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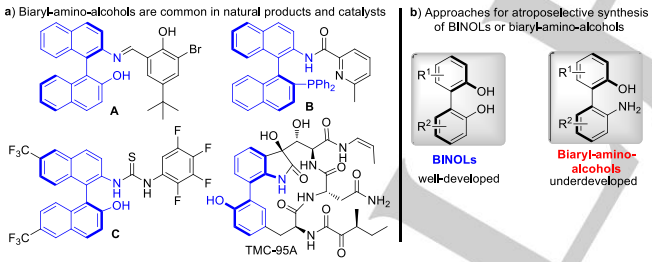
# Practical Approach to Axially Chiral Biaryl-amino-alcohols via Organocatalytic Atroposelective Arylation of 2-Naphthylamines

Ye-Hui Chen, Liang-Wen Qi, Fang Fang, and Bin Tan*

*Dedicated to Professor Shizheng Zhu on the occasion of his 70th birthday*

**Abstract:** The first phosphoric acid-catalyzed direct arylation of 2-naphthylamines with iminoquinones for the atroposelective synthesis of axially chiral biaryl-amino-alcohols has been developed. This reaction features a highly functional group tolerant route to the rapid construction of enantioenriched axially chiral biaryl-amino-alcohols with good results. This represents a rare example of 2-naphthylamines acting as nucleophiles in organocatalytic enantioselective transformation. Furthermore, the products which have various halogen atoms offer access to structurally diverse axially chiral amino alcohols through further transformation.

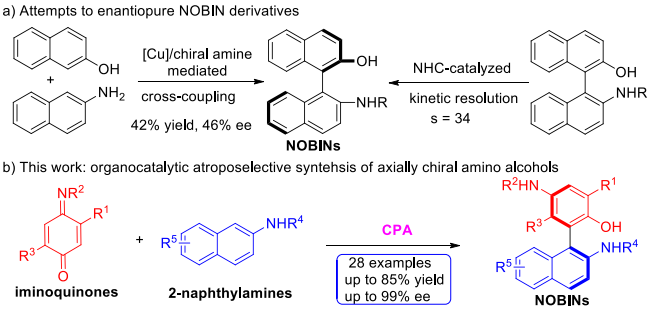
The axially chiral 1,1'-bi-2-naphthol (BINOL) and its derivatives are among the most successful chiral ligands/catalysts in asymmetric catalysis, with extensive applications in various catalytic enantioselective transformations.[1] Recently, axially chiral biaryl-amino-alcohols have been extensively implemented as chiral ligands/organocatalysts in the field of enantioselective catalysis.[2] For example, ligand **A** has been successfully applied in numerous Ti-catalyzed enantioselective aldol reactions.[3] Ligand **B**, a NOBIN-derived N,P ligand, has shown high efficiency in the Cu-catalyzed Michael addition with good results.[4] The NOBIN-derived organocatalyst **C** proved to be efficient in promoting the [2+2] photocycloaddition of 4-alkenyl-substituted coumarins with high enantioselectivity.[5] In addition, this motif has been found in natural products or biologically active compounds (Scheme 1a).[6]




***Scheme 1.*** a) Selected ligands/catalysts and natural products with axially chiral biaryl-amino-alcohol moiety. b) Current status of enantioselective synthesis of axially chiral BINOLs and biaryl-amino-alcohols.

The enantioselective construction of BINOL and its derivatives has attracted considerable attention and relatively practical approaches have already been accomplished.[7] In contrast, enantioselective synthesis of axially chiral biaryl-amino-alcohols remains largely unexplored (Scheme 1b). There have only been a few enantioselective attempts toward biaryl-amino-alcohol derivatives, including metal-catalyzed enantioselective oxidative cross-coupling reactions,[8] kinetic resolution of racemic NOBIN (a kind of biaryl-amino-alcohol) derivatives,[9] and transformation of enantiopure binaphthyl derivatives.[10] In this context, Kocovsky and co-workers pioneered the development of an enantioselective version of the cross-coupling reaction of 2-naphthol and 2-naphthylamine using copper/chiral amines (10 equiv.) as mediator compounds to afford (*R*)-NOBIN in 42% yield with 46% enantioselectivity excess (ee) (Scheme 2a).[8b] After further crystallization, the ee could be improved to a very high level. Obviously, there is a room for improvement of this method, as it utilizes a large excess of chiral amine and multistep crystallization. More recently, Zhao and co-workers reported an efficient approach to synthesize enantioenriched NOBIN derivatives with good results (selectivity factor is up to 42) via NHC-catalyzed kinetic resolution.[9e] Although this elegant approach has been one of the most powerful and reliable strategies for the synthesis of enantiopure NOBIN derivatives, the chemical yield is limited to no more than 50%. Thus, the catalytic enantioselective synthesis of optically active NOBIN derivatives via a more practical process remains challenging.

