

Enantioselective Construction of 2-Aryl-2,3-dihydrobenzofuran Scaffolds Using Cu/SPDO-Catalyzed [3 + 2] Cycloaddition

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natural corsifurans A and B from commercially available starting materials has also been achieved in two or three steps using this reaction as a key transformation.

C hiral 2-aryl-2,3-dihydrobenzofuran scaffolds are widely found in many bioactive natural products and drugs (Figure 1).¹ Due to their outstanding potential properties in

broad substrate tolerance. Additionally, asymmetric synthesis of



Figure 1. Selected biologically active compounds bearing 2-aryl-2,3dihydrobenzofuran core.

functionalized molecules, the preparation of scaffolds in a diastereo- and enantioselective manner has attracted the attention of synthetic communities; consequently, some synthetic strategies have been developed in the past decade.² Representative approaches include Ru/NHC-catalyzed asymmetric hydrogenation developed by Glorius,³ Rh/Davies's catalyst-catalyzed asymmetric C–H insertion reactions by Shaw and others,⁴ Cu/BOX-catalyzed asymmetric O–H insertion/annulation by Wang,⁵ a boron-catalyzed cyclopropanation/intramolecular rearrangement sequence by Ryu,⁶ Pd/py-Box-catalyzed oxy-Heck–Matsuda arylations by Correia,⁷ and chiral phosphoric acid catalyzed formal [3 + 2] cycloaddition by Zhou (Scheme 1a).⁸ However, these developed synthetic methods have some disadvantages, such as multistep manipulation to prepare intramolecular reaction





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substrates, use of noble metal catalysts (Pd, Rh, etc.), narrow substrate scope, and unsatisfactory enantioselectivities.

At the same time, as one of the most valuable commodity chemicals in the chemical industry, styrene and its derivatives have served as important synthetic starting materials, and the functionalization of styrene has become a hot research topic in recent years, especially its asymmetric difunctionalization of double bonds to construct two vicinal stereocenters. However, asymmetric [3 + 2] cycloadditions involving styrene to construct the above-mentioned 2-aryl-2,3-dihydrobenzofuran core have rarely been explored. To the best of our knowledge, only two relative formal transformations have been independently reported, namely, those by Correia⁷ and Zhou.⁸ Unfortunately, poor enantioselectivity was observed in the former report (up to 76% ee), and a narrow scope of substrates (i.e., only suitable for 1-styrylnaphthol and its derivatives) is a main limitation in the later transformation. Therefore, the exploration of a general and efficient asymmetric synthetic method for 2-aryl-2,3-dihydrobenzofuran scaffolds using [3 + 2] cyclization is highly demanded.

Recently, an SPD-organocatalyst-catalyzed enantioselective one-pot intramolecular Robison cyclization to construct 2alkyl-2,3-dihydrobenzofuran scaffolds, unfortunately not efficient for 2-aryl-2,3-dihydrobenzofuran scaffolds, have been developed by our group (Scheme 1b).¹⁰ Subsequently, another asymmetric intermolecular oxidative cross-coupling of 3methyloxycarbonyl-2-naphthol with 2-naphthol for the preparation of C1-symmetric BINOLs through our well designed Cu/SPDO catalysis system also has been explored,¹¹ in which a proposed intermediate involving Cu/dioxygen of the quinone ester model plays a crucial role in the stereocontrol. Inspired by these previous studies and our continued research interest in the development of novel SPDO catalysts and their application in the asymmetric synthesis of bioactive natural products, herein, we envisioned that a [3 + 2] cyclization between quinone ester and styrene could be catalyzed by a suitable Cu/SDPO catalyst to provide alternative access to 2aryl-2,3-dihydrobenzofuran derivatives with high enantioselectivities (Scheme 1c).

