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Article

Design and synthesis of axially chiral aryl-pyrroloindoles via the strategy of organocatalytic asymmetric (2 + 3) cyclization

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ABSTRACT

The catalytic asymmetric construction of axially chiral indole-based frameworks is an important area of research due to the unique characteristics of such frameworks. Nevertheless, research in this area is still in its infancy and has some challenges, such as designing and constructing new classes of axially chiral indole-based scaffolds and developing their applications in chiral catalysts, ligands, etc. To overcome these challenges, we present herein the design and atroposelective synthesis of aryl-pyrroloindoles as a new class of axially chiral indole-based scaffolds via the strategy of organocatalytic asymmetric (2 + 3) cyclization between 3-arylindoles and propargylic alcohols. More importantly, this new class of axially chiral scaffolds was derived into phosphines, which served as efficient chiral ligands in palladium-catalyzed asymmetric reactions. Moreover, theoretical calculations provided an in-depth understanding of the reaction mechanism. This work offers a new strategy for constructing axially chiral indole-based scaffolds, which are promising for finding more applications in asymmetric catalysis.

1. Introduction

Axially chiral biaryls belong to a class of intriguing chiral frameworks that constitute the core units of privileged chiral catalysts or ligands [1], natural products [2], bioactive molecules [3] and functional materials [4]. Consequently, catalytic atroposelective construction of such frameworks has attracted considerable interest in the chemistry community and resulted in excellent achievements in this research area [5–16]. However, the most prevalent axially chiral biaryls constructed are six-membered (hetero)biaryls, as exemplified by binaphthyl, biphenyl and 1-arylisoquinolines (Fig. 1a) [5–10]. In contrast, the catalytic asymmetric construction of axially chiral five-membered heterobiaryls is underdeveloped [11–16] because there are more challenges associated with constructing this class of scaffolds, such as more distant ortho-groups, lower rotational barriers and less stable configuration [11,12].

Indole, a five-membered heteroaryl, is electronically rich and highly aromatic and bears a free NH group (Fig. 1b). The structure and properties of indoles bring some unique characteristics to axially chiral indole-based frameworks, such as changing the electron density, modulating steric congestion, enabling postfunctionalization and acting as hydrogen bond donors [17]. Therefore, in recent years, the catalytic asymmetric construction of axially chiral indole-based frameworks has become an emerging research area [17]. Chemists have made great endeavors in this area and constructed *N*-arylindoles [18–20], 3-arylindoles [21–29], 2-arylindoles [30–32], bisindoles [33–36] and other indole-based frameworks [37–43] (Fig. 1c). Nevertheless, research in this area is still in its infancy and has some challenging issues, such as the design and construction of new classes of axially chiral indole-based scaffolds and the development of their applications in chiral catalysts or ligands, pharmaceuticals and materials.

Among the frameworks constructed to date, axially chiral 3-arylindoles are of particular concern because this class of scaffolds has potential utility in chiral phosphine catalysts and bioactive molecules (Fig. 2a) [25]. Asymmetric organocatalysis has recently proven to be a powerful method for constructing axially chiral backbones [5]. Currently, representative organocatalytic approaches for atroposelective construction of axially chiral 3-arylindoles include three main strategies (Fig. 2b). Strategy I involves coupling of an indole ring with an aryl ring and has been well utilized in our previous coupling of 2-indolylmethanols with 2-naphthols (Eq. 1) [21] and Tan's coupling of 2-substituted indoles with azonaphthalenes or nitrosonaphthalenes

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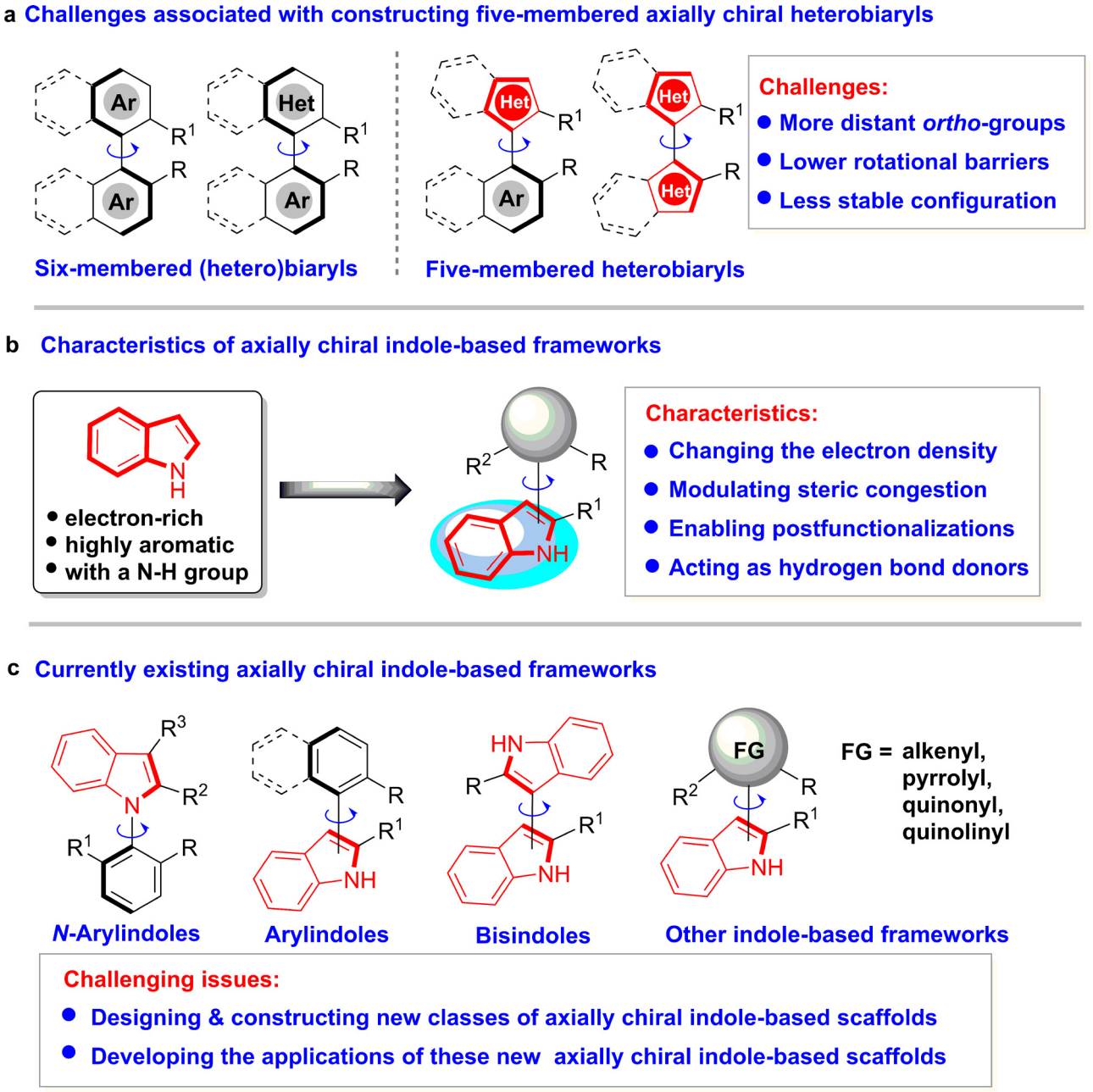


Fig. 1. Profile of the catalytic asymmetric construction of axially chiral (hetero)biaryls.