The electrophilic substitution of arenes represents one of the most powerful and reliable strategies for the synthesis of aromatic compounds. However, most of the examples reported in the literature with respect to this reaction were concerned with the use of indoles, pyrroles and naphthols as nucleophilic partners, whilst other nucleophiles, such as naphthylamines, have been less investigated as regarding to enantioselective transformations.[11] Consequently, the expansion of the substrate scope to include naphthylamines is of great importance in order to construct more chiral naphthylamine derivatives. Motivated by the recent developments in the synthesis of axially chiral compounds,[12] we herein report the chiral phosphoric acids (CPAs) catalyzed atroposelective arylation of 2-naphthylamine derivatives with iminoquinones, which provides a practical process to enantio-enriched axially chiral biaryl-amino-alcohols with good enantioselectivities (Scheme 2b). To the best of our knowledge, this transformation represents the first example of 2-naphthylamines acting as nucleophiles in phosphoric acid-catalyzed enantioselective reaction.




***Scheme 2.*** Enantioselective strategies for the synthesis of enantiopure NOBINs or axially chiral biaryl-amino-alcohols.

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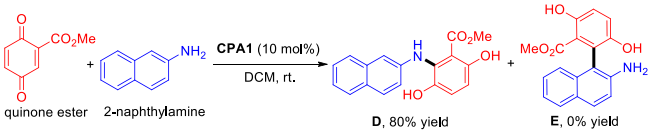
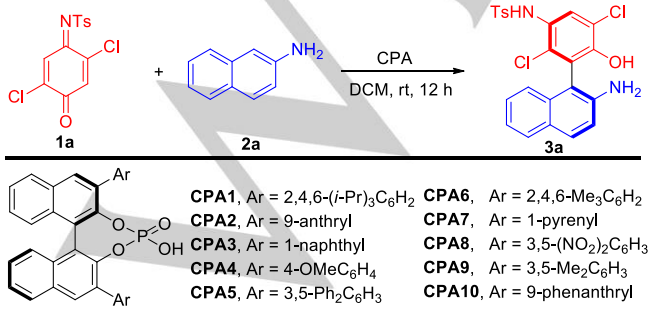
As part of an ongoing effort in our group to construct axially chiral compounds via organocatalysis,[7g,13] we recently successfully exploited the phosphoric acid-catalyzed enantioselective arylation of 2-naphthols with quinone derivatives to access BINOLs in good yields with excellent enantioselectivities.[7g] We envisioned that 2-naphthols could be replaced by 2-naphthylamines, affording the possibility to construct enantiomerically enriched axially chiral biaryl-amino-alcohols via a similar process. The biggest challenge might be the reactivity and chemoselectivity of the reaction and the information is largely unknown due to the lack of published data involving 2-naphthylamines as nucleophiles. We initiated our studies by evaluating the reaction between quinone ester and 2-naphthylamine in dichloromethane (DCM) at room temperature in the presence of chiral phosphoric acid **CPA1** (Scheme 3). Unfortunately, the reaction afforded the unexpected product **D** in 80% yield without the formation of axially chiral amino alcohols derivative **E**. Despite making great efforts toward optimization of the reaction conditions, we could not obtain the desired product by using the current model reaction.