To test our assumptions, quinone ester (1a) and 4methoxystyrene (2a) were selected as reaction partners. Actually, there are still some challenges in this designed asymmetric transformation. (1) Quinone esters formed by another competitive cycloaddition reaction such as [2 + 2]cyclization has been reported; $^{12}(2)$ excellent enantioselectivity of the transformation of styrene has rarely been reported due to the lack of a "holder" of efficient asymmetric [3 + 2]cycloaddition.¹³ To address these problems, a series of new SPDO ligands (Table 1) were first synthesized according to our previously developed method.¹¹ With these new ligands in hand, various Cu salts with ligand (R,S)-L1 as catalysts were first investigated to explore suitable reaction conditions, in which $Cu(OTf)_2$ could facilitate this transformation, affording desired adduct 3aa in excellent yield (97%) with moderate enantioselectivity (62% ee) in toluene at room temperature for 6 h (entry 1, Table 1; for more details, see Supporting Information (SI)). Encouraged by these results, L1 was replaced by other synthesized SPDO ligands (L2-L6) to further improve the enantioselectivity of the reaction. In detail, (R,R)-L2 with C4-^{*i*}Pr gave a little higher ee than our previous corresponding (R,S)-L1, and (R,R)-L5 with C4-Bn gave the best result in 95% isolated yield with 79% ee among L2-L6 (entries 2-6). Then, reaction media were screened, and no

Table 1. Optimization of Reaction Conditions^a



^{*a*}The reactions were conducted with 1a (0.10 mmol, 1.0 equiv), 2a (1.2 equiv), $Cu(OTf)_2$ (10 mol %), and Ligand (10 mol %) in 2.0 mL toluene under Ar. ^{*b*}Isolated yields. ^{*c*}Determined by chiral UPC². ^{*d*}2a was added slowly with a syringe pump for 3 h.

better results were observed (for details, see the SI). Subsequently, lowering the reaction temperature can efficiently suppress the unexpected background reaction as we expected. And the enantioselectivity could be significantly increased to 90% ee when the reaction temperature was lowered to -80 °C (entries 7–9). Finally, the ee value of 3aa was further increased to 93% by changing the addition of 4-methoxystyrene (2a) to the reaction system using a syringe pump for longer reaction times at -80 °C. (entry 10) As a comparison, L5' with racemic C4-Bn could not maintain efficiency like L5, which indicates that the enantioinduction depends on not only the main spirocenter but also the C4 site of oxazoline (entry 11). Therefore, the reaction parameters listed in entry 10 were selected as the optimal reaction conditions for subsequent investigations.

Having established the optimal reaction conditions, the scope of quinone esters 1 for asymmetric [3 + 2] cycloaddition was first explored. The results (Scheme 2) showed that most examples worked well to generate the expected 3aa-3ea and **3ab–3ib** with good to high enantioselectivities (up to 99% ee) and high yields (up to 96%).¹⁴ In detail, first, the substituents (Me, Et, ^{*i*}Pr, ^{*t*}Bu, and Ph) on the ester moiety of the quinone were investigated. The results showed that the ester group had an obvious influence on enantioselectivity but a slight influence on chemical yield, and a more sterically hindered alkyl group led to excellent enantioselectivities (3aa-3da) using 2a ($R^3 =$ H) as a reaction partner. For comparison, the reaction proceeded well without any decrease in the yield, and enantioselectivity, affording 3ab-3db bearing two vicinal stereocenters when 2b ($R^3 = Me$) was used. Fortunately, only (R,R)-products were isolated. Notably, the absolute configuration of the resulting products could be determined by





^{*a*}Reaction conditions: Unless otherwise noted, the reactions were conducted with quinone ester (0.1 mmol 1.0 equiv), substituted styrene (1.2 equiv), $Cu(OTf)_2$ (10 mol %), and L5 (10 mol %), in 2.0 mL of toluene at -80 °C under Ar for 36 h. ^{*b*}**3ab** (1.0 mmol, 1.0 equiv), 4-bromobenzoyl chloride (1.2 equiv), Et₃N (1.0 equiv), DMAP (1.0 equiv), DCM (10 mL).

