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Chiral Cobalt(II) Complex Catalyzed Friedel-Crafts-Aromatization for Synthesis of Axially Chiral Biaryldiols

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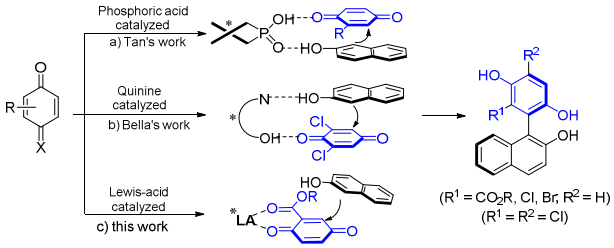
An efficient atroposelective synthesis of axially chiral biaryldiols via asymmetric Friedel-Crafts-aromatization between *p*-quinones and 2-nathphols was developed. A chiral cobalt(II) complex of *N,N'*-dioxide enabled the process to generate axially chiral biaryldiols in up to 98% yield and 95% ee. A large range of substituents at different positions of *p*-quinones and 2-nathphols were tolerable. The configuration of the product and the chiral *N,N'*-dioxide-Co(ClO_4)$_2$ catalyst was identified by X-ray crystal diffraction analysis and a possible catalytic model was suggested.

Biaryls are commonly encountered in natural products with biological activity[1], and their derivatives, such as biaryldiols also serve as useful backbone of chiral ligands and catalysts[2] for asymmetric transformations. Over the past decade, several strategies have been reported for the atroposelective synthesis of biaryl derivatives[3-8], which can be summarized as five methods: transition metal catalyzed aryl-aryl coupling[3], classical resolution[4] and dynamic kinetic resolution[5], desymmetrization of prochiral biaryls[6], atroposelective construction of an aromatic ring[7] and central-to-axial chirality exchange[8]. Recently, chiral organocatalysts have shown efficiency for the construction of axially chiral biaryl derivatives. For example, chiral phosphoric acids are used for the synthesis of biaryl derivatives[6a], 2,2'-binaphthyldiamines[8e,f], and naphthyl-indole skeletons[8h]. In addition, pyrrolidinyl-tetrazole was used to catalyze aldol condensation to generate 1,1'-binaphthalene-2-carbaldehydes.[7a] For the atroposelective synthesis biaryldiol or biaryltriol derivatives, the method of central-to-axial chirality exchange makes a breakthrough. BINOL/NOBIN biaryls by [3,3]-rearrangement was achieved by Kürti, Xu and coworkers[8b]. Biaryltriols were generated from asymmetric arylative reaction of 2-naphthols with quinone derivatives as reported by Tan,[8a]



Scheme 1. Access to Axially Chiral Biaryldiols.

Salvio and Bella[8c] (Scheme 1; a, b). However, the phosphoric acid could give excellent enantioselectivity but limiting to 2-substituted 1,4-quinone, and chiral quinine derivative could tolerate several substituents on 2,6-dichloro-1,4-quinones but lacking of high enantioselectivity. Interestingly, none of chiral Lewis acid catalysts has been reported efficiency in these cases. The coordination ability of the formed biarylols to the metal ions, and Lewis-acid initiated polymerization of quinone substrate[11] might be big trouble. Additionally, the previous usage of BINOL derivatives in asymmetric catalysis exhibits that substituents on the biaryl backbone have significantly influence the stereocontrol of the reaction. Therefore, to develop an alternative chiral Lewis acid catalytic system to synthesize various substituted biaryltriols in high enantioselectivity is interesting.

We envisioned the possibility of chiral Lewis acid-promoted Friedel-Crafts reaction/aromatization process to establish biaryltriols. The introduction of an ester group into 1,4-quinone enhances both the coordination preferences and the reactivity (Scheme 1, c). Asymmetric Friedel-Crafts reactions of arylols were suitable for using chiral *N,N'*-dioxide complex catalytic systems[10]. Herein, we demonstrated the application of a chiral *N,N'*-dioxide-cobalt(II) catalyst in the development of a Friedel-Crafts-Aromatization reaction with 2-nathphols and 1,4-quinones. A series of biaryltriol derivatives were obtained in moderate to excellent yields with good to excellent enantioselectivities.