***Scheme 3.*** Initial investigation involving 2-naphthylamine as nucleophile.

Inspired by the pioneering works of Akiyama[14a] and Terada[14b] on the use of chiral phosphoric acids as organocatalysts in the activation of imine for enantioselective transformations, we postulated iminoquinones might have additional interactions with the catalyst to construct axially chiral compounds. Additionally, we aimed to inhibit the formation of the cyclization product; therefore a substituent was introduced into the ortho position. We decided to select readily available *N*-sulfonyl iminoquinone **1a** as a substrate to take the place of quinone ester for the above-mentioned model reaction. As expected, the desired product **3a** was obtained in 71% isolated yield with 88% ee (Table 1, entry 1). Then various chiral phosphoric acid catalysts were screened but insufficient results were obtained (Table 1, entries 2-10). **CPA1** proved to be the best catalyst with respect to enantioselectivity for the model reaction. Of the solvents investigated for the reaction catalyzed by **CPA1** (Table 1, entries 11−15), DCM proved optimal. Having identified **CPA1** as the best catalyst and DCM as the best solvent, we turned our attention to other reaction variables. Lower concentration had a positive effect on enantioselectivity. When 4 mL of DCM was employed, the ee of product increased to 91% (Table 1, entry 16).

***Table 1.*** Screening results of reaction conditions.[a]







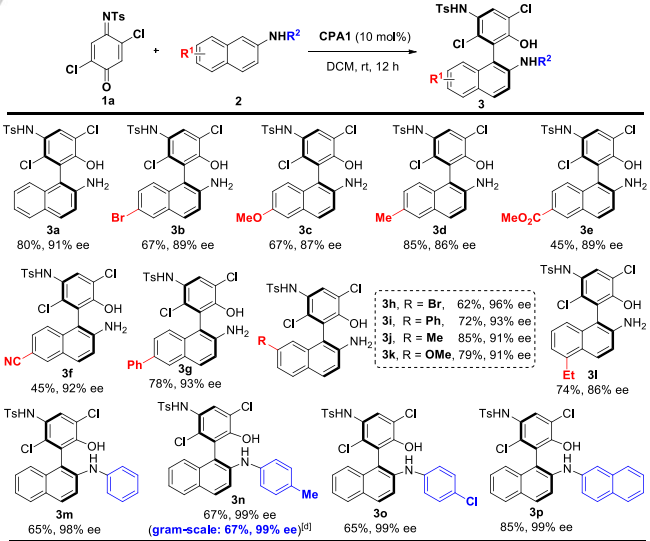
**CPA1**, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ **CPA6**, Ar = 2,4,6-Me$_3$C$_6$H$_2$
**CPA2**, Ar = 9-anthryl **CPA7**, Ar = 1-pyrenyl
**CPA3**, Ar = 1-naphthyl **CPA8**, Ar = 3,5-(NO$_2$)$_2$C$_6$H$_3$
**CPA4**, Ar = 4-OMeC$_6$H$_4$ **CPA9**, Ar = 3,5-Me$_2$C$_6$H$_3$
**CPA5**, Ar = 3,5-Ph$_2$C$_6$H$_3$ **CPA10**, Ar = 9-phenanthryl

| entry | catalyst | solvent | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **CPA1** | DCM | 98 | 88 |
| 2 | **CPA2** | DCM | 98 | 36 |
| 3 | **CPA3** | DCM | 99 | 14 |
| 4 | **CPA4** | DCM | 98 | 14 |
| 5 | **CPA5** | DCM | 93 | 11 |
| 6 | **CPA6** | DCM | 93 | 19 |
| 7 | **CPA7** | DCM | 95 | 18 |
| 8 | **CPA8** | DCM | 93 | 7 |
| 9 | **CPA9** | DCM | 97 | 7 |
| 10 | **CPA10** | DCM | 96 | 20 |
| 11 | **CPA1** | DCE | 99 | 86 |
| 12 | **CPA1** | $CHCl_3$ | 95 | 83 |
| 13 | **CPA1** | toluene | 99 | 86 |
| 14 | **CPA1** | THF | 93 | 7 |
| 15 | **CPA1** | ethyl acetate | 93 | 42 |
| 16[d] | **CPA1** | DCM | 98 (80)[e] | 91 |
| 17[f] | **CPA1** | DCM | 96 | 84 |
| 18[g] | **CPA1** | DCM | 92 | 89 |

[a] Reaction was carried out with **1a** (0.10 mmol), 2-naphthylamine (**2a**, 0.15 mmol), and **CPA** (10 mol%) in 2 mL of solvent for 12 h at room temperature under Ar, unless noted otherwise. [b] Determined by $^1$H NMR analysis of the crude reaction mixture with 1, 3, 5-triethylbenzene as an internal standard. [c] Determined by HPLC analysis. [d] 4 mL of DCM; [e] Isolated yield. [f] 5.0 mol% **CPA1** in 4 mL of DCM. [g] At 0 $^0$C in 4 mL of DCM.