(Eq. 2) [22,23], both of which are catalyzed by chiral phosphoric acid (CPA) [44]. Strategy II involves construction of an indole ring *in situ*, as elegantly demonstrated by Tan's rearrangement of 2-substituted indoles with azonaphthalenes or nitrosonaphthalenes in the presence of CPA (Eq. 3) [22,23] and Zhao's cascade reaction of propargylic alcohols with enals catalyzed by chiral *N*-heterocyclic carbene (NHC*) to access bridged 3-arylindoles fusing an eight-membered lactone ring (Eq. 4) [24]. Strategy III involves the nucleophilic addition of racemic 3-arylindoles, which was devised in our previous work in which azodicarboxylates or o-hydroxybenzyl alcohols were used as acceptors for the CPA-catalyzed addition reaction (Eq. (5)) [25]. Despite these approaches, the strategies for atroposelective construction of such scaffolds are still rather limited and require innovative design. Therefore, there is an urgent need to develop new strategies for designing and constructing 3-arylindole-related axially chiral scaffolds.

2. Results and discussion

2.1. Design of a new strategy and new axially chiral scaffolds

To achieve the above mentioned goal and to continue our long-term efforts in chiral indole chemistry [45], we devised a new strategy of (2 + n) cyclization of racemic 3-arylindoles to construct a new class of axially chiral 3-arylindole-fused frameworks (Fig. 3a). In this strategy, we aimed to utilize the indole C2-position and the NH group as nucleophilic sites, thus making 3-arylindoles act as 1,2-dinucleophiles to undergo (2 + n) cyclization with suitable dielectrophiles (E^1-E^2) under the catalysis of a chiral Brønsted acid (B^*-H). Due to the steric congestion between the newly formed ring system and the OH group around the axis, a new class of axially chiral 3-arylindole-fused frameworks is constructed. This strategy has unique advantages and is capable of forming a new ring,

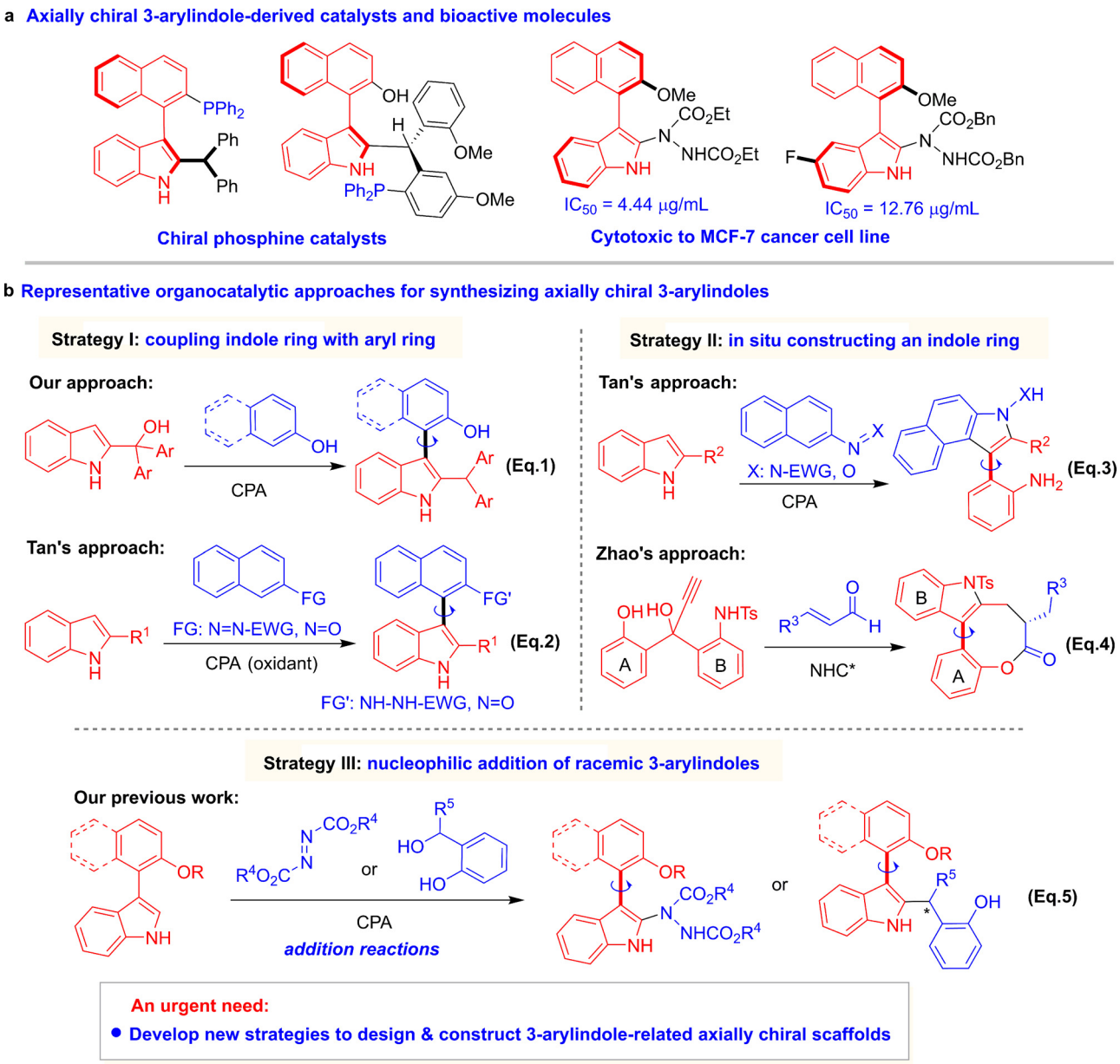


Fig. 2. Profile of the organocatalytic asymmetric synthesis of axially chiral 3-arylindoles.

constructing a new class of axially chiral scaffolds and generating multiple chiral elements [46]. Nevertheless, there are also some challenges to overcome, which mainly include (1) finding suitable dielectrophiles that can be activated by B*-H to realize (2 + n) cyclization with 3-arylindoles; (2) controlling the regioselectivity and enantioselectivity of the (2 + n) cyclization since there are two competitive reactive sites in both reaction partners; and (3) controlling both the axial chirality and the central chirality of the constructed frameworks when employing racemic dielectrophiles in the (2 + n) cyclization.

To overcome these challenges, we considered whether propargylic alcohols [47–50] bearing a para-hydroxyphenyl or para-alkoxyphenyl group could be utilized as suitable dielectrophiles in our designed (2 + n) cyclization. This idea was based on the pioneering work of Sun's group (Fig. 3b) [51], who discovered that this class of propargylic alcohols could be transformed into *para*-quinone methide intermediates (*p*-QMs) via dehydration under the catalysis of B*-H, thus undergoing asymmetric 1,8-addition with nucleophiles (Nu) to generate axially chiral allenes [51,52].

