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COMMUNICATION

Organocatalytic asymmetric synthesis of arylindolyl indolin-3-ones with both axial and central chirality

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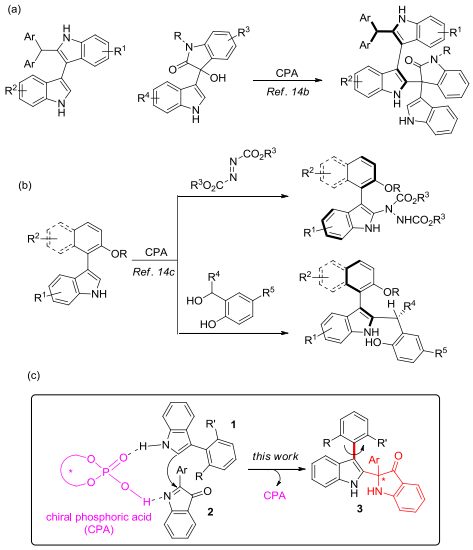
An efficient method for chiral phosphoric acid-catalyzed asymmetric synthesis of arylindolyl indolin-3-ones with both axial and central chirality has been developed via reaction of 3-arylindoles with 2-aryl-3*H*-indol-3-ones, and the target products were obtained in high yields with excellent enantioselectivity and diastereoselectivity.

Axially and centrally chiral molecules are ubiquitous in nature, chemical and pharmaceutical fields. Axially chiral biaryl compounds are privileged structures in natural products and biologically active molecules,[1,2] and they also are key cores of chiral ligands and catalysts.[3] Recently, the rapid progress has been achieved in the asymmetric synthesis of axially chiral scaffolds.[4-10] However, the six-membered biaryls are overwhelming in previous prepared axially chiral backbones. In sharp contrast, the construction of axially chiral five-membered aryl, especially five-membered heteroaryl scaffolds remains limited[11] because lower rotation barriers and conformational stability of five-membered heteroaryl scaffolds.[12] 3-Arylindoles exhibit diverse biological functions.[13] For example, they are used as HCV NS5B polymerase inhibitors, glucocorticoid receptor antagonists, antioxidant, antibacterial, and antibiofilm agents. Therefore, the catalytic asymmetric synthesis of the axially chiral arylindole scaffolds has recently attracted increasing attention.[14] On the other hand, indolin-3-ones containing a centrally chiral C2 quaternary carbon are one of the privileged structural motifs in natural products and biologically active molecules such as (-)-isatisine A, (-)-isatisine A acetonide , strobilanthoside A,[15] and they have been widely used as the building blocks in the synthesis of some natural alkaloids.[16] Recently, some excellent methods for the enantioselective synthesis of the indolin-3-one skeletons have been developed.[17,18] Since the original works from the research groups of Akiyama[19a] and Terada[19b] in 2004, the axially chiral phosphoric acids (CPA) have been widely applied in the asymmetric synthesis.[20] In 2019, Shi and co-workers reported CPA-catalyzed asymmetric synthesis of 3,3′-bisindole skeletons via reaction of 2-substituted 3,3'-bisindoles with 3-indolylmethanols (Scheme 1a).[14b] Subsequently, the group developed CPA-catalyzed asymmetric addition reactions of racemic naphthyl-indoles with bulky electrophiles (Scheme 1b).[14c] Inspired by the previous works, we envisioned a CPA-catalyzed asymmetric synthesis of arylindolyl indolin-3-ones containing both axial and central chirality via reaction of 3-arylindoles with 2-aryl-3*H*-indol-3-ones. (Scheme 1c).



Scheme 1 Asymmetric synthesis of axially chiral 3-arylindoles

To verify our design in Scheme 1c, reaction of methyl 3,6-dihydroxy-2-(1*H*-indol-3-yl)benzoate (**1a**) with 2-phenyl-3*H*-indol-3-one (**2a**) was used as the model to optimize conditions including chiral phosphoric acids, solvents, time and ratios of the two substrates. The results showed that the optimal conditions were as follows: 10 mol% (*R*)-**4a** as the organocatalyst, chloroform as the solvent at room temperature under Ar atmosphere for 24 h with 1.2:1 ratio of **1a**/**2a** (see Table S1 in ESI for details).

