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Article

Catalytic Asymmetric Diastereodivergent Synthesis of 2-Alkenylindoles Bearing both Axial and Central Chirality

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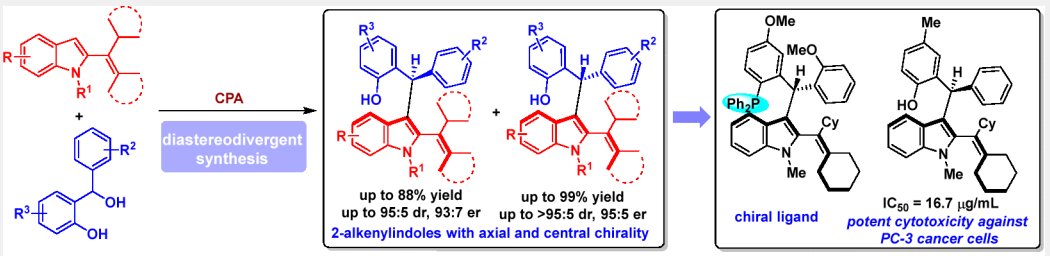

ABSTRACT: The catalytic asymmetric diastereodivergent synthesis of axially chiral 2-alkenylindoles was established via chiral phosphoric acid-catalyzed addition reactions of C3-unsubstituted 2-alkenylindoles with *o*-hydroxybenzyl alcohols under different reaction conditions. Using this strategy, two series of 2-alkenylindoles bearing both axial and central chirality were synthesized in a diastereodivergent fashion with moderate to high yields and good stereoselectivities (up to 99% yield, 95:5 er, >95:5 dr). Moreover, theoretical calculations were performed on the key transition states leading to different stereoisomers, which provided an in-depth understanding of the origin of the observed stereoselectivity and diastereodivergence of the products under different reaction conditions. More importantly, these 2-alkenylindoles were utilized in asymmetric catalysis as chiral organocatalysts and in medicinal chemistry for evaluation of their cytotoxicity, which demonstrated their potential applications. This study has not only established the catalytic atroposelective synthesis of axially chiral 2-alkenylindoles, but also provided an efficient strategy for catalytic asymmetric diastereodivergent construction of indole-based scaffolds bearing both axial and central chirality.

KEYWORDS: *2-Alkenylindole, Axial chirality, Central chirality, Diastereodivergent synthesis, Chiral phosphoric acid*

INTRODUCTION

Chiral compounds bearing multiple stereogenic centers are widely found in pharmaceuticals and materials.[1,2] The absolute and relative configurations of these compounds have an impact on their physiological or pharmacological properties.[3,4] Therefore, developing efficient strategies to access all stereoisomers of chiral compounds bearing multiple stereocenters is crucial.

Catalytic asymmetric diastereodivergent reactions have recently been recognized as a class of powerful methods for synthesizing each stereoisomer of chiral compounds using the same set of starting materials by slightly modulating the reaction conditions.[5−10] Thus, developing catalytic asymmetric diastereodivergent reactions has attracted intensive attention from the scientific community.[11−28] Among them, catalytic asymmetric diastereodivergent reactions for the synthesis of chiral compounds bearing multiple central chirality have been well-developed (Scheme 1a).[17−28] However, in stark contrast, catalytic asymmetric diastereodivergent reactions for the synthesis of chiral compounds bearing both axial and central chirality remain largely unexplored (Scheme 1b)[29,30] in spite of the importance of atropisomers bearing multiple chiral elements.[31] The challenges in realizing such diastereodivergent reactions mainly include: 1) simultaneously controlling the axial chirality and central chirality to achieve excellent diastereoselectivity and enantioselectivity; 2) finding suitable reaction conditions for diastereodivergent generation of two chiral elements. Therefore, it is highly desired to develop efficient strategies toward settling these challenges and realize catalytic asymmetric diastereodivergent reactions for the synthesis of chiral compounds bearing both axial and central chirality.