After the optimization of the reaction conditions, we set out to explore various substituted 2-naphthylamines substrates **2** (Table 2). All of the tested 2-naphthylamines reacted completely within 12 h to afford the corresponding products **3a**-**3p** in moderate to good yields (45−85%) with high enantioselectivities (86−99% ee). The position and the electronic properties of the substituents of 2-naphthylamines had a negligible impact on the enantioselectivity of the reaction. However, the electronic properties of the substituents on the aromatic ring appeared to have significant effects on chemical yields. Relatively, electron-withdrawing groups (CN, $CO_2Me$) gave low yields (**3e**, **3f**), whereas the electron-donating groups such as Me or OMe

***Table 2.*** Substrates scope with respect to variation of 2-naphthylamines.[a],[b],[c]

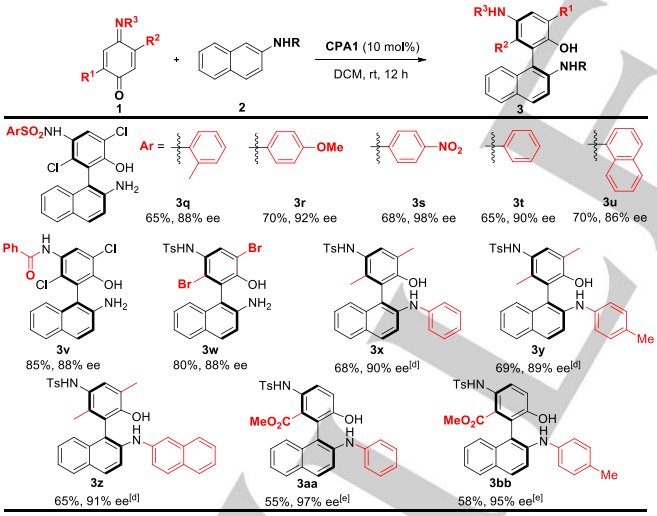



[a] Reaction was carried out with **1a** (0.10 mmol), 2-naphthylamines **2** (0.15 mmol), and catalyst **CPA1** (5 mol%) in 4 mL of DCM at room temperature for 12 h under Ar, unless noted otherwise. [b] Isolated yields based on **1a**. [c] ee values were determined by HPLC analysis. [d] Reaction was carried out with **1a** (1.65 g, 5 mmol), **2n** (1.40 g, 6 mmol).

afforded higher yields (**3d**, **3k**). Notably, when *N*-substituted 2-naphthylamines were employed to react with **1a**, the desired products (**3m-3p**) were afforded in moderate yields (65-85%) with excellent enantioselectivities (>98% ee). To show the practicality of this transformation, a gram-scale reaction of **1a** (1.65 g) and **2n** was carried out in the presence of 5 mol% **CPA1** to afford **3n** in 67% yield with 99% ee. The results indicate that this direct arylation reaction for construction of axially chiral biaryl-amino-alcohols could easily be scaled up without decreasing the chemical yield or enantioselectivity. The absolute configuration of **3a** was determined as (a*S*) by X-ray diffraction analysis (see Supporting Information), and those of other products were assigned by analogy.

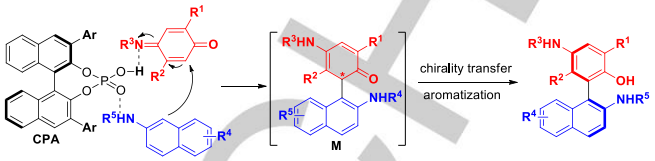
Encouraged by these results, we next expanded the generality of the reaction with regard to the variation of the iminoquinone derivative **1**. As shown in Table 3, the nature of the sulfonyl group had limited influence on chemical yields and enantioselectivities of the products **3q**-**3u**. When the N-benzoyl-protected iminoquinone was used as substrate, the reaction proceeded very well under the optimized conditions, producing the desired axially chiral biaryl-amino-alcohols in 85% yield with 88% ee. By replacing the Cl group with Br or Me at the iminoquinone moiety, the corresponding products **3w**-**3z** were also obtained with good results. To our delight, the iminoquinone ester **1j** was a suitable substrate to react with N-substituted 2-naphthylamines **2m** and **2n** in the presence of 5 mol% of **CPA2**, giving the expected axially chiral amino alcohols **3aa** and **3bb** with excellent enantioselectivities.