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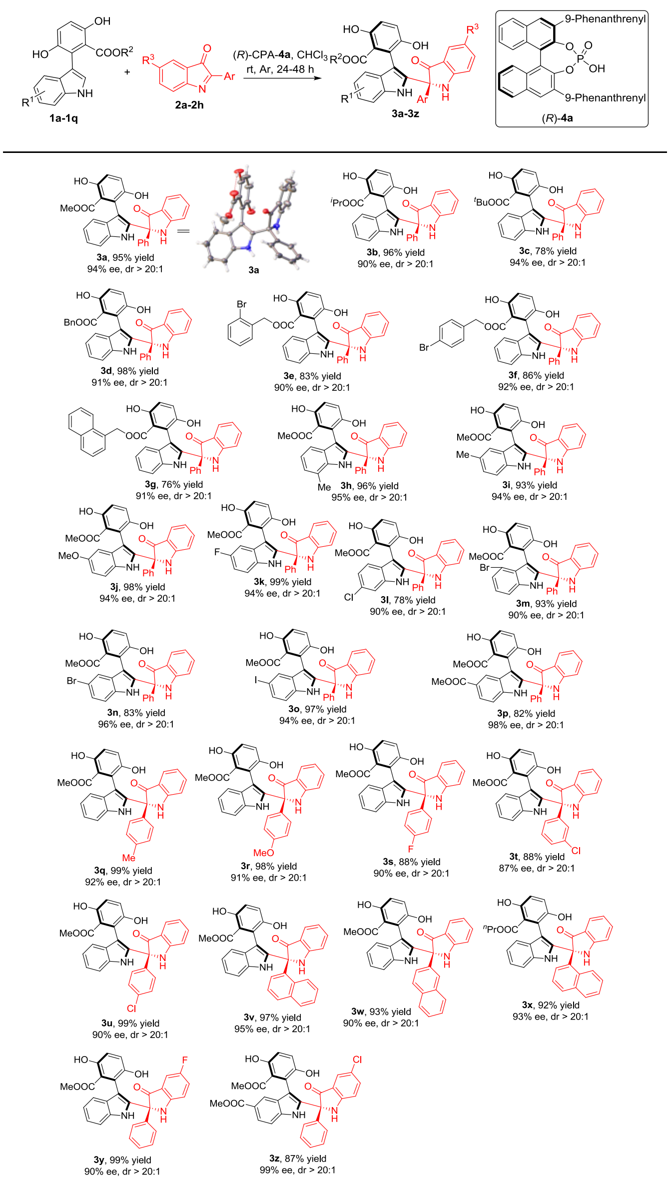
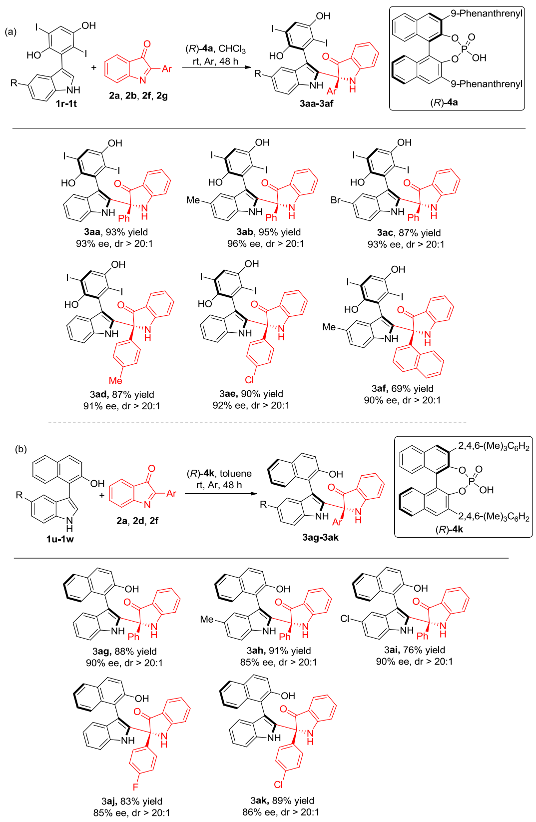
Table 1 Substrate scope for reactions of 3-arylindoles (**1**) and 2-aryl-3*H*-indol-3-ones (**2**)[a]