In our design (Fig. 3c), we envisioned that this class of propargylic alcohols could act as 1,3-dielectrophiles to react with 3-arylindoles under the catalysis of CPA, therefore establishing an enantioselective (2 + 3) cyclization and constructing a new class of axially chiral aryl-pyrroloindole scaffolds [53]. This reaction is anticipated to proceed via 1,8-addition to generate chiral allene intermediates via a dynamic kinetic resolution (DKR) process, followed by protonation and intramolecular cyclization to afford axially chiral aryl-pyrroloindoles. During the reaction sequence, it is suggested that CPA successively activates the OH group and the NH group of 3-arylindoles, thus controlling the regioselectivity of the (2 + 3) cyclization. Moreover, the interaction of CPA with the substrates and intermediates facilitates a DKR process and stereoselective intramolecular cyclization, thus controlling the axial and central chirality of the constructed aryl-pyrroloindole frameworks. Therefore,

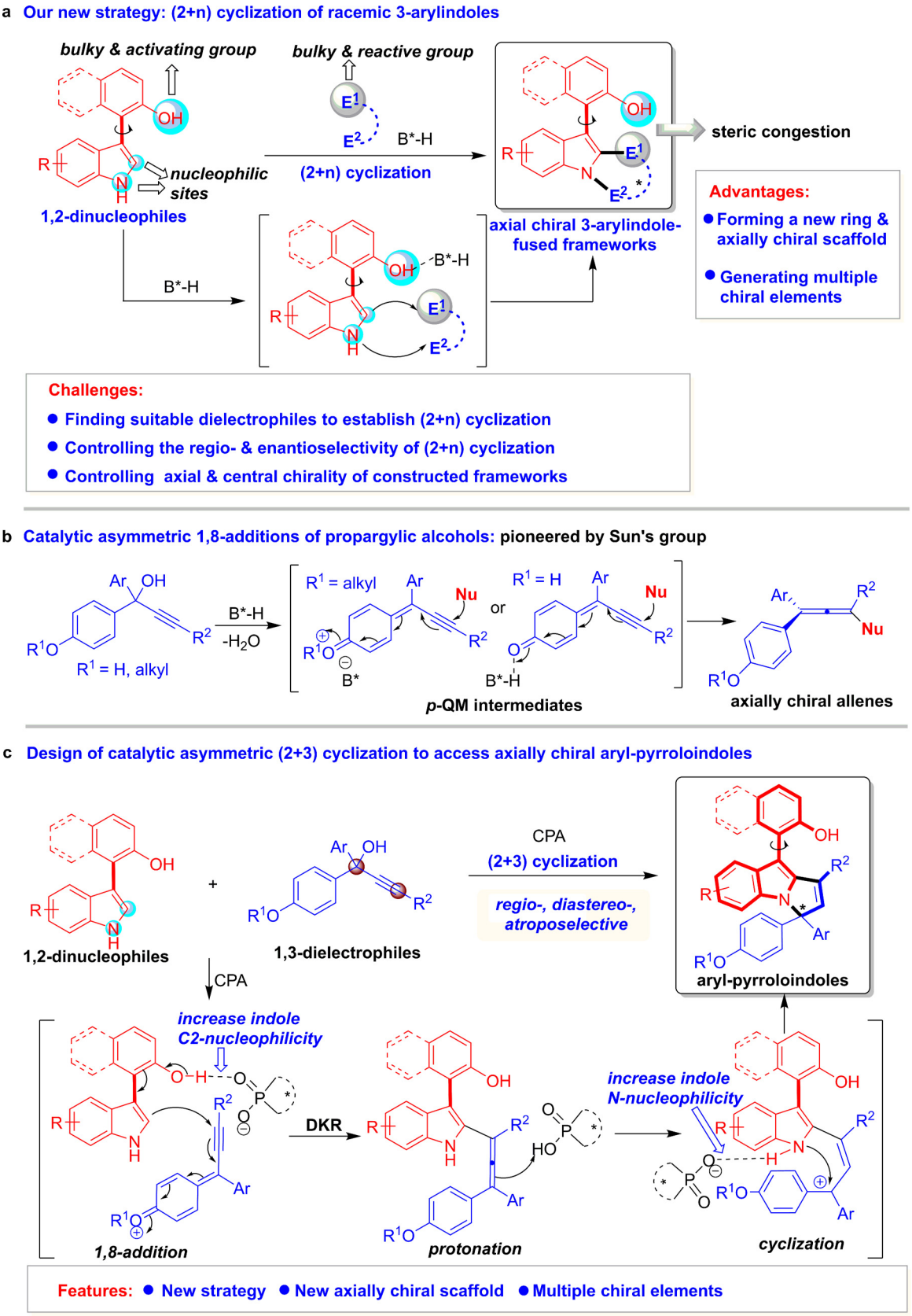


Fig. 3. Design of a new strategy for constructing a new class of axially chiral 3-arylindole-fused frameworks.

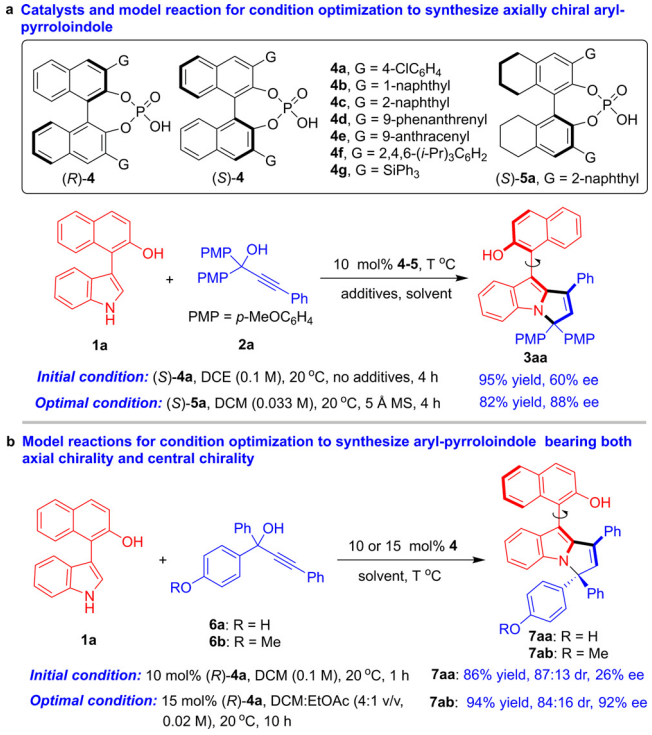


Fig. 4. Catalysts and model reactions employed for condition optimization.

our designed (2 + 3) cyclization is expected to provide a new strategy for constructing a new class of axially chiral indole-based scaffolds with simultaneous control of multiple chiral elements.

2.2. Optimization of reaction conditions

Based on our design, we optimized the conditions used in the organocatalytic asymmetric (2 + 3) cyclization to construct axially chiral aryl-pyrroloindole scaffolds. The details are included in Tables S1, S2 and the related discussion of the Supporting Information. For clarity, the chiral catalysts and model reactions employed in this condition optimization are illustrated in Fig. 4. In brief, the reaction of 3-arylindole **1a** with propargylic alcohol **2a** was utilized as a model reaction to test the feasibility of our design (Fig. 4a). Gratifyingly, in the presence of CPA (*S*)-**4a**, asymmetric (2 + 3) cyclization between **1a** and **2a** in 1,2-dichloroethane (DCE) at 20 °C successfully occurred in a regiospecific manner, generating axially chiral aryl-pyrroloindole **3aa** in a high yield of 95% with a moderate enantioselectivity of 60% ee. This preliminary result demonstrated the feasibility of our strategy for designing and constructing this class of new axially chiral scaffolds. The subsequent condition optimization was carried out by evaluating CPAs **4**-**5**, solvents, reagent ratios, additives, reactant concentrations and temperatures (see Table S1 of the Supporting Information). Finally, the optimal reaction conditions were determined to include CPA (*S*)-**5a** as a catalyst, dichloromethane (DCM) as a solvent and 5 Å molecular sieves (MS) as additives, which afforded axially chiral aryl-pyrroloindole **3aa** in a high yield of 82% with a good enantioselectivity of 88% ee.