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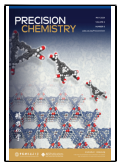

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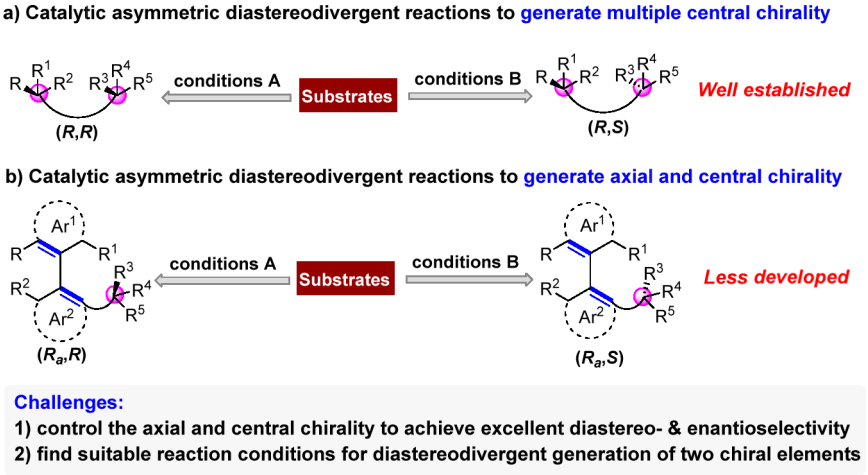
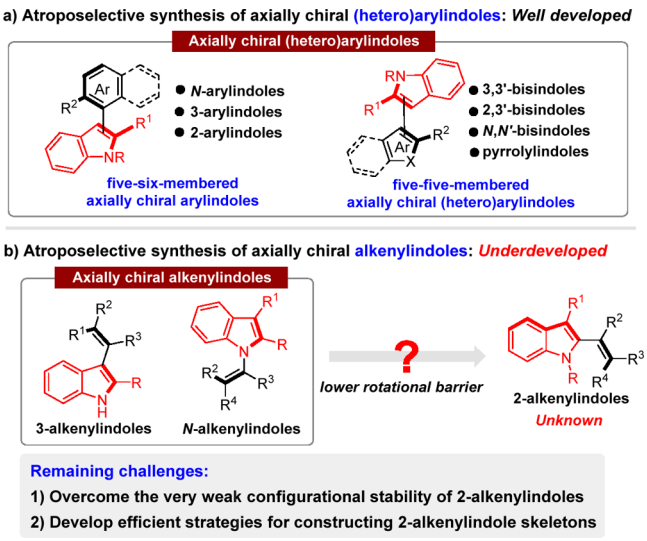
Scheme 1. Profile of Catalytic Asymmetric Diastereodivergent Reactions



Axially chiral indole-based scaffolds, a class of unique axially chiral skeletons,[31−45] are widely found in natural products,[46−48] pharmaceutically relevant molecules,[49−51] and chiral catalysts.[52−55] Therefore, catalytic asymmetric construction of axially chiral indole-based scaffolds has become an emerging field.[56,57] As shown in Scheme 2a, various elegant strategies

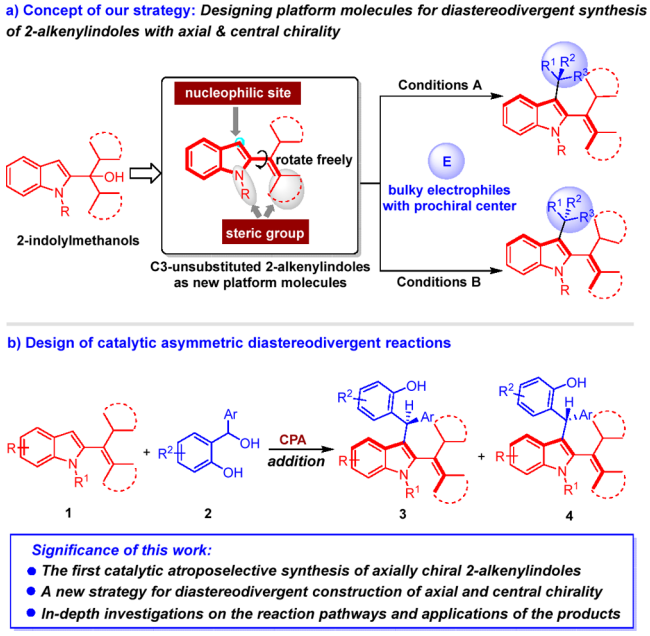
Scheme 2. Profile of Catalytic Atroposelective Construction of Axially Chiral Indole-Based Scaffolds