[a] Reaction conditions: under argon atmosphere, 3-arylindole (**1**) (0.12 mmol, 1.2 equiv, 0.06 M), 2-aryl-3*H*-indol-3-one (**2**) (0.1 mmol, 1.0 equiv, 0.05 M), (*R*)-**4a** (10 µmol, 10 mol%), $CHCl_3$ (2.0 mL), temperature (rt, ~25 °C), time (24-48 h, see ESI for details) in a sealed Schlenk tube. Isolated yield, and the ee values were determined by HPLC analysis on a chiral stationary phase. The dr values were determined by ^1H NMR analysis of the crude reaction mixtures after removal of $CHCl_3$. Absolute configurations of products **3b-3z** were determined by comparing structure of (S_a,*R*)-**3a** (absolute configuration of (S_a,*R*)-**3a** was confirmed by X-ray diffraction analysis).

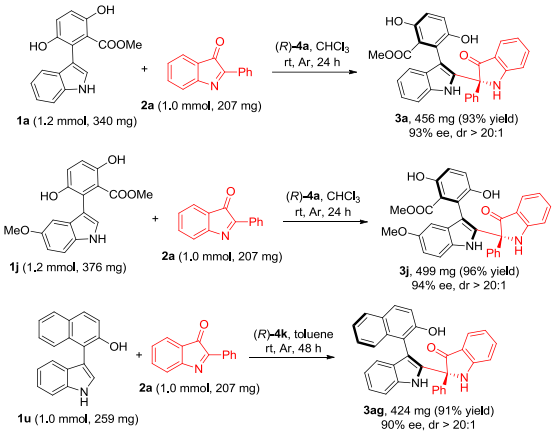
With the optimized conditions in hand, substrate scope was surveyed for reaction of different substituted 3-arylindoles (**1**) with 2-phenyl-3*H*-indol-3-one (**2a**) leading to arylindolyl indolin-3-ones (**3**) under catalysis of (*R*)-**4a**. As shown in Table 1, we first investigated different ester groups R^2 in **1** and found that steric hindrance of ester groups was not obvious for enantioselectivity (90-94% ee), but the esters containing bigger steric hindrance provided lower yields (see **3c** and **3g**). Subsequently, substrates **1** containing different R^1 substituents including electron-donating (see **3h-3j**), weak electron-withdrawing (see **3k-3o**) and stronger electron-withdrawing (see **3p**) groups were tested, and the results showed that the electronic effect of R^1 substituents did not lead to obvious difference in the enantioselectivity. However, reactivity of the substrates was related to position of R^1 substituents, and the substrate containing 6-Cl in **1** gave lowest yield (see **3l**). Furthermore, 2-aryl-3*H*-indol-3-ones (**2**) with different aromatic groups were attempted, and they all gave the satisfactory yields and ee values (see **3q-3w**). Simultaneous variation of R^1, R^2 and Ar substituents in **1** and **2** was investigated, and these substrates afforded high yields (87-99%) and excellent ee values (90-99% ee) (see **3x-3z**). We attempted reactions of 3*H*-indol-3-ones with alkyl group such as 2-methyl-3H-indol-3-one with **1**. Unfortunately, the corresponding target products were not obtained. The present protocol could tolerate various functional groups including ester, carbonyl, hydroxyl, ether groups, and C-F, C-Cl, C-Br, C-I bonds. In addition, the synthesized arylindolyl indolin-3-ones (**3**) are a new type of axially and centrally chiral backbones, and we believe that the arylindolyl indolin-3-ones (**3**) will find application in medicinal chemistry.



Scheme 2 (*a*) Synthesis of **3aa-3af**. Conditions: under argon atmosphere, substituted 3-(1*H*-indol-3-yl)-2,5-diiodobenzene-1,4-diol (**1r-1t**) (0.1 mmol, 1.0 equiv, 0.05 M), 2-aryl-3*H*-indol-3-one (**2**) (0.1 mmol, 1.0 equiv, 0.05 M), (*R*)-**4a** (10 µmol, 10 mol%), $CHCl_3$ (2.0 mL), temperature (rt, ~25 °C), time (48 h) in a sealed Schlenk tube. (*b*) Synthesis of **3ag-3ak**. Conditions: under argon atmosphere, substituted 1-(1*H*-indol-3-yl)naphthalen-2-ol (**1u-1w**) (0.1 mmol, 1.0 equiv, 0.2 M), 2-aryl-3*H*-indol-3-one (**2**) (0.1 mmol, 1.0 equiv, 0.2 M), (*R*)-**4k** (10 µmol, 10 mol%), toluene (0.5 mL), temperature (rt, ~25 °C), time (48 h) in a sealed Schlenk tube. Isolated yields. The ee values of products **3aa-3ak** were determined by HPLC analysis on a chiral stationary phase, and their dr values were determined by ^1H NMR analysis of the crude reaction mixtures after removal of solvents. Absolute configurations of products **3aa-3ak** were

