR analysis of the crude mixture. The ee values were determined by chiral HPLC analysis.

nitrobenzofuran was employed under the same reaction conditions, and the reaction proceeded to deliver the chiral tricyclic product **3la** with good results, but with slightly lower enantioselectivity (92% ee).

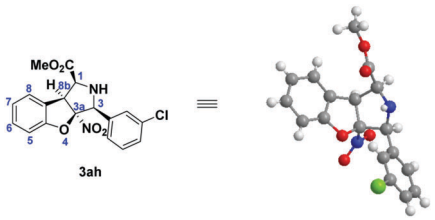
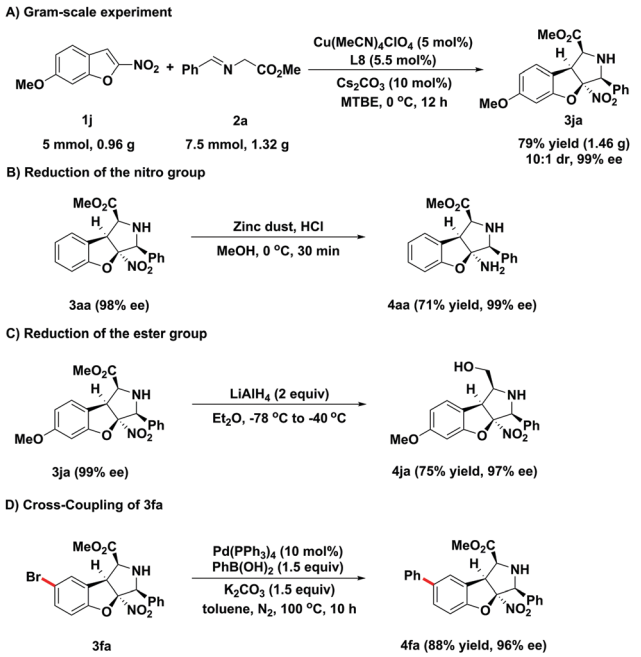


Fig. 2 The absolute configuration of the cycloadduct **3ah**.



Scheme 4 Gram-scale synthesis and transformation.

The absolute configuration of [2,3]-fused benzofuranpyrrolidine product **3ah** (Fig. 2), determined by single-crystal X-ray diffraction analysis, was unambiguously found to be (1*S*,3*S*,3*aS*,8*bS*).

To further explore the prospective use of this methodology, the gram-scale synthesis of [2,3]-fused benzofuranpyrrolidine was carried out. As shown in Scheme 4A, **3ja** was obtained, with 79% yield, 10 : 1 dr, and 99% ee, by treating 5.0 mmol 2-nitro-6-methoxy-benzofuran **1j** with *N*-benzylidene glycine methyl ester **2a** in the presences of 5 mol% $Cu(MeCN)_4ClO_4$ and 5.5 mol% (S,S_p)-^{i}Pr-Phosferrox-**L8**. The transformations of [2,3]-fused benzofuranpyrrolidine products were carried out. Firstly, zinc dust in a methanolic hydrogen chloride solution was used to reduce the nitro group to the respective amine **4aa** (Scheme 4B). After that, the ester group was selectively reduced using $LiAlH_4$ (2 equiv.) as a reducing agent, and the corresponding product containing a hydroxyl group **4ja** was obtained with good results (Scheme 4C). Additionally, the phenyl group was attached to the aromatic ring *via* the Suzuki–Miyaura cross coupling of **3fa** with phenylboronic acid, and 5-phenyl substituted nitrobenzofuranpyrrolidine **4fa** was obtained with 88% yield and 95% ee (Scheme 4D).

In summary, we successfully developed a highly enantioselective dearomative 1,3-dipolar cycloaddition reaction of nirtobenzofurans with iminoesters. Using Cu(I)/^{i}Pr-phosferrox complex

as the catalyst, a wide range of [2,3]-fused benzofuranpyrrolidines bearing nitro groups on the chiral tetrasubstituted carbon center were obtained with moderate to high yields, diastereoselectivities and enantioselectivities (up to 86% yields, 11 : 1 dr and 99% ee). The reaction features a general scope for both azomethine ylides and nitrobenzofurans. This work provides a facile synthesis strategy for the construction of a highly substituted chiral tricyclic hydrobenzofuran scaffold.

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Conflicts of interest

There are no conflicts to declare.

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