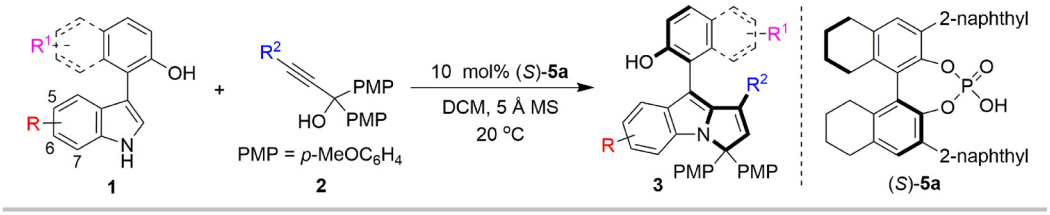
Then, we aimed to construct aryl-pyrroloindole frameworks bearing both axial and central chirality, which is far more challenging due to the difficulty of simultaneous control of multiple chiral elements in one molecule. Initially, the reaction of 3-arylindole **1a** with racemic propargylic alcohol **6a** bearing a *para*-hydroxyphenyl group was employed as a model reaction for condition optimization (Fig. 4b). In the presence of CPA (*R*)-**4a**, the (2 + 3) cyclization of **6a** with **1a** in DCM at 20 °C rapidly occurred to afford aryl-pyrroloindole product **7aa** bearing both axial and central chirality in a high yield of 86% and a good diastereoselectivity of 87:13 dr, albeit with a low enantioselectivity of 26% ee. However, other CPAs could not catalyze the reaction with greater enantio control than **4a**. To further improve the enantio control of the reaction, racemic propargylic alcohol **6b** bearing a *para*-methoxyphenyl group was employed as a substrate for subsequent condition optimization. After systematic and careful evaluation of different reaction conditions (see Table S2 of the Supporting Information), the optimal reaction conditions were discovered to include a mixed solvent of dichloromethane with ethyl acetate (4:1 v/v) in the presence of 15 mol% (*R*)-**4a**, which afforded aryl-pyrroloindole **7ab** bearing both axial and central chirality in an excellent yield of 94% with high diastereo- and enantioselectivity (84:16 dr, 92% ee).

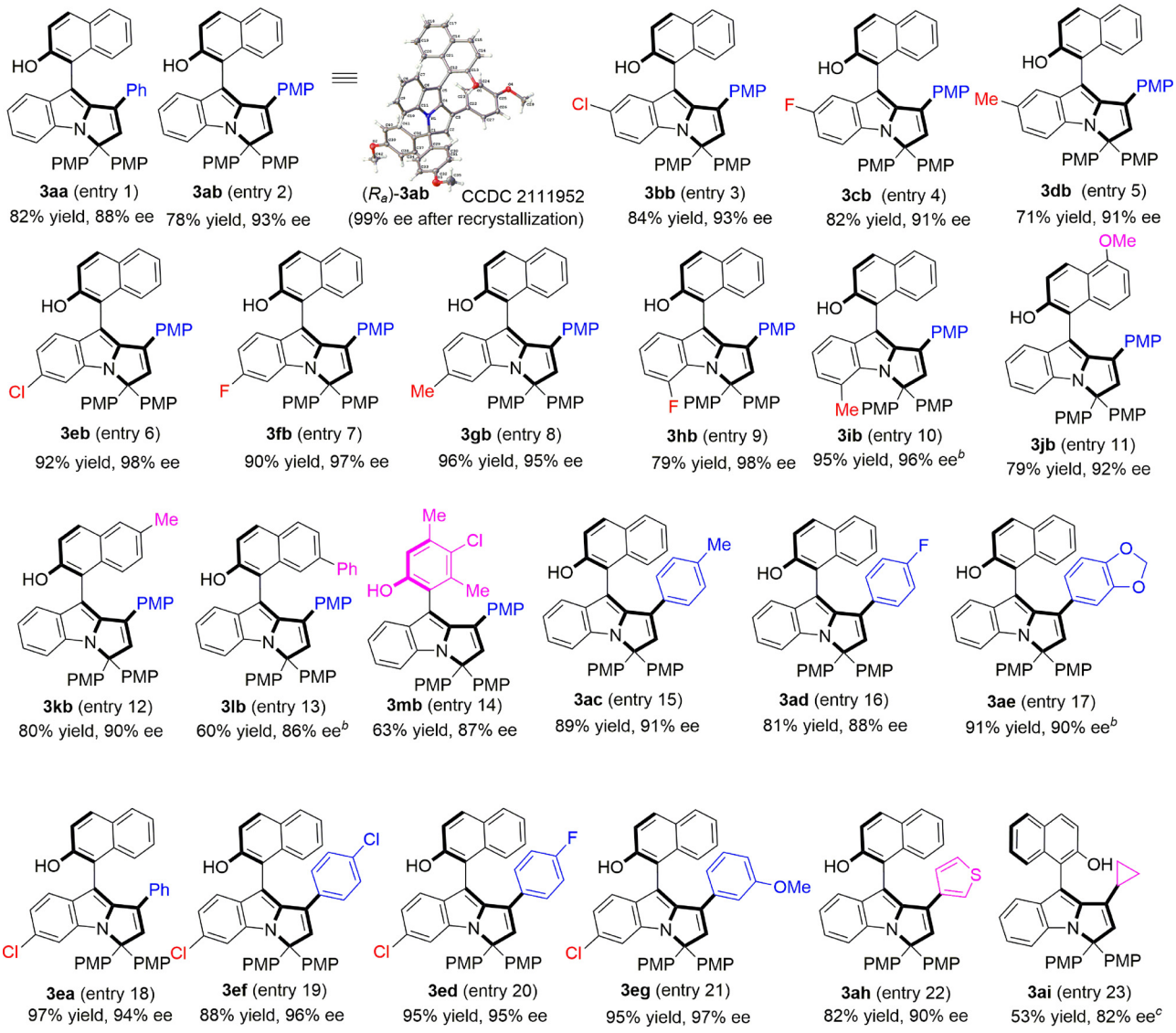
2.3. Investigation on the substrate scope

With the optimal reaction conditions known, we investigated the generality of organocatalytic asymmetric (2 + 3) cyclization for constructing chiral aryl-pyrroloindole scaffolds. First, the substrate scope for synthesizing axially chiral aryl-pyrroloindoles **3** was studied by the (2 + 3) cyclization of 3-arylindoles **1** with propargylic alcohols **2**. As illustrated in Table 1, this reaction was amenable to a wide range of substrates **1** and **2** bearing different substituents, thus generating axially chiral aryl-pyrroloindole frameworks **3** with structural diversity in overall high yields (53–97%) and excellent enantioselectivities (82–98% ee). In brief, the R substituent of the indole ring in 3-arylindoles **1** could vary from chloro and fluoro- to methyl at the C5-C7 positions (entries 3–10). Moreover, when substituted-naphthyl moiety derived substrates **1** were used (entries 11–13), products **3jb**-**3lb** bearing different R^1 groups could be smoothly generated in moderate to good yields (60–80%) with high enantioselectivities (86–92% ee). Notably, this organocatalytic asymmetric (2 + 3) cyclization could be used not only for synthesizing axially chiral naphthyl-pyrroloindoles **3** (entries 1–13 and 15–23) but also for constructing phenyl-pyrroloindole scaffold **3mb** in a good atroposelective manner (entry 14). In addition, the R^2 substituent in propargylic alcohols **2** could be not only various substituted phenyl groups (entries 1,2 and 15–21) but also heteroaromatic groups, as exemplified by the 3-thienyl group (entry 22), which afforded product **3ah** in a high yield of 82% with an excellent enantioselectivity of 90% ee under standard conditions. More importantly, the cyclopropanyl group, which is an aliphatic group, could serve as a suitable R^2 substituent for substrates **2**, which smoothly participated in the reaction to give product **3ai** in a good enantioselectivity of 82% ee under modified reaction conditions (entry 23).