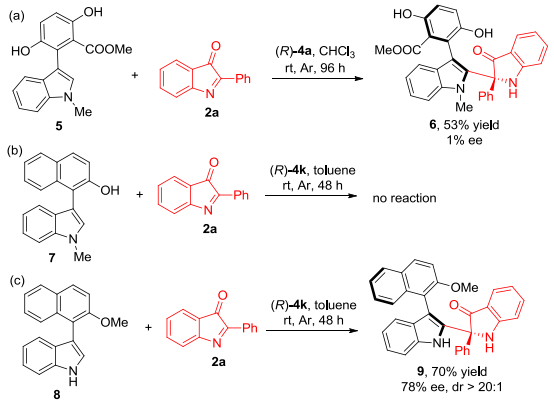
determined by comparing structure of (S_a,*R*)-**3a** (absolute configuration of (S_a,*R*)-**3a** was confirmed by X-ray diffraction analysis).

Inspired by the excellent results above, we extended substrate scope of **1** to substituted 3-(1*H*-indol-3-yl)-2,5-diiodobenzene-1,4-diols (**1r-1t**) with 2-phenyl-3*H*-indol-3-ones (**2a**, **2b**, **2f** and **2g**) as the partners under the standard conditions in Table 1, and their reaction provided 69-95% yields and 90-96% ee with diastereoselectivity (dr > 20:1) (Scheme 2a). Subsequently, we investigated reaction of substituted 1-(1*H*-indol-3-yl)naphthalen-2-ols (**1u-1w**) with **2a**, **2d** or **2f** in toluene using (*R*)-**4k** as the organocatalyst (see Table S2 in ESI for the optimization of conditions), and the corresponding products were obtained in 76-91% yields with 85-90% ee and dr > 20:1 (Scheme 2b). Therefore, the present method shows universality of extensive substrates.



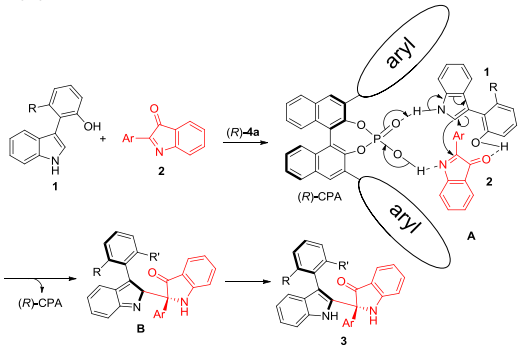
Scheme 3 Scale synthesis of (S_a,*R*)-**3a**, (S_a,*R*)-**3j** and (S_a,*R*)-**3ag**.

We attempted scale up synthesis of (S_a,*R*)-**3a**, (S_a,*R*)-**3j** and (S_a,*R*)-**3ag**. As shown in Scheme 3, reaction of **1a**, **1j** or **1u** with **2a** under the standard conditions provided (S_a,*R*)-**3a**, (S_a,*R*)-**3j** and (S_a,*R*)-**3ag** almost without loss of reactivity and enantioselectivity comparing with the small-scale reactions in Table 1 and Scheme 2, which showed that the present method was a very effective and practical approach to the axially and centrally chiral arylindolyl indolin-3-ones.



Scheme 4 Investigations on the reaction mechanism.