Initially, quinone **1a** and 2-naphthol **2a** were chosen as the model substrates to optimize the reaction conditions (Table 1). Using chiral *N,N'*-dioxide ***L*-RaPr$_2$** as the ligand, several cheap

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Electronic Supplementary Information (ESI) available: CCDC 1551259 (**3da**) and CCDC 1551260 (**L-RaPr$_2$**/Co(ClO_4)$_2$ complex). For ESI and crystallographic data in CIF or other elecnic format See DOI: 10.1039/x0xx00000x

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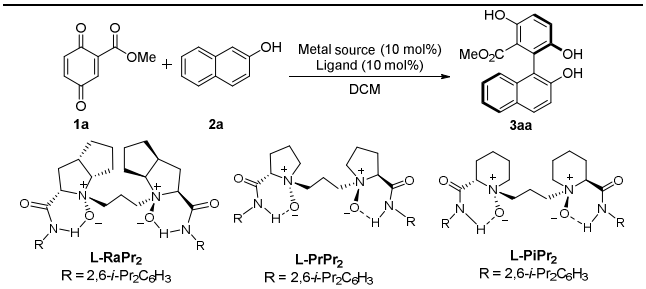
metal salts that are capable of bonding bidentate 1,3-dicarbonyl compounds were tested for the model reaction. It was found that $Mg(OTf)_2$, $Cu(OTf)_2$, and $Ni(OTf)_2$ gave the desired product **3aa** in moderate to good yield as a racemate, although a complete background reaction occurred within 15 minutes at -10 °C (entries 2-4 vs entry 1). The lack of enantioselectivity might result from the strong non-asymmetric catalytic process and the destroy of chiral *N,N'*-dioxide-metal complex by the biaryltriol products. To our delight, the ***L*-RaPr$_2$**/$Co(ClO_4)_2$·complex was much better at promoting the reaction than ***L*-RaPr$_2$**/$Zn(OTf)_2$ catalyst, and the product **3aa** was obtained with 90% yield and 64% ee (entry 6 vs entry 5). Next, screening of chiral backbone of the ligand suggested that the *L*-ramipril derived ***L*-RaPr$_2$** gives better enantioselectivity than *L*-proline and *L*-pipecolic acid derived ones (entries 6-8). With the reaction temperature dropped gradually, the enantioselectivity of the reaction increased due to the fade background reaction (entries 9-11). The reaction run at -78 °C gave a 91% yield and 83% ee. Similar to the work of Salvio and Bella,[8c] $NaBH_4$ dissolved in MeOH was used to quench the reaction before flash chromatography, and a slight enhanced enantioselectivity was obtained (87% ee; entry 12). Quinones easily undergo polymerization and other side reactions at room temperature[11]. To avoid impurity contained in benzoquinone which affects the ee value remarkably, newly oxidated quinone **1a** from 2-methoxycarbonyl-1,4-phendiol without further purification was used. It was found that the enantioselectivity of the reaction increased to 90% ee with a 91% yield (entry 13). Therefore, the optimized condition involved the use of ***L*-RaPr$_2$**/$Co(ClO_4)_2·6H_2O$ as catalyst in DCM at -78 °C for 60 h, and quenching the reaction with $NaBH_4$ in MeOH (entry 12).

With the optimized condition in hand, the reaction scope was next examined (Table 2). Satisfyingly, using 2-naphthol **2a** as the partner, 1,4-quinones **1a-1k** with various 2-ester substituents were smoothly converted into the desired products **3aa**-**3ka** in good yields and excellent enantioselectivities (55-96% yield, and 80-96% ee). Considering critical role of the substituents on the 3,3'-positions of BINOL on the stereocontrol of the reaction, we further explored the scope of 2-carboxylate substituted 1,4-quinones with substituents at C5 position (Table 2). To our delight, changing the substituted group on the 5-position of quinone moiety had limited influence on the reactivity. Good to excellent yields

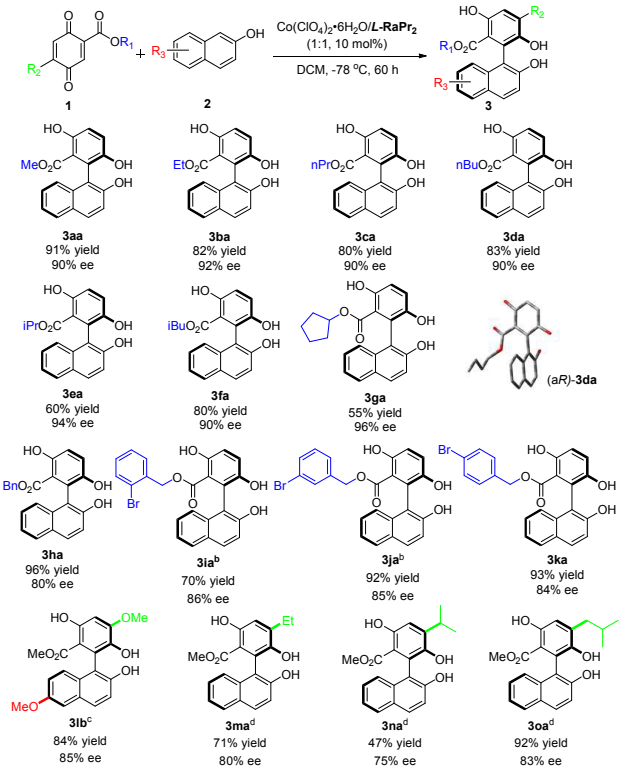
Table 1. Optimization of the Reaction Conditions[a]