have been developed for the enantioselective construction of axially chiral (hetero)arylindoles, such as five-six-membered axially chiral arylindoles[49,58−103] and five-five-membered axially chiral (hetero)arylindoles.[51,52,104−116] However, in sharp contrast, axially chiral alkenylindoles, more challenging axially chiral indole-based scaffolds,[50,117−123] remain rarely studied except for a few examples on the synthesis of axially chiral 3-alkenylindoles[117] and *N*-alkenylindoles[118−123] (Scheme 2b). Despite this progress, catalytic atroposelective synthesis of axially chiral 2-alkenylindoles is still unknown due to the much lower rotational barrier of this class of molecules. Therefore, how to overcome the very weak configurational stability of axially chiral 2-alkenylindoles and to develop efficient strategies for constructing such skeletons in a catalytic asymmetric manner remain challenging.

To overcome the challenges in developing catalytic asymmetric diastereodivergent reactions for the synthesis of chiral compounds bearing both axial and central chirality, and to construct axially chiral 2-alkenylindole skeletons, we proposed the concept of our strategy as designing new platform molecules for diastereodivergent synthesis of 2-alkenylindoles bearing both axial and central chirality. As shown in Scheme 3a, C3-unsubstituted 2-alkenylindoles were

Scheme 3. Our Strategy for Catalytic Asymmetric Diastereodivergent Synthesis of 2-Alkenylindoles Bearing Both Axial and Central Chirality



designed as indole-based platform molecules. The structural features of C3-unsubstituted 2-alkenylindoles mainly include: (1) the unsubstituted C3-position of the indole ring could not only act as a nucleophilic site, but also make the indole ring and the alkenyl group be able to rotate freely around the axis and result in rapid racemization; (2) the bulky cyclohexyl group and the N-substituent could serve as steric groups to generate rotational restriction for the products and increase the configurational stability of the products; (3) this kind of C3-

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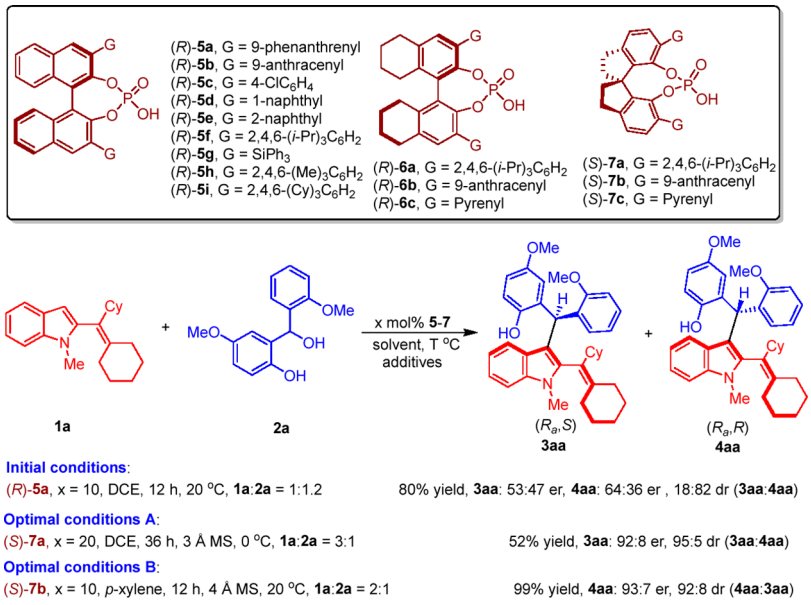
Scheme 4. Catalysts and Model Reaction Employed for Condition Optimization



unsubstituted 2-alkenylindoles could be easily synthesized from the corresponding 2-indolylmethanols[124−126] via dehydration. These structural features enable C3-unsubstituted 2-alkenylindoles to undergo catalytic asymmetric diastereodivergent addition reactions with bulky electrophiles bearing a prochiral center under different reaction conditions, thus leading to the generation of two series of 2-alkenylindoles bearing both axial and central chirality in a diastereodivergent manner. Although this strategy seems feasible, there are still some challenging issues to be solved, such as finding suitable bulky electrophiles bearing a prochiral center and selecting suitable chiral catalysts to control the reactivity and the stereoselectivity.

