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# Enantioselective synthesis of 3-arylindole atropisomers *via* organocatalytic indolization of iminoquinones

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## Abstract

The direct enantioselective construction of axially chiral 3-arylindole frameworks *via* nucleophilic addition of 2-substituted indoles to iminoquinones has been achieved with high efficiencies under mild chiral phosphoric acid (CPA) catalytic conditions. The utility of this method was demonstrated in successful scale-up syntheses without compromising the product yields and enantioselectivities. The oxidation of products yields axially chiral heteroaryl-*p*-quinone monoimine, which could be subjected to structural diversification *via* addition of nucleophiles.

**Keywords:** Organocatalysis, iminoquinones, axial chirality, 3-arylindoles

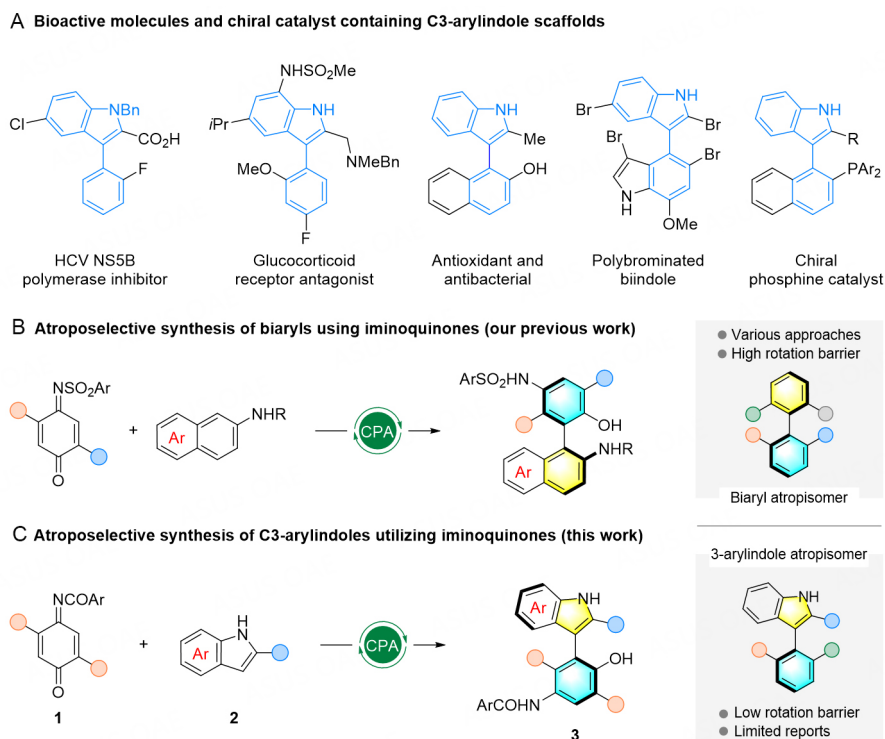
## INTRODUCTION

Indole-based compounds are an important class of small organic molecules. They are broadly present as core structural components in bioactive natural products, organic functional materials and pesticides<sup>[1-4]</sup>. As one of the prominent subclass, axially chiral 3-arylindole and its derivatives are valuable candidates used to derive bioactive molecules<sup>[5-8]</sup> and chiral catalysts [Scheme 1A]<sup>[9]</sup>. In line with the progression of axial chirality chemistry, the design and synthesis of axially chiral 3-arylindole frameworks have also emerged



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**Scheme 1.** The applications of representative molecules containing C3-arylidole framework and our designed strategy for their asymmetric synthesis. (A) Bioactive molecules and chiral catalysts containing C3-arylidole scaffolds; (B) the asymmetric construction of biaryl aminoalcohols using iminoquinones reported by our group; (C) our strategy for organocatalytic enantioselective synthesis of 3-arylidole atropisomers with iminoquinones.