Second, we investigated the substrate scope for synthesizing aryl-pyrroloindoles **7** bearing both axial and central chirality (Table 2), which is far more challenging because of the difficulty in simultaneously controlling multiple chiral elements. As shown in Table 2, a series of 3-arylindoles **1** and propargylic alcohols **6** bearing different R^3/R^4 groups could undergo (2 + 3) cyclization to generate aryl-pyrroloindoles **7** in generally high yields (56–98%), good diastereoselectivities (84:16 to >95:5 dr) and moderate to excellent enantioselectivities (79–99% ee). In short, both the R^3 groups (entries 1–6) and the R^2 groups (entries 7–12) in substrates **6** could be different substituted phenyl groups, and the R^4 group could be changed from a PMP to a piperonyl group (entry 13). Moreover, naphthylindoles **1d**-**1i** bearing different R substituents (entries 14–19) could serve as suitable substrates for this reaction. In addition, substituted-naphthyl moiety derived substrates **1k**-**1l** (entries 20,21) could react with propargylic alcohol **6h**, which afforded products **7kh**-**7lh** bearing axial and central chirality in moderate to high yields with good to excellent diastereo- and enantioselectivities. Furthermore, phenylindole **1m** was a suitable substrate for this reaction (entry 22), affording phenyl-pyrroloindole **7mh** in a high yield with excellent control of both the axial and central chirality. Notably, most of the diastereomeric products **7** could be readily separated by chromatography, and

Table 1
Substrate scope for synthesizing axially chiral aryl-pyrroloindoles 3[a].





[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), (*S*)-**5a** (10 mol%), 5 Å MS (100 mg), DCM (3 mL), 20 °C for 4 h. Isolated yields were provided and ee values were determined by HPLC analysis on a chiral stationary phase.
[b]The reaction time was 10 h. [c]Catalyzed by (*R*)-**4e** (20 mol%) in toluene (1 mL) without 5 Å MS.

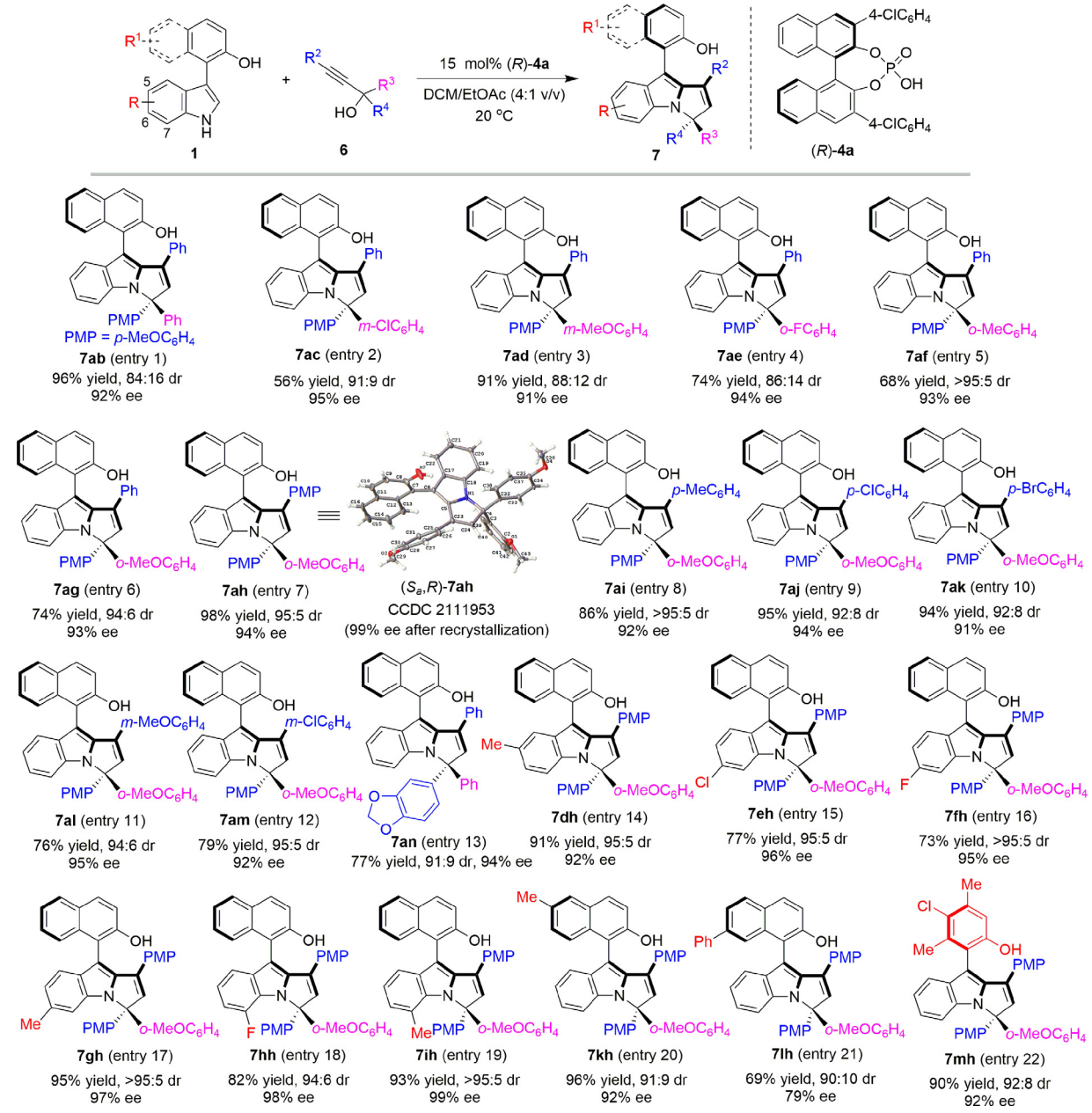
only diastereomeric products **7ad** were inseparable diastereomers with 88:12 dr.

2.4. Synthetic transformations and applications in asymmetric catalysis

To demonstrate the potential utility of this class of new axially chiral aryl-pyrroloindole scaffolds, synthetic transformations and applications of products in asymmetric catalysis were carried out (Fig. 5). First, the one-mmol-scale reactions of 3-arylindole **1a** with propargylic alcohols **2b** and **6h** occurred smoothly under standard conditions (Fig. 5a) to afford aryl-pyrroloindoles **3ab** and **7ah**, respectively, in high yields with excellent stereoselectivities, demonstrating that organocatalytic asymmetric (2 + 3) cyclization could be scaled up.

Then, aryl-pyrroloindole products **3ab** and **7ah** were subjected to synthetic transformations. As illustrated in Fig. 5b, axially chiral aryl-pyrroloindole **3ab** (99% ee after recrystallization) easily transformed to its triflate **8a**, which further underwent a phosphorylation reaction to generate phosphine oxide **9a**. The reduction of **9a** readily af-

Table 2
Substrate scope for synthesizing aryl-pyrroloindoles 7 bearing axial and central chirality[a].