To address these issues, based on our long-lasting efforts in chiral indole chemistry,[127−130] we designed a chiral phosphoric acid (CPA)-catalyzed asymmetric diastereodivergent addition reaction of C3-unsubstituted 2-alkenylindoles **1** with *o*-hydroxybenzyl alcohols **2** (Scheme 3b). In this design, the selection of *o*-hydroxybenzyl alcohols as suitable bulky electrophiles bearing prochiral center is based on that *o*-hydroxybenzyl alcohols can be converted into highly reactive *o*-quinone methides (*o*-QMs) in the presence of Brønsted acids and generate a new chiral center by the addition reaction.[131−133] CPA was selected as a suitable chiral catalyst due to its ability to activate *o*-hydroxybenzyl alcohols, thus simultaneously controlling both the axial chirality and central chirality of products **3** and **4**.[134−141] Therefore, the significance of this study lies in that it will not only establish the first catalytic atroposelective synthesis of axially chiral 2-alkenylindoles, but also provide a new strategy for diastereodivergent construction of indole-based scaffolds bearing both axial and central chirality. Moreover, the in-depth investigations on the reaction pathways and potential applications of the products will be carried out.

RESULTS AND DISCUSSION

To verify the feasibility of our design, the reaction of C3-unsubstituted 2-alkenylindole **1a** with *o*-hydroxybenzyl alcohol **2a** was conducted (Scheme 4). As anticipated, this addition reaction occurred under the catalysis of CPA (*R*)-**5a** in 1,2-dichloroethane (DCE) at 20 °C and delivered axially chiral 2-alkenylindoles **3aa** and **4aa** in high total yields albeit with low enantioselectivity and moderate diastereoselectivity (80% yield, **3aa**: 53:47 er, **4aa**: 64:36 er, 18:82 dr). To realize asymmetric diastereodivergent addition reaction, various reaction parameters such as catalysts, solvents, additives, reagents ratio, reaction temperature, and catalyst loading were screened (see the Supporting Information for details). Finally, product **3aa** was obtained as the major diastereomer in a moderate yield of 52% with a high enantioselectivity of 92:8 er and an excellent diastereoselectivity of 95:5 dr under the optimal conditions A (**1a**:**2a** = 3:1, 20 mol % (*S*)-**7a**, DCE, 36 h, 3 Å MS, 0 °C). On the other hand, product **4aa** could be obtained as the major diastereomer in an excellent yield of 99% with a high enantioselectivity of 93:7 er and a good diastereoselectivity of 92:8 dr under the optimal conditions B (**1a**:**2a** = 2:1, 10 mol % (*S*)-**7b**, *p*-xylene, 12 h, 4 Å MS, 20 °C).

After establishing the optimal reaction conditions, we investigated the substrate scope of this catalytic asymmetric diastereodivergent addition reaction. First, the substrate scope for atroposelective synthesis of 2-alkenylindoles **3** as the major diastereomers bearing both axial and central chirality was examined under optimal conditions A. As shown in Table 1, a series of *o*-hydroxybenzyl alcohols **2a**−**2k** bearing various R^2/R^3 groups were successfully employed to generate chiral 2-alkenylindoles **3ab**−**3ak** in moderate to good yields (up to 88%) with high enantioselectivities (up to 93:7 er) and diastereoselectivities (up to 95:5 dr). For C3-unsubstituted 2-alkenylindoles **1**, substrates **1b**−**1d** with different R groups on the C5-position of the indole ring were suitable reactants for this addition reaction to produce chiral 2-alkenylindoles **3ba**−**3da** in moderate yields (up to 55%) with good enantioselectivities (up to 92:8 er) and diastereoselectivities (up to 91:9 dr). Besides, *N*-benzyl substituted 2-alkenylindole **1e** could participate in the reaction to afford chiral 2-alkenylindole **3ei** in a moderate yield (44%) with a high enantioselectivity (91:9 er) and a moderate diastereoselectivity (75:25 dr).