recently<sup>[10]</sup>. Organocatalysis proved to be a useful synthetic tool and has unlocked strategies that range from atroposelective functionalization of preformed arylindole scaffolds<sup>[11-13]</sup> to direct arylation of indoles<sup>[14-19]</sup> and heteroarene formation<sup>[20-22]</sup>. The pioneering work in catalytic asymmetric construction of axially chiral arylindoles came from Zhang *et al.*<sup>[19]</sup>, who achieved atroposelective arylation of 2-naphthols or phenols with C3-electrophilic 2-indolylmethanols in the presence of chiral phosphoric acid (CPA) catalyst. In 2019, He *et al.*<sup>[21]</sup> prepared axially chiral 3-pyrrolylidole skeletons with asymmetric Barton-Zard reaction, following a sequence of pyrrole ring construction and central-to-axial chirality conversion. Differently, Lu *et al.*<sup>[22]</sup> successfully synthesized the axially chiral bridged C3-arylidoles through an ingenious cascade reaction between propargylic alcohols and enals by employing chiral N-heterocyclic carbene catalyst.

Although these strategies represent significant advances in the asymmetric synthesis of axially chiral indole compounds, more efficient synthetic methodologies are highly anticipated to enhance their availability and further accelerate their development and applications<sup>[10]</sup>. In particular, methods that could directly construct and define the configuration of stereogenic axis would enable modular assembly of these useful scaffolds. Our ongoing research on atroposelective organocatalytic arylation reactions has established the use of iminoquinone and its derivatives as arene precursors, which could undergo addition with different arene nucleophiles<sup>[23-25]</sup>. As an illustration, a CPA-catalyzed direct arylation of 2-naphthylamine with iminoquinones as electrophiles could accomplish the asymmetric construction of axially chiral biaryl aminoalcohols [Scheme 1B]<sup>[24]</sup>. In light of these preceding studies and the verified use of iminoquinones in the synthesis of axially chiral scaffolds, we envisioned the assembly of new axially chiral 3-arylidole framework through the asymmetric coupling of indoles with iminoquinones, as shown in Scheme 1C.

Although the reaction is conceptually feasible, substantial challenges could lie in achieving the enantioselective construction of this framework. In contrast with prior studies that employ iminoquinone substrates to generate six-membered (hetero)biaryls, the lower rotational barrier of five-membered 3-arylindole scaffolds might promote racemization and compromises the reaction enantioselectivity. The configuration stability of such scaffolds is typically lower than the six-membered (hetero)biaryl atropisomers<sup>[26,27]</sup>. To impede the free rotation around the newly formed C-C axis, we sought to amplify the steric effect at the iminoquinone moiety or at the C2-position of indoles. On the other hand, the presence of multiple reactive sites on both reacting substrates could interfere with the control of regio- and enantioselectivity in the synthesis of 3-arylindole atropisomers **3**. In this regard, a suitable bifunctional organocatalyst such as chiral phosphoric acid (CPA) should overcome the substrate-imposed selectivity bias, thereby providing exquisite chemo- and stereoselectivity control during the C-C bond formation. In addition, the *N*-protecting groups of iminoquinones could be a useful tuning parameter to modulate selectivities.

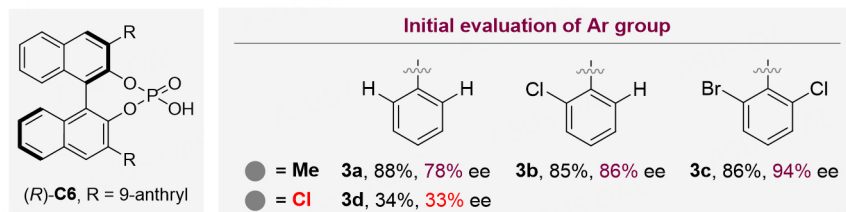
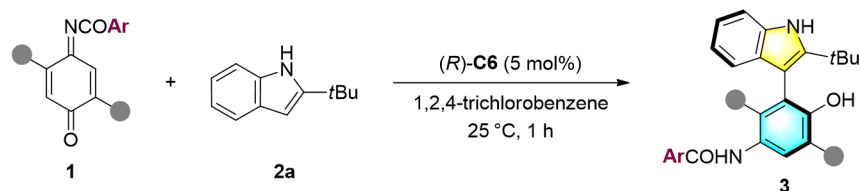
## EXPERIMENTAL

Chiral phosphoric acid (*R*)-**C6** (5 mol%), **1** (0.28 mmol) and **2** (0.20 mmol) were added to a Schlenk tube, then 4 mL of 1,2,4-trichlorobenzene was added *via* syringe in one portion. Upon the completion of the reaction (about 1 h), the mixture was purified by preparative TLC (CH<sub>2</sub>Cl<sub>2</sub>/PE = 5/1 to 6/1) to give the pure products **3**.