Entry	Matel salt	Ligand	T (°C)	t (h)	Yield (%)[b]	Ee (%)[c]
1	-	-	-10	0.25	21	0
2	$Mg(OTf)_2$	***L*-RaPr$_2$**	-10	12	62	0
3	$Cu(OTf)_2$	***L*-RaPr$_2$**	-10	12	87	0
4	$Ni(OTf)_2$	***L*-RaPr$_2$**	-10	12	58	0
5	$Zn(OTf)_2$	***L*-RaPr$_2$**	-10	12	91	42
6	$Co(ClO_4)_2$	***L*-RaPr$_2$**	-10	12	90	64
7	$Co(ClO_4)_2$	***L*-PrPr$_2$**	-10	12	92	44
8	$Co(ClO_4)_2$	***L*-PiPr$_2$**	-10	12	92	20
9	$Co(ClO_4)_2$	***L*-RaPr$_2$**	-30	12	86	66
10	$Co(ClO_4)_2$	***L*-RaPr$_2$**	-50	24	90	71
11	$Co(ClO_4)_2$	***L*-RaPr$_2$**	-78	60	91	83
12[d]	$Co(ClO_4)_2$	***L*-RaPr$_2$**	-78	60	89	87
13[d,e]	$Co(ClO_4)_2$	***L*-RaPr$_2$**	-78	60	91	90

[a] Unless noted otherwise, reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), and ligand/metal salt (1:1, 10 mol%) in DCM (2.5 mL) under N_2. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] After 60 h, $NaBH_4$ (0.8 mg) in MeOH (0.2 mL) was added at -78 °C. [e] Use newly oxidated **1a** without further purification. $Co(ClO_4)_2·6H_2O$ was used. DCM = dichloromethane

Table 2. Substrate Scope of Qinones[a]



[a] Unless noted otherwise, all reactions were carried out with **1** (0.1 mmol), 2-naphthol **2** (0.1 mmol), and ***L*-RaPr$_2$**/$Co(ClO_4)_2·6H_2O$ (1:1, 10 mol%) in DCM (2.5 mL) under N_2 for 60 h. Newly oxidated **1** without further purification was used. After 60 h, $NaBH_4$ (0.8 mg) in MeOH (0.2 mL) was added at -78 °C. Isolated yield, and ee was determined by HPLC analysis on a chiral stationary phase. [b] 1,4-benzoquinone **1** (2.0 equiv) for 36 h. [c] Reaction at -60 °C, 60 h. [d] Reaction at -50 °C, 36 h.

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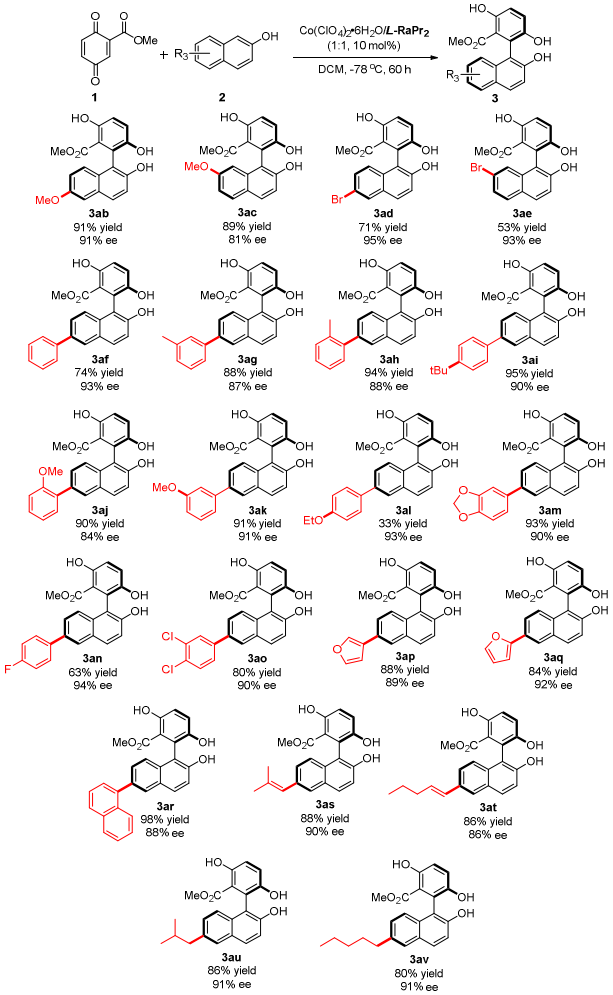
(47-92% yield) and good ee values (75-85% ee) for **3lb**-**3oa** could be achieved after raising the temperature to -60 °C or -50 °C.