X-ray analysis of derivative **3ab-1** of product **3ab**. However, when phenyl ester was used, the ee value of product **3ea** and **3eb** declined slightly to 88% and 96%. Second, the substituents on the quinone ester ring were investigated, and a variety of substrates **1f**-**1i** reacted with **2b** smoothly, generating the expected 2,3-dihydrobenzofuran derivatives **3fb**-**3ib** with high enantioselectivity in 92–99% ee, respectively.

Next, various styrene derivatives were further investigated, and all examples also worked well to give high enantioselectivities (up to 99% ee) and good to high yields (up to 96%)¹⁵ (Scheme 3). First, 1-isopropenyl-4-methoxybenzene was proven to be an amenable substrate, yielding the product 3ac bearing a challenging all-carbon quaternary stereocenter at the C-2 position, albeit with a slight decrease in the yield and an increase in ee value (69% yield and 96% ee). Second, when 2,4-dimethoxystyrene (2d) was used as a reaction partner, desired product 3ad was isolated in 92% ee and 95% yield. Third, cyclic styrene substrates were also subjected to the optimal reaction conditions, affording the desired products with excellent diastereoselectivity (>20:1 dr) and enantioselectivity (86-99% ee), albeit with slightly decreased yields (3ae-3ag, 62-78%). Especially, two N-Bz-protected indoles were proven to be amenable substrates, providing important benzofuroindoline skeletons, which exist in many bioactive natural products and drugs.¹ Unfortunately, the chemical yield was lower. Subsquently, oxygen-heteroaromatic substrates were tested, and the results demonstrated that L4 was a superior catalyst to L5. When 7-methoxy-2H-chromene was used as a substrate, the reaction afforded another important bioactive benzofuranyl-benzopyran moiety, either with quinone ester or with naphthoquinone ester. These reaction results from Schemes 2 and 3 demonstrated that the current asymmetric transformation provides a potential platform for the preparation of structurally diverse 2-aryl-2,3-dihydrobenzofuran compounds.

Based on our previous work with the SPDO system, a possible mechanism is proposed (Figure 2). When styrene attacks from the Re face of **B**, which formed from Cat **A**

Scheme 3. Scope of Substrate Styrene 2^b



^{*a*}Reaction conditions: Unless otherwise noted, the reactions were conducted with quinone ester (0.1 mmol, 1.0 equiv), substituted styrene (1.2 equiv), $Cu(OTf)_2$ (10 mol %), and L5 (10 mol %), in 2 mL of toluene at -80 °C under Ar for 36 h. ^{*b*}L4 used at rt.



Figure 2. A possible mechanism for Cu/SPDO-catalyzed [3 + 2] cycloaddition.

coordinated with 1a, a favored transient state would be formed to give intermediate D via C, leading to the (R,R)-product E. However, when styrene attacks from the *Si* face of B, a bigger steric hindrance would exist to hinder the formation of (S,S)product E.

To further showcase the practical utility of the asymmetric transformation we developed above, syntheses of corsifuran A and B^{16} were carried out (Scheme 4). Starting from resulting product 3da, subsequent hydrolysis and decarboxylation could yield the corsifuran B in 60% yield, and further methylation of the phenolic hydroxyl group afforded corsifuran A. Therefore,

Letter

Scheme 4. Synthesis of (R)-Corsifuran A and (R)-Corsifuran B



a more straightforward approach to access two natural products has been developed.

In summary, we have accomplished the asymmetric [3 + 2] cyclization of quinone esters and styrene to produce a series of chiral 2-aryl-2,3-dihydrobenzofurans, featuring a broad substrate scope and high to excellent yield and enantioselectivity, by using our developed novel Cu-SPDO complex catalytic system. This approach enables the most straightforward synthesis of 2,3-dihydrobenzofuran bearing two contiguous stereocenters. Further investigations of the reaction mechanism of SPDO ligands in this catalytic system and other asymmetric reactions catalyzed by SPDO ligands/metal complexes are underway in our laboratory.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04241.

Experimental procedures, characterizations and analytical data of products, NMR and HPLC spectra (PDF)

Accession Codes

CCDC 2048013 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Letter