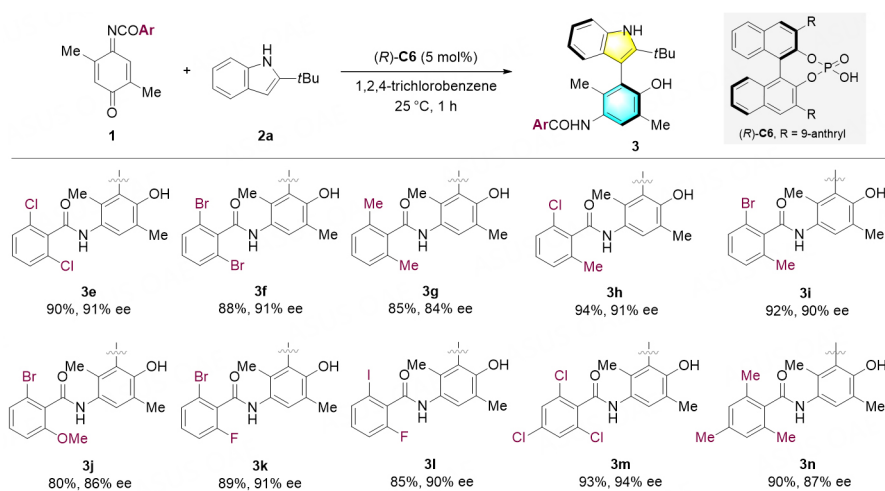
## RESULTS AND DISCUSSION

To validate the approach, we initiated exploration with *N*-benzoyl iminoquinone **1a** and 2-(*tert*-butyl)-1*H*-indole **2a** as the model nucleophile in view of its good nucleophilicity. The large steric hindrance at C2-position was expected to stabilize the newly formed chiral axis. Different chiral phosphoric acids were first evaluated and all were found to smoothly promote the model reaction to afford axially chiral product **3a** at room temperature (see [Supplementary Materials](#) for details). This screening revealed (*R*)-**C6** to afford the best overall product yield and enantioselectivity. Other solvents were subsequently investigated based on (*R*)-**C6** as the optimal catalyst. The discovery that toluene could deliver better enantioselectivity than dichloromethane and 1,2-dichloroethane led us to screen a series of benzene-derived solvents. 1,2,4-trichlorobenzene was thus chosen as the reaction solvent due to its best performance. Having noticed that further fine-tuning of other parameters did not improve the results (**3a**, 88% yield, 78% *ee*, [Scheme 2](#)), we turned to modulating the *N*-protecting group of iminoquinones for a breakthrough. As shown in [Scheme 2](#), we were delighted to find that the replacement of H atom by Cl atom at C2-position on the benzoyl group would enhance the product *ee* to 86% (**3b**). When the C2 and C6 positions were occupied by Cl and Br substituents respectively, product **3c** could be derived with 94% *ee* under the same conditions (see [Supplementary Materials](#) for details). The dramatic decrease of yield and *ee* value (**3d**, 34%, 33% *ee*) observed for **1d** suggested the great influence that the iminoquinone substituents have had on the reaction.

The substrate generality of iminoquinones was then systematically examined under optimal reaction conditions. As shown in [Scheme 3](#), all of the tested iminoquinones reacted smoothly with **2a** to afford the corresponding products with moderate to high efficiencies (up to 94% yield and 94% *ee*). Notably, different aromatic substituents and substitution positions on the benzoyl group were tolerated. Overall, various halogen atoms (F, Cl, Br, I) or Me group could be incorporated as the C2 and C4 substituents without significant influence on the reaction outcomes. The benzoyl group could also bear 2,4,6-trisubstitution with Cl or Me groups to afford **3m** and **3n** in good results. Nonetheless, slightly inferior enantioselectivities (84%-87% *ee*) could be seen for substrates with methyl substitutions (**3g** and **3n**) or with methoxy group (**3j**).