[a] Reaction conditions: **1** (0.1 mmol), **6** (0.12 mmol), (*R*)-**4a** (15 mol%), DCM/EtOAc (4:1 v/v, 5 mL), 20 °C for 10–90 h. Isolated yields were provided and the dr values were determined by ^{1}H NMR. The ee values referred to those of the major diastereomers and were determined by HPLC analysis on a chiral stationary phase.

forded axially chiral phosphine **10a** with optical purity. Similarly, aryl-pyrroloindole **7ah** bearing both axial and central chirality could undergo this synthetic transformation to generate chiral phosphine **10b** with retained enantioselectivity. More importantly, compound **10a**, as a new axially chiral scaffold-based phosphine, could be applied as an efficient ligand in palladium-catalyzed asymmetric reactions. As shown in Fig. 5c, under the catalysis of the Pd(II)/**10a** complex, the asymmetric hydrosilylation of styrene **11** with trichlorosilane generated intermediate product **12**, which was further oxidized into chiral 1-phenylethanol **13** in moderate yield with good enantioselectivity. Moreover, a Pd(II)/**10a** complex-catalyzed asymmetric allylic alkylation reaction between **14** and **15** successfully afforded product **16** in high yield with excellent enantioselectivity. These results demonstrated that this new class of axially chiral aryl-pyrroloindole scaffolds can be used to develop new chiral ligands or catalysts and will find more applications in asymmetric catalysis.

2.5. Stability of axially chiral aryl-pyrroloindoles and control experiments

To obtain more information on this new class of axially chiral scaffolds and organocatalytic asymmetric (2 + 3) cyclization, we investigated the stability of axially chiral aryl-pyrroloindoles and some control experiments (Fig. 6). As shown in Fig. 6a, after stirring in isopropanol at 80 °C for 12 h, aryl-pyrroloindoles **3ab** and **7ad** could be recovered in high yields with maintained diastereo- and enantioselectivities. In addition, aryl-pyrroloindole-derived phosphine **10a** could be recovered without any loss of enantioselectivity after stirring in *o*-xylene at 120 °C for 12 h. These experiments demonstrated the high stability of this class

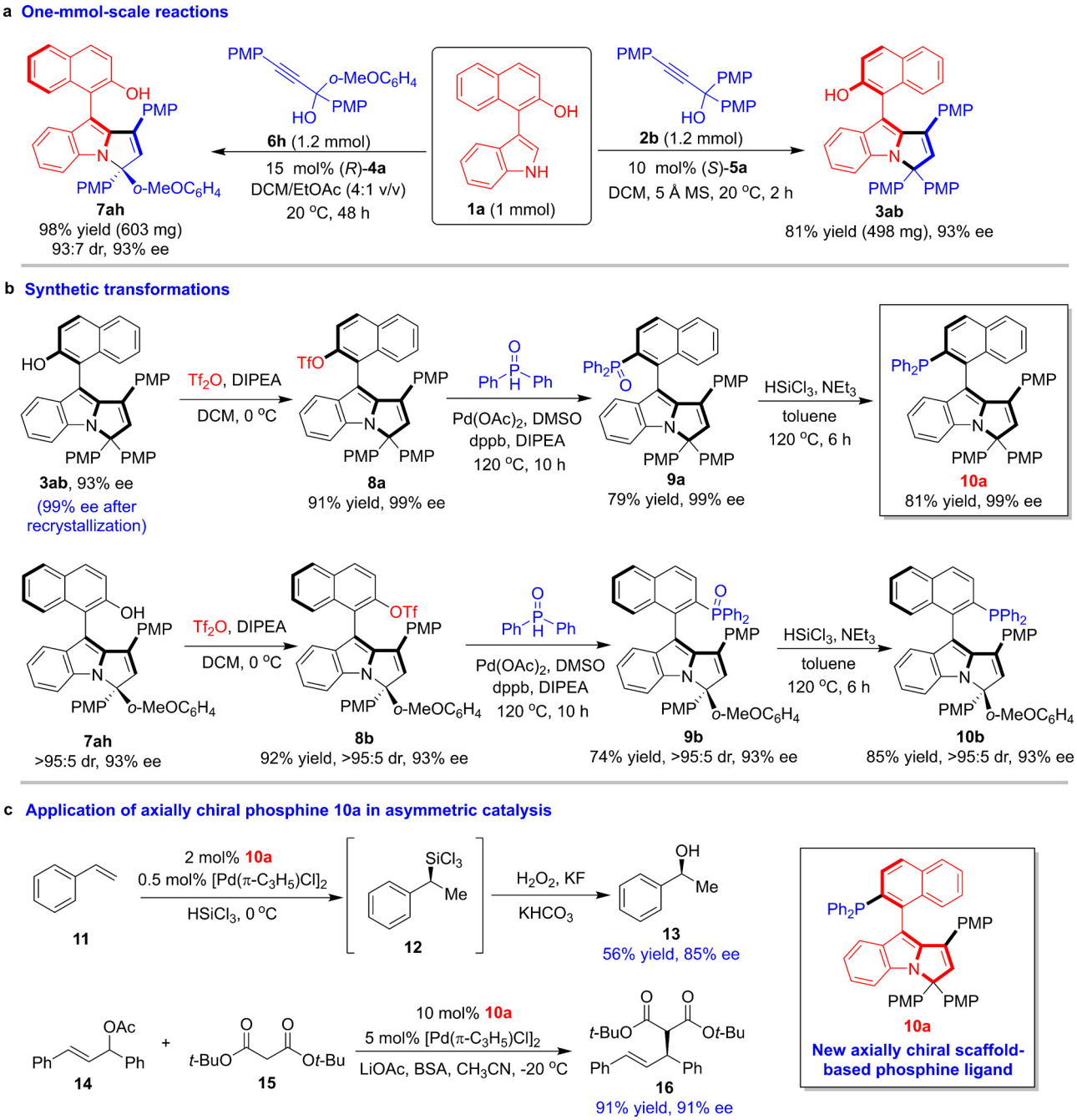


Fig. 5. Synthetic transformations and applications in asymmetric catalysis.

of axially chiral aryl-pyrroloindole scaffolds. Moreover, the rotational barriers of the three compounds were calculated, and it was discovered that their rotational barriers (32.93 to 37.70 kcal·mol^{-1}) are much higher than the required rotational barrier (24 kcal·mol^{-1}) for isolating the individual atropisomers at room temperature, thus explaining the observed high stability of these compounds. Notably, the higher stability and rotational barrier of compound **10a** might be associated with the large group of Ph_2P, which generated more steric congestion with the PMP group around the axis of the aryl-pyrroloindole scaffold.

In addition, to investigate the role of the OH group in substrates **1** and the role of the OMe group in substrates **2** and **6**, we performed control experiments (Fig. 6b). First, 3-naphthylindole **1n** bearing a methoxy group was utilized as a substrate in the reactions with propargylic alcohol **2a** or **6g** under standard conditions (Eq. (6)). In both cases, aryl-pyrroloindole products **3na** and **7ng** could be generated in good yields but with extremely low stereoselectivities, which implied that the OH group in 3-arylindoles **1** played a crucial role in controlling the stereoselectivity of the organocatalytic asymmetric (2 + 3) cyclization, possibly by forming a hydrogen bond with the CPA catalysts.