To investigate the generality of this strategy for atroposelective synthesis of chiral 2-alkenylindoles **4** as the major

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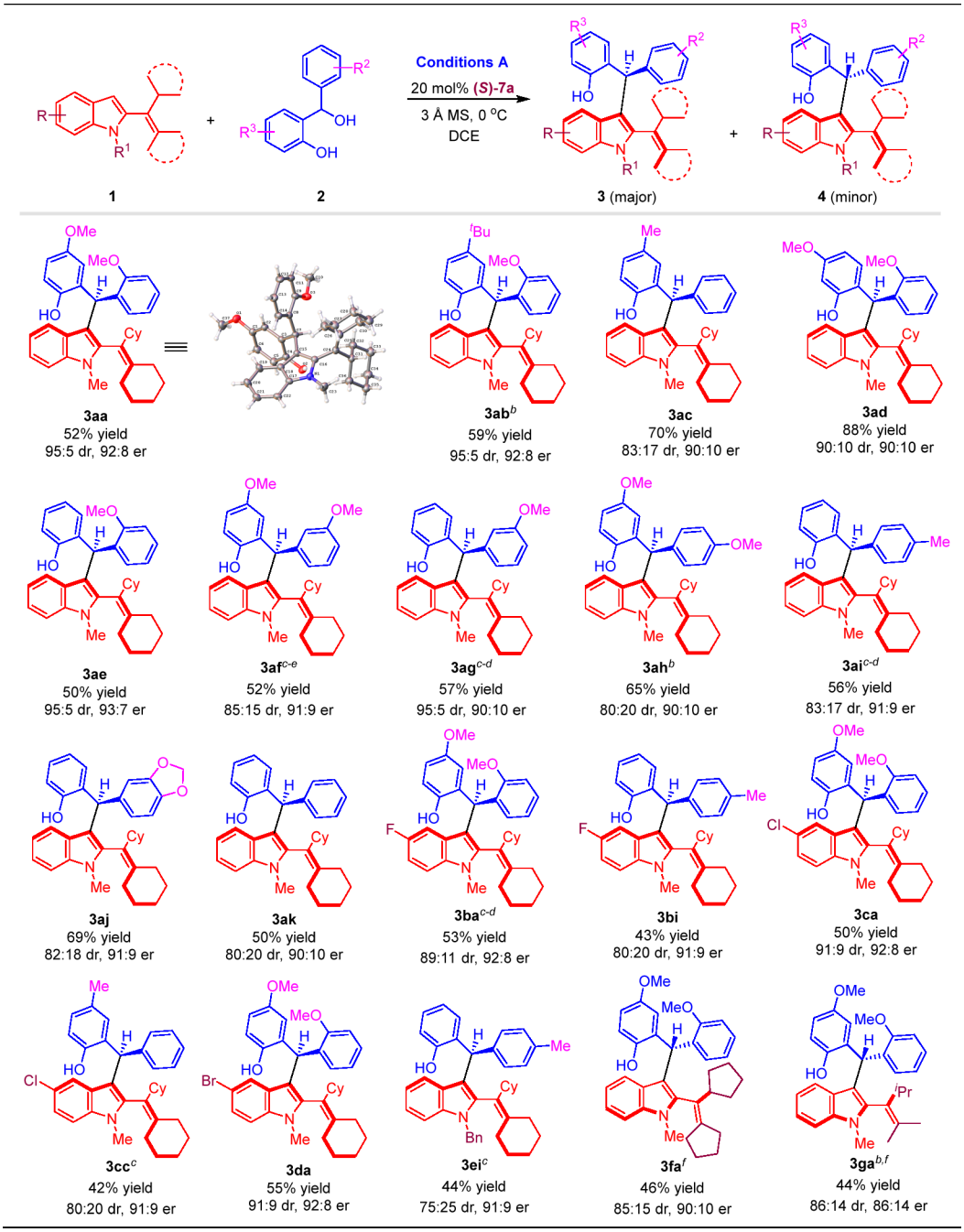
Precis. Chem. 2024, 2, 208−220