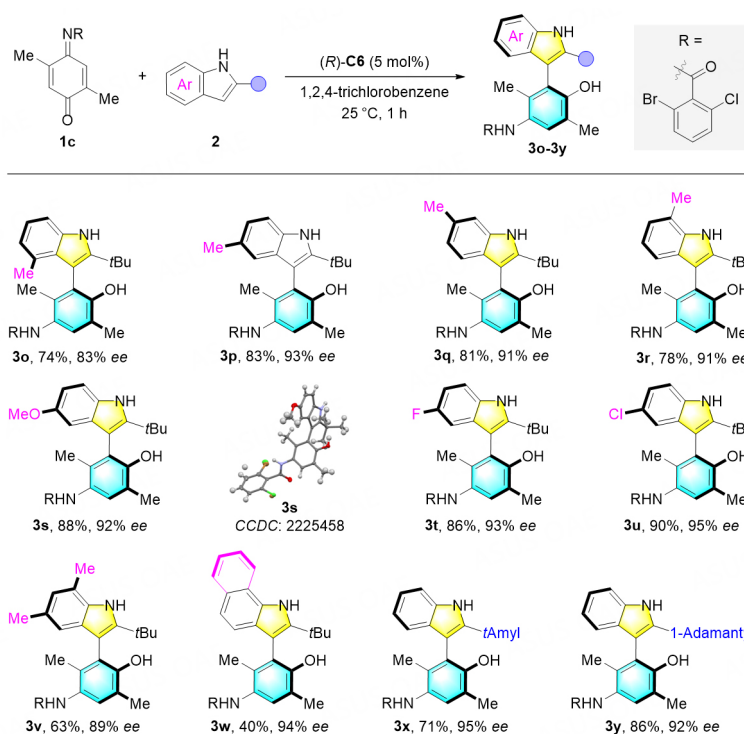
**Scheme 2.** Evaluation of different *N*-protecting groups and substituents on iminoquinones.



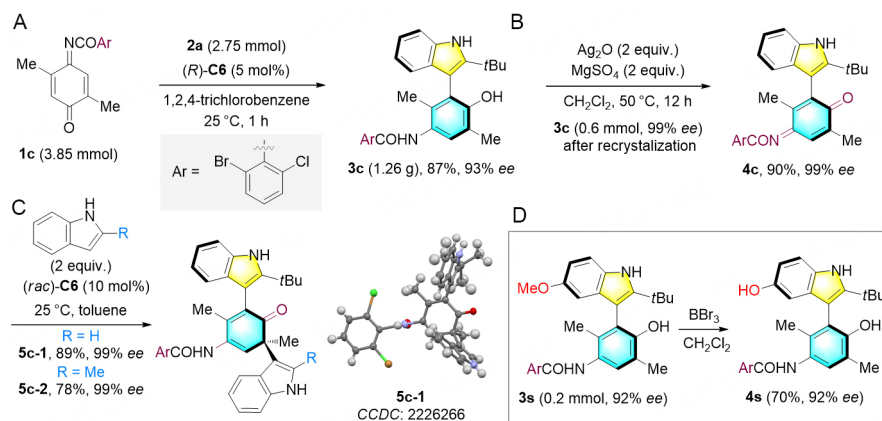
**Scheme 3.** Substrate scope with respect to iminoquinones.

Inspired by the above results, we then turned our attention to investigating the generality of indole substrates [Scheme 4]. From the selected examples (**3p**, **3s**, **3t** and **3u**), it could be recognized that the electronic properties of the indole substituents presented limited impact on the product yields and enantioselectivities. However, a more pronounced structural variation of substrates such as disubstitution (**3v**) and an additional fused ring (**3w**) could negatively affect the product yields. As expected, 2-(*tert*-pentyl)-1*H*-indole and 2-(1-adamantyl)-1*H*-indole were also effective nucleophiles to give the corresponding products **3x** and **3y**. Our method thus represents one of the most straightforward ways to access axially chiral C3-arylindoles. The absolute configuration of the product **3s** was confirmed by X-ray crystallography (CCDC: 2225458) and the stereochemistry of other products has been assigned by analogy.