To explore mechanism of the reaction above, we attempted reaction of methyl 3,6-dihydroxy-2-(1-methyl-1*H*-indol-3-yl)benzoate (**5**) with 2-phenyl-3*H*-indol-3-ones (**2a**) under the standard conditions. As shown in Scheme 4a, the reaction afforded product **6** in 53% yield almost without enantioselectivity, and a long reaction time (96 h) was needed. Further, reaction of **7** with **2a** did not work under the standard conditions (Scheme 4b). Comparing the results in Table 1, Scheme 2 and Scheme 4, we think that interaction between NH in 3-arylindoles (**1**) and CPA is of great concern in controlling both the reactivity and enantioselectivity. We attempted reaction of **8** with **2a** under the standard conditions, and product **9** was obtained in 70% yield with 78% ee (Scheme 4c), which indicated that an additional hydrogen bond could be formed between the hydroxyl of **1u** and the carbonyl of **2a** during synthesis of **3ag** (see complex A in Scheme 5). According to the results above, a reaction pathway of this CPA-catalyzed asymmetric synthesis of arylindolyl indolin-3-ones (**3**) is proposed. As shown in Scheme 5, substrates **1** and **2** first enter the catalytic active region of (*R*)-CPA, and simultaneous formation of three hydrogen bonds between (*R*)-CPA and **1** or **2** leads to three-component complex **A**. Subsequently, transfer of the two protons in the complex provides intermediate **B** releasing (*R*)-CPA, and tautomerization in **B** gives the target product (**3**).



Scheme 5 A possible mechanism for the CPA-catalyzed enantioselective reaction of **1** with **2**.

Furthermore, we investigated stability of (S_a,*R*)-**3ag** at different temperatures (Fig. 1). No racemization was observed by chiral HPLC determination after treatment of (S_a,*R*)-**3ag** in *o*-xylene below 120 °C for 12 h, but incubation above 120 °C decreased the diastereoselectivity (see ESI for details).

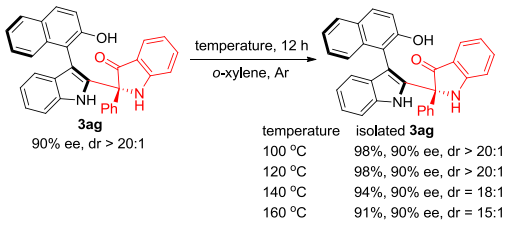
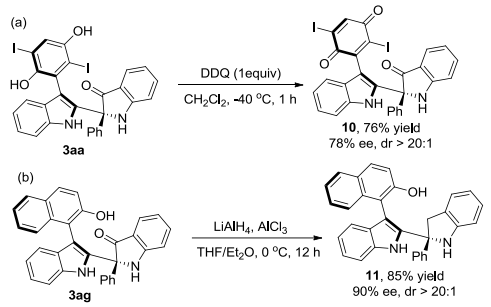


Fig. 1 Investigations on the stability of the axially chirality in (S_a,*R*)-**3ag** at different temperatures.

Furthermore, derivatization of the chiral products was carried out (Scheme 6). Product **3aa** was efficiently converted into aryl-*p*-quinone atropisomer **10** under oxidation of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 76% yield with 78% ee, which would be platform molecules for the preparation of non-C_2 symmetric biaryldiols.[21a] Reduction of **3ag** in the presence of $LiAlH_4$ and $AlCl_3$[21b] gave **11** in 85% yield with 90% ee.



Scheme 6 Derivatization of the chiral products

In summary, we have developed an efficient method for chiral phosphoric acid-catalyzed asymmetric synthesis of arylindolyl indolin-3-ones with an axial chirality and a quaternary stereocenter chirality via reaction of 3-arylindoles with 2-aryl-3*H*-indol-3-ones, and the target products were obtained in high yields with excellent enantioselectivity and diastereoselectivity. The present method not only provides a new kind of axially and centrally chiral arylindolyl indolin-3-one backbones, but also affords an organocatalytic protocol for the simultaneous construction of both axial and central chirality in a molecule.

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Conflicts of interest

There are no conflicts to declare

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Graphical abstract

Organocatalytic asymmetric synthesis of arylindolyl indolin-3-ones with both axial and central chirality

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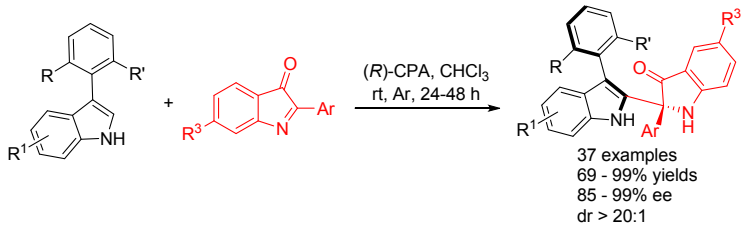

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