Second, propargylic alcohols **2j** and **6a**, bearing no OMe group on the phenyl ring, were employed for the reactions with 3-naphthylindole **1a** under standard conditions (Eq. (7)). In the case of propargylic alcohol **2j**, no reaction occurred, which demonstrated that the formation of *p*-QM intermediates from propargylic alcohols **2** is necessary for accomplishing (2 + 3) cyclization. In the case of propargylic alcohol **6a**, (2 + 3) cyclization could occur but with moderate enantioselectivity, which indicated that the formation of *p*-QM cation intermediates is superior to that of neutral *p*-QM intermediates in controlling the enantioselectivity. Therefore, these results demonstrated that the OMe group in substrates **2** and **6** played an important role in controlling both the reactivity and the

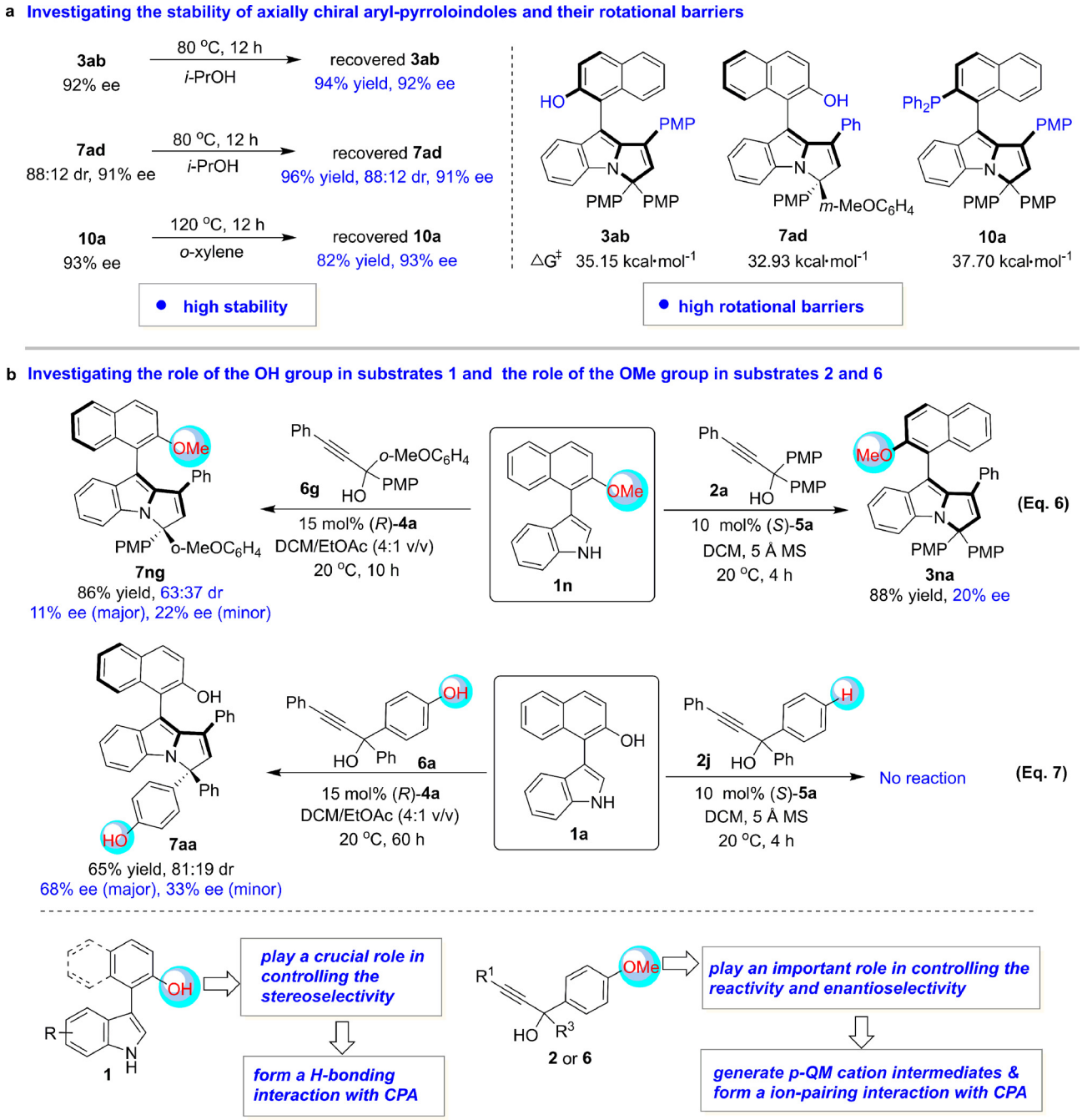


Fig. 6. Investigation of the stability of axially chiral aryl-pyrroloindoles and control experiments.

enantioselectivity by generating *p*-QM cation intermediates and forming an ion pair with CPA catalysts.

2.6. Theoretical calculations of the reaction mechanism

To provide an in-depth understanding of the CPA-catalyzed asymmetric (2 + 3) cyclization for the construction of axially chiral aryl-pyrroloindole scaffolds, we performed theoretical calculations of the possible reaction pathway and activation mode for the synthesis of product (R_a)-**3ab** (Fig. 7).

First, the rotational barrier of substrate **1a** was calculated to be 19.79 kcal·mol^{-1} (Fig. 7a), much lower than the 24 kcal·mol^{-1} required for separable atropisomers, which illustrated that (R_a)-**1a** could readily transform into (S_a)-**1a** at room temperature, thus facilitating the subsequent DKR process.

Second, the calculations suggested that propargylic alcohol **2b** easily underwent dehydration under the catalysis of CPA (*S*)-**5a** to afford the *p*-QM cation intermediate (**INT-1**) via transition state **TS-1** with a low energy barrier of 8.75 kcal·mol^{-1} (Fig. 7b).

As illustrated in Fig. 7c, when substrate **1a** was added to the reaction system of **INT-1**, there were different activation modes between the anion of CPA (*S*)-**5a** and the two atropisomers of (S_a)-**1a** and (R_a)-**1a**. Specifically, as shown in **INT-2** and **TS-2**, CPA (*S*)-**5a** not only simultaneously formed two hydrogen bonds with both the OH group and the CH group of (S_a)-**1a** but also generated an ion-pairing interaction with the *p*-QM cation, thus facilitating 1,8-addition between them. However, in the case of (R_a)-**1a**, as shown in **INT-2′** and **TS-2′**, CPA (*S*)-**5a** formed only one hydrogen bond with the CH group of (R_a)-**1a** and did not form a hydrogen bond with the OH group of (R_a)-**1a** because the OH group was too far from CPA (*S*)-**5a**. Consequently, the fewer hydrogen bonds