***Table 3.*** Substrates scope in terms of variation of iminoquinones.[a],[b],[c]



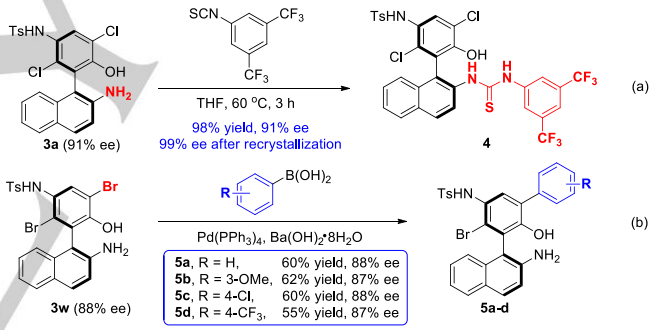

[a] Reaction was carried out with standard condition. [b] Isolated yields based on **1**. [c] ee values were determined by HPLC analysis. [d] Reacted at room temperature for 24 h. [e] 5 mol% of **CPA2** was used.

Based on the experimental results and the elegant work of Rodriguez and Bonne involving central-to-axial chirality conversion strategy,[15] a possible reaction process was proposed (Scheme 4). The reaction process involves a regioselective conjugate addition followed by aromatization with a central-to-axial chirality conversion.[16] First, the enantioselective conjugative addition of 2-naphthylamines to iminoquinones catalyzed by chiral phosphoric acid **CPA1** is proceeded to form intermediate **M**. The following step transferred the central chirality information to the axial chirality, affording the final axially chiral biaryl-amino-alcohols via aromatization.[7g,i] Another pathway via a cascade process that involves sequential aminal formation, sigmatropic rearrangement, and aromatization cannot be ruled out at the present stage.[7h]




***Scheme 4.*** Proposed reaction mechanism.

To demonstrate the synthetic utility of the current method, the products were subjected to further transformations. **3a** reacted with bis(trifluoromethyl)phenyl isothiocyanate to produce axially chiral thiourea which is a potential organocatalyst with complete retention of enantiomeric purity (91% ee). After recrystallization from petroleum ether/DCM, the ee of thiourea was enriched to 99% (Scheme 5a). To expand the diversely functionalized axially chiral amino alcohols (Scheme 5b), the resultant product **3w** can be further transformed into aryl substituted axially chiral biaryl-amino-alcohols (**5a**-**5d**) without erosion of enantioselectivities via palladium-catalyzed-Suzuki cross-coupling reaction (for details, see Supporting Information).[17]




***Scheme 5.*** Further transformations to expand the diversity.

In conclusion, we have successfully developed the first phosphoric acid-catalyzed direct arylation approach for the atroposelective synthesis of axially chiral biaryl-amino-alcohols in moderate to good yields (up to 85% yield) with high enantioselectivities (up to 99% ee). Moreover, the reaction utilizes starting from readily available 2-naphthylamines and iminoquinones. This reaction features a rare example of 2-naphthylamines acting as nucleophiles in organocatalytic enantioselective transformation. Furthermore, the resultant products which contain various halogen atoms provide the possibility of transformation into structurally diverse axially chiral biaryl-amino-alcohols through further functionalization. Studies are ongoing in our group to apply these compounds as ligands and catalysts for asymmetric catalysis.

## Acknowledgements

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**Keywords:** biaryl-amino-alcohols • atroposelective • iminoquinones • arylation • 2-naphthylamines

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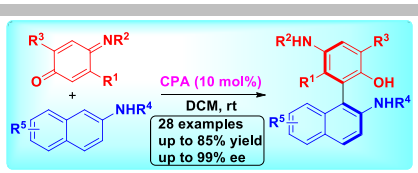
# COMMUNICATION

The first phosphoric acid-catalyzed direct arylation of 2-naphthylamines with iminoquinones for the atroposelective synthesis of axially chiral biaryl-amino-alcohols has been developed. This reaction features a highly functional group tolerant route to the rapid construction of enantio-enriched axially chiral amino alcohols with good results. This represents a rare example of 2-naphthylamines acting as nucleophiles in organocatalytic enantioselective transformation.

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**Practical Approach to Axially Chiral Biaryl-amino-alcohols via Organocatalytic Atroposelective Arylation of 2-Naphthylamines**