To further demonstrate the utility of this strategy, the scale-up synthesis of **3c** and a series of chemical transformations were conducted. First, the gram-scale reaction could deliver product **3c** with nearly the same yield (87%) and enantioselectivity (93% *ee*) as the small-scale reaction [Scheme 5A]. The oxidative treatment of compound **3c** with Ag<sub>2</sub>O gave the atropisomeric heteroaryl-*p*-quinone monoimine **4c** in 90% yield without any erosion of enantioselectivity [Scheme 5B]. The unsaturated nature of this novel axially chiral heteroaryl-*p*-quinone monoimine compound sets the stage for nucleophilic addition: With indoles as

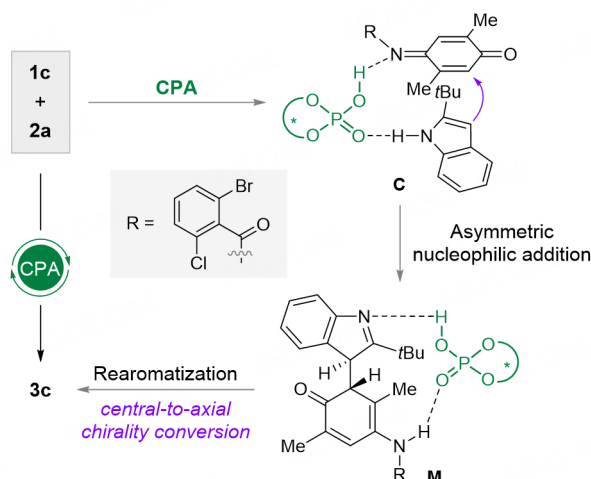


Scheme 4. Substrate scope of indoles.

Scheme 5. Gram-scale reaction and derivatization of C3-arylindole products. (A) Gram-scale synthesis of **3c**; (B) oxidation reaction of **3c**; (C) nucleophilic addition of indoles with **4c**; (D) demethylation reaction of **3s**.

the representative C-nucleophiles, products **5c-1** and **5c-2** that display both axial and central chirality could be accessed in the presence of phosphoric acid catalyst *rac*-C6. The absolute configuration of **5c-1** (CCDC: 2226266) was unambiguously assigned by single-crystal X-ray diffraction analysis [Scheme 5C]. Next, the methoxy group of **3s** could be readily deprotected by  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  to yield compound **4s**, which should serve as useful skeleton to design chiral catalysts and ligands [Scheme 5D].

Based on the experimental results and reported literature<sup>[23,24]</sup>, a plausible reaction mechanism with representative substrates was put forward, as illustrated in Scheme 6. At the beginning of reaction, CPA catalyst simultaneously activates **1c** and **2a** through a bifunctional H-bonding activation mode (C).



Scheme 6. Proposed reaction pathway.

Subsequently, a stereoselective coupling proceeds and gives rise to adduct **M** with well-defined contiguous chiral centers. Rearomatization of product **M** under standard conditions is accompanied by efficient central-to-axial chirality conversion to give the final product **3c**.

## CONCLUSIONS

In summary, the enantioselective construction of 3-arylidole atropisomers was efficiently accomplished by organocatalytic indolization of iminoquinones in the presence of CPA catalyst. The conditions were proven to be scalable and various downstream synthetic transformations demonstrated the utilities of this strategy. The oxidation of the obtained products furnished a novel axially chiral heteroaryl-*p*-quinone monoamine compound, which could serve as an enantioenriched precursor to construct functionalized axially chiral indoles *via* nucleophilic addition. Further exploration of this reactivity is underway in our laboratory.

## DECLARATIONS

### Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Tan B, Chen YH

Performing the experiments and synthesizing the substrates: Liu YW, Cheng JK, Xiang SH

### Availability of data and materials

The X-ray crystallographic coordinates for the structure of **3s** and **5c-1** reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 2225458 and 2226266. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). Experimental procedures and characterization of new compounds are available in the [Supplementary Materials](#).

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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