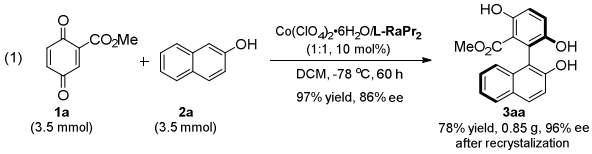
2-Naphthol derivatives with electron-withdrawing or electron-donating substituents at 6- or 7-position (Table 3) can react smoothly to afford the corresponding products **3ab**-**3ae** in moderate to good yields (53-91% yield) and excellent ee values (81-95% ee). Moreover, a wide range of 2-naphthols (**2f**-**2o**) with different substituted 6-aryl groups reacted quite well with quinone **1a** to form the products **3af**-**3ao** in satisfied results (33-95% yield, 84-94% ee). Additionally, the heteroaromatic substituted **2p**, **2q** and [1,2'-binaphthalen]-6'-ol **2r** were also suitable for the reaction, and the corresponding biaryltriols (**3ap**-**3ar**) were afforded in 84-98% yield and 88-92% ee. Notably, the use of alkenyl or alkyl substituted naphthols also afforded the desired products (**3as**-**3av**) in good to excellent stereocontrol (86-91% ee) and excellent isolated yields. X-ray crystal diffraction analysis allowed to attribute a*R* absolute configuration of the product **3da**.

Table 3. Substrate Scope of 2-naphthols [a]



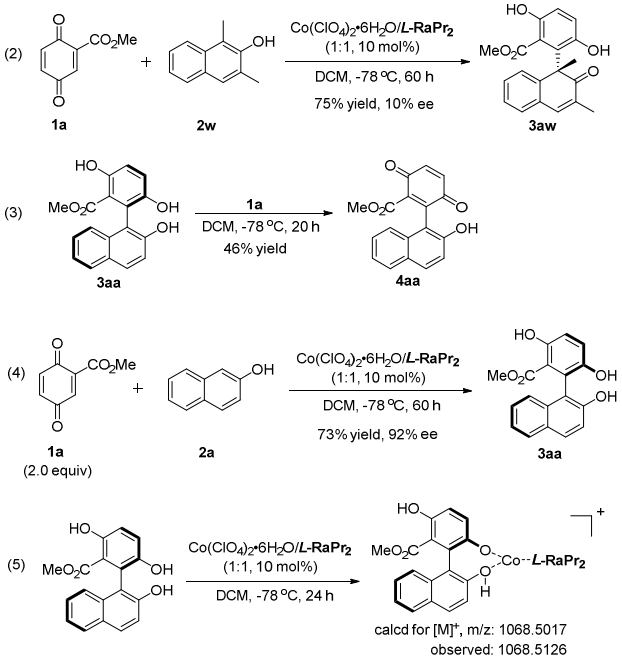
[a] The same as the footnote a in Table 2.

To show the synthetic utility of the catalyst system, the reaction of quinone **1a** and 2-naphthol **2a** was performed on a gram scale (eq 1). The desired product **3aa** was obtained in 97% yield with 86% ee, and can be recrystallized to give an excellent enantiomeric excess (96% ee).