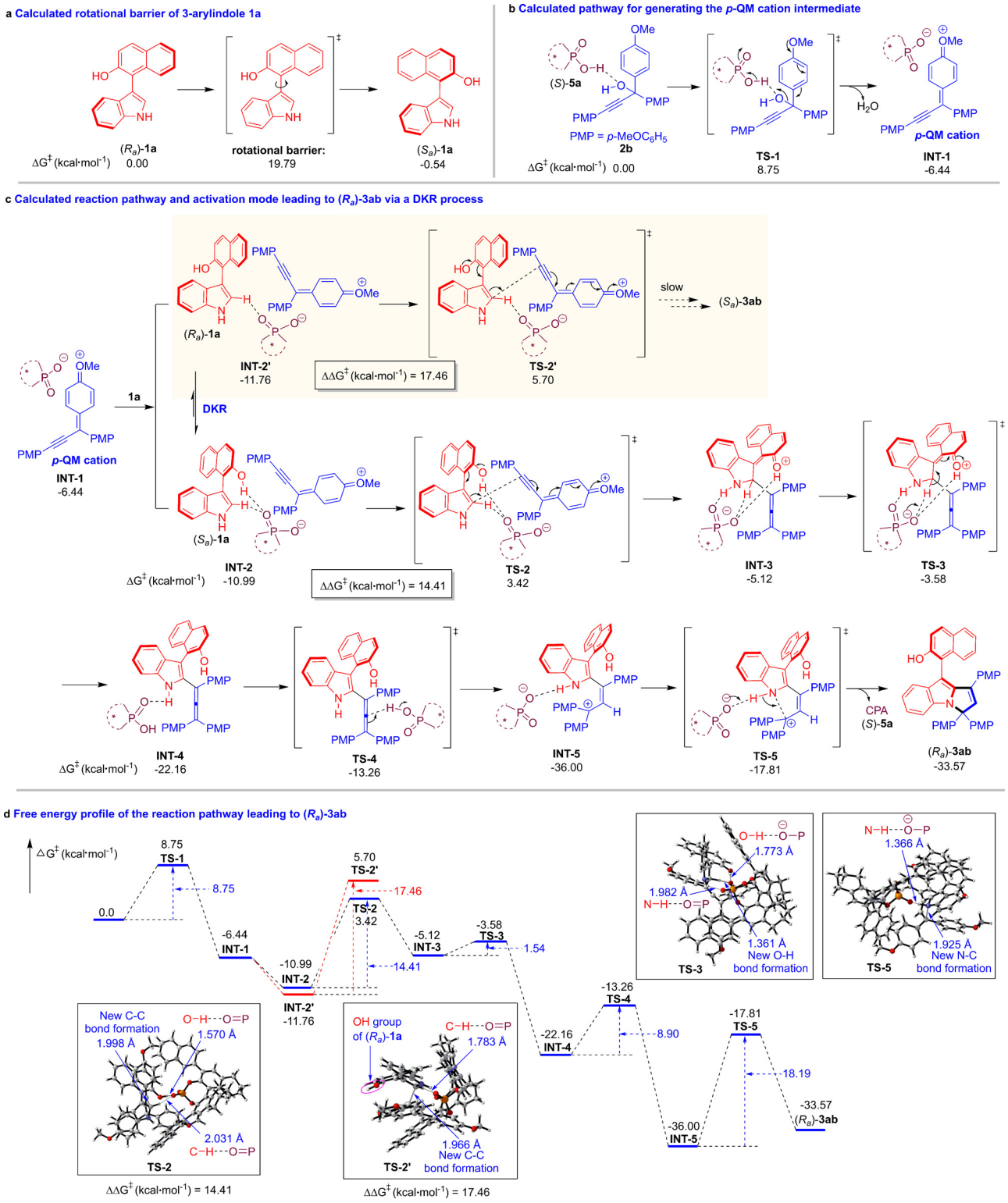


Fig. 7. Theoretical calculations of the possible reaction pathway and activation mode.

between CPA and (R_a)-**1a** resulted in the higher energy barrier of **TS-2′** (17.46 kcal·mol^{-1}) than of **TS-2** (14.41 kcal·mol^{-1}) in the case of (S_a)-**1a**. Because this 1,8-addition reaction was the key step for initiating (2 + 3) cyclization, the difference in the energy barriers (3.05 kcal·mol^{-1}) of this step indicated that substrate (S_a)-**1a** can undergo (2 + 3) cyclization more easily and quickly than (R_a)-**1a**. Therefore, (R_a)-**1a** continuously transformed into (S_a)-**1a** to undergo (2 + 3) cyclization, thus realizing the DKR process.

Notably, as shown in **TS-2**, the theoretical calculation suggested that the OH group of (S_a)-**1a** played an important role in the 1,8-addition by forming a hydrogen bond with CPA (*S*)-**5a** and increasing the C2-nucleuphilicity of the indole ring, thus leading to the generation of a

transient dearomatized intermediate (**INT-3**). Due to the driving force of rearomatization, the prompt transformation of **INT-3** via **TS-3** generated an axially chiral 3-arylindole intermediate (**INT-4**) bearing an allene moiety. As shown in **TS-4**, the subsequent protonation of the allene functionality gave rise to carbocation **INT-5**, which utilized the *N*-nucleophilicity of the indole ring to undergo an intramolecular addition reaction via **TS-5**, therefore accomplishing (2 + 3) cyclization and generating axially chiral aryl-pyrroloindole (R_a)-**3ab**. In the calculated reaction pathway, CPA (*S*)-**5a** activated the substrates and intermediates by forming multiple hydrogen bonds and ion pairs, thus controlling the reactivity and enantioselectivity of the reaction. In addition, CPA (*S*)-**5a** successively activated the OH group and the NH group of 3-arylindoles, thus controlling the regioselectivity of the (2 + 3) cyclization.

The calculated free energy profile of the reaction pathway leading to (R_a)-**3ab** is summarized in Fig. 7d. Obviously, the free energies of **TS-2** (14.41 kcal·mol^{-1}) and **TS-5** (18.19 kcal·mol^{-1}) are much higher than those of other transition states, which demonstrates that the 1,8-addition (**TS-2**) and intramolecular addition (**TS-5**) steps are key steps for accomplishing (2 + 3) cyclization. In addition, to better understand the higher energy barrier of **TS-2′** (17.46 kcal·mol^{-1}) than of **TS-2** (14.41 kcal·mol^{-1}), we compared the structures of **TS-2** and **TS-2′**. In **TS-2**, the P=O group of CPA (*S*)-**5a** not only formed a hydrogen bond (1.570 Å) with the OH group of (S_a)-**1a** but also interacted with the indole CH via hydrogen bonding (2.031 Å). Conversely, in **TS-2′**, the P=O group of CPA (*S*)-**5a** had no interaction with the OH group (pink ellipse) of (R_a)-**1a** and hydrogen bonded with only the indole CH (1.783 Å). Therefore, the different nonbonding interactions resulted in an energy barrier difference (3.05 kcal·mol^{-1}) between **TS-2** and **TS-2′**, thus explaining the DKR process and high enantioselectivity of **3ab**.

3. Conclusion

In summary, we have accomplished the design and atroposelective synthesis of aryl-pyrroloindoles as a new class of axially chiral indole-based scaffolds via the strategy of organocatalytic asymmetric (2 + 3) cyclization. This strategy makes avail of chiral phosphoric acid-catalyzed dynamic kinetic resolution of 3-arylindoles by (2 + 3) cyclizations with propargylic alcohols, thus affording a wide range of aryl-pyrroloindoles with simultaneous control of the axial and central chirality in overall high yields with excellent stereoselectivities (up to 98% yield, 99% ee, >95:5 dr). More importantly, this new class of axially chiral aryl-pyrroloindole scaffolds has high stability and can be derived into axially chiral phosphines, which have acted as efficient chiral ligands in palladium-catalyzed asymmetric reactions. In addition, we performed theoretical calculations on the possible reaction pathway and activation mode of this organocatalytic asymmetric (2 + 3) cyclization, thus providing an in-depth understanding of the reaction mechanism and the process of dynamic kinetic resolution for the construction of axially chiral aryl-pyrroloindole scaffolds. This work not only offers an aryl-pyrroloindole framework as a new member of the family of axially chiral scaffolds but also provides a new strategy for designing and constructing 3-arylindole-related axially chiral scaffolds. This new class of axially chiral aryl-pyrroloindole scaffolds is promising for developing new chiral ligands or catalysts and will find more applications in asymmetric catalysis.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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Supplementary materials

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