Table 1. Substrate Scope for Atroposelective Synthesis of Chiral 2-Alkenylindoles 3[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), (*S*)-**7a** (20 mol %), 3 Å MS (100 mg), DCE (2 mL), 0 °C for 36 h. Isolated yields were provided, the er value was determined by HPLC and the dr value (**3**:**4**) was determined by ^{1}H NMR. The absolute configuration of **3aa** was determined as (R_a,*S*) via single-crystal X-ray diffraction analysis (see the Supporting Information for details).[142] [b]4 mL of DCE was used. [c]1 mL of DCE was used. [d]Catalyzed by 30 mol % (*S*)-**7a** for 48 h. [e]Using 5 Å MS (100 mg) as additives. [f]Catalyzed by 20 mol % (*S*)-**5i**.

diastereomers bearing both axial and central chirality, a wide scope of C3-unsubstituted 2-alkenylindoles **1** with different R/R^1 groups and *o*-hydroxybenzyl alcohols **2** bearing various R^2/R^3 groups were employed as substrates under optimal conditions B. As shown in Table 2, a variety of 2-alkenylindoles **4** bearing axial and central chirality were synthesized in good yields (up to 99%) with high enantioselectivities (up to 95:5 er) and moderate to excellent diastereoselectivities (up to >95:5 dr).

Notably, cyclopentyl- and isopropyl-substituted 2-alkenylindoles **1f**−**1g** successfully participated in this catalytic asymmetric diastereodivergent addition reaction to deliver axially chiral 2-alkenylindoles **3fa**−**3ga** and **4fa**−**4ga**, respectively, in acceptable yields with good to excellent enantioselectivities and diastereoselectivities.

Subsequently, we evaluated the stereodivergence of this catalytic asymmetric addition reaction. As shown in Scheme 5a, the addition reactions of **1a** and **2a** under conditions A or B in the presence of CPA **7a** or **7b** with different absolute