To gain insight into the reaction process, several control experiments were carried out. Firstly, 1,3-dimethyl-2-nathphol **2w** was used to react with quinone **1a**, and the corresponding dearomatization product **3aw** was obtained in 75% yield albeit with 10% ee (eq 2). This result confirmed that 2-nathphol could initially undergo a Friedel-Crafts arylation process. It was found that the biaryltriol product **3aa** could be oxidized into 3-β-nathphol-substituted 1,4-quinone **4aa** by the substrate **1a** even at low reaction temperature (eq 3). It was in consistence with the result that the yield of the biaryl product **3aa** dropped when excessive amount of 1,4-quinone **1a** was used (eq. 4). Furthermore, HRMS spectra confirmed that the product **3aa** can coordinate with chiral ***L*-RaPr$_2$**/Co(ClO$_4$)$_2$ complex (eq. 5), which implied that the catalyst probably suffered poisoning from the products which hampered the asymmetric catalytic process.

The X-ray crystal diffraction analysis of the catalyst[12] showed that *N,N'*-dioxide ***L*-RaPr$_2$** coordinated with cobalt(II) via tetra-oxygen bonding, forming a polycyclic octahedron metal complex. The coordination manner of *N,N'*-dioxide to cobalt(II) is similar to our previous reports[9], confirming the coordination characteristic of this type of novel ligand. In light of the structures of the catalyst and the product **3da**, a catalytic model was proposed for the reaction (Scheme 2). The



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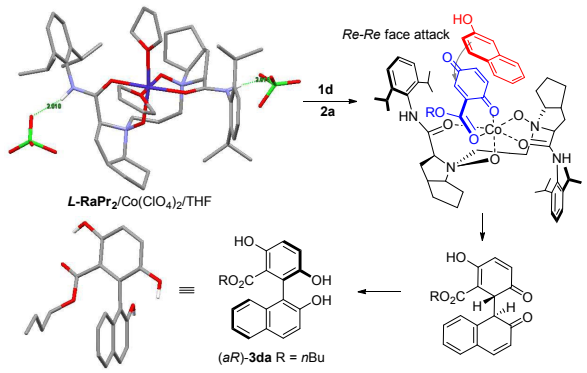

Scheme 2. Proposed catalytic model.

tetradentate *N,N'*-dioxides ***L*-RaPr$_2$** and the bidentate quinone ester **1d** coordinate to the Co^{II} center. The *Si* face of the quinone ester is shielded by the neighboring amide group of the ligand and the 2-nathphol attack takes from the *Re* face to form the intermediate **4da** with good diastereo- and enantioselectivity. Central-to-axial chirality exchange occurring in the rearomatization of **4da** affords the desired product (*aR*)-**3da**.

In summary, an efficient Lewis-acid-catalyzed asymmetric Friedel-Crafts-aromatization between *p*-benzoquinone derivatives and 2-naphthols has been developed by using a chiral cobalt(II) complex of *N,N'*-dioxide. The corresponding axially chiral products were obtained in up to 98% yield and 95% ee under mild reaction conditions. This highly convergent and functional group tolerable approach allows for the rapid construction of axially chiral biaryldiols from simple starting materials. An X-ray crystal diffraction analysis was used to identify the configurations of the product and the chiral *N,N'*-dioxide-Co(ClO$_4$)$_2$ catalyst, and a possible catalytic model was suggested. Further application of the catalyst to develop other novel asymmetric reactions is ongoing in our laboratories.

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12 CCDC 1551259 (**3da**) and CCDC 1551260 (***L*-RaPr$_2$**/Co(ClO$_4$)$_2$ complex) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

13 For more details, see the Supporting information.

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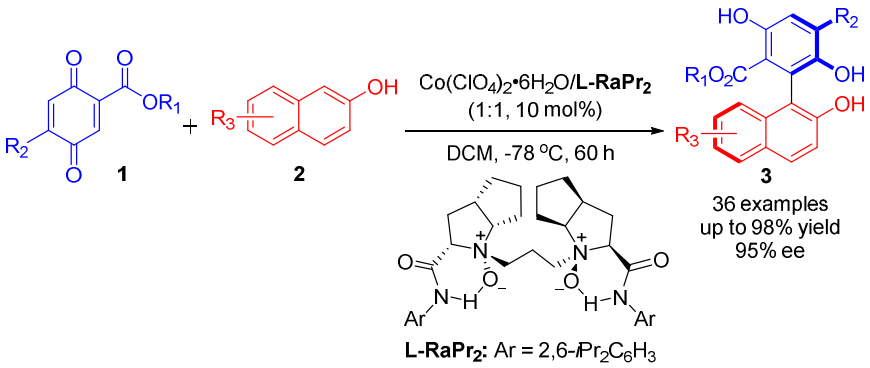

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