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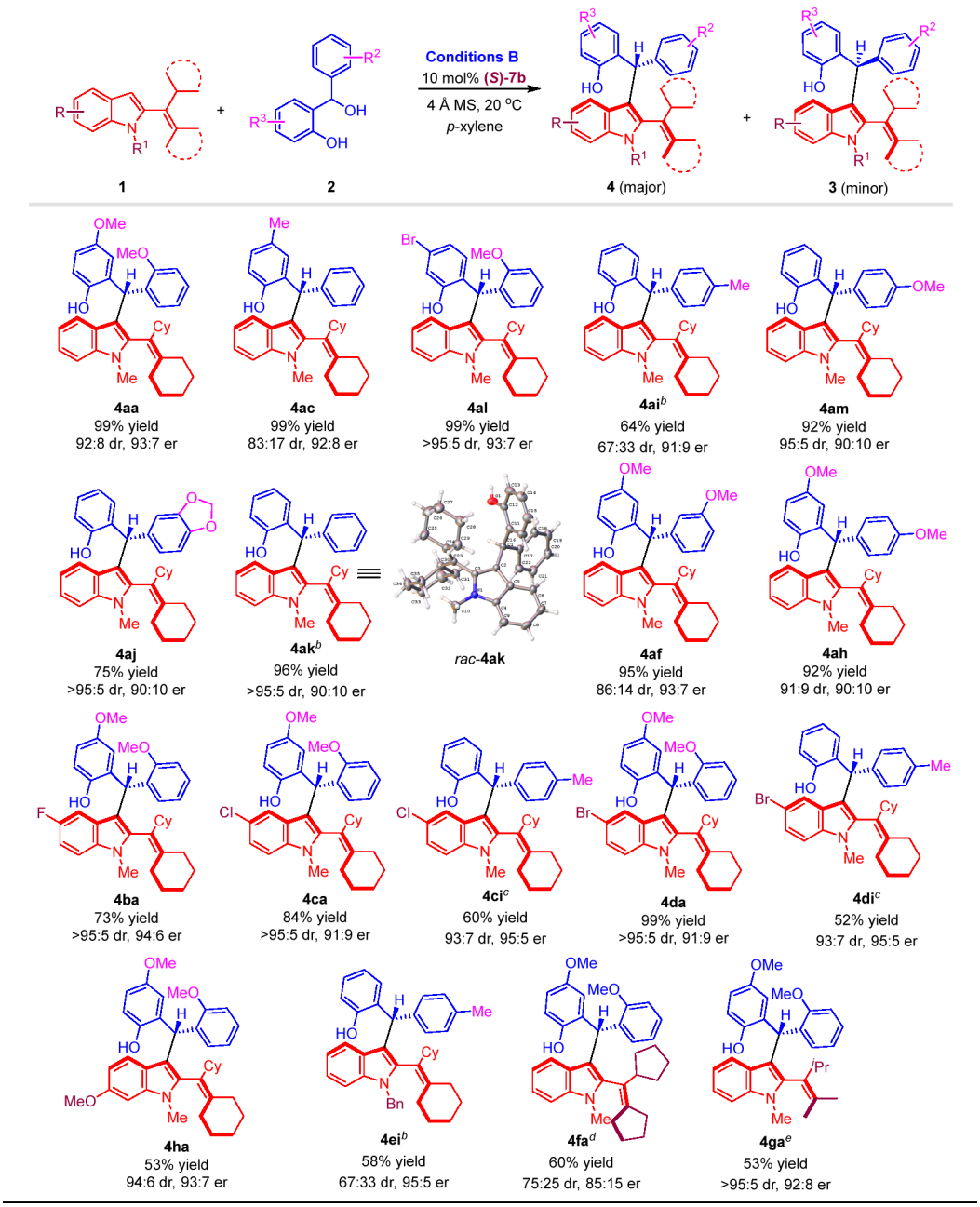
Table 2. Substrate Scope for Atroposelective Synthesis of Chiral 2-Alkenylindoles 4[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), (*S*)-**7b** (10 mol %), 4 Å MS (100 mg), *p*-xylene (4 mL), 20 °C for 12 h. Isolated yields were provided, the er value was determined by HPLC and the dr value (**4**:**3**) was determined by ^{1}H NMR. The structure of *rac*-**4ak** was confirmed by single-crystal X-ray diffraction analysis,[142] and the absolute configuration of **4ak** was determined to be (R_a, *R*) by comparison with a known chiral compound (see the Supporting Information for details). [b]Catalyzed by 10 mol % (*S*)-**7c**. [c]Catalyzed by 10 mol % (*S*)-**7c** at −30 °C in mesitylene for 24 h. [d]Catalyzed by 10 mol % (*R*)-**6b**. [e]Catalyzed by 20 mol % (*R*)-**6b** at 0 °C in mesitylene for 24 h, **1g**:**2a** = 3:1.

configurations were carried out, which delivered four stereoisomers of 2-alkenylindoles **3aa** and **4aa** bearing both axial and central chirality in moderate to good yields with high enantioselectivities and diastereoselectivities, respectively. In addition, we investigated the configurational stability and rotational barriers of axially chiral 2-alkenylindoles **3aa** and **4aa** (Scheme 5b). Products **3aa** and **4aa** were stirred in *i*-PrOH at 100 °C for 5 h and recovered in high yields with retained enantioselectivities and diastereoselectivities. These results indicated that products **3aa** and **4aa** have high configurational stability. The rotational barriers of products **3aa** and **4aa** were theoretically calculated as 39.5 and 46.3 kcal mol^{-1}, respectively, which were in accordance with the experimentally observed high configurational stability of these products.

To demonstrate the utility of the reaction, we performed the synthesis of products **3aa** and **4aa** on 1 mmol scale (Scheme 6a). Compared with the small-scale reactions, these 1 mmol scale reactions smoothly afforded products **3aa** and **4aa** in similar yields with maintained high enantioselectivities and diastereoselectivities. Moreover, we further investigated the utility of this new class of 2-alkenylindoles bearing both axial and central chirality (Scheme 6b). For instance, product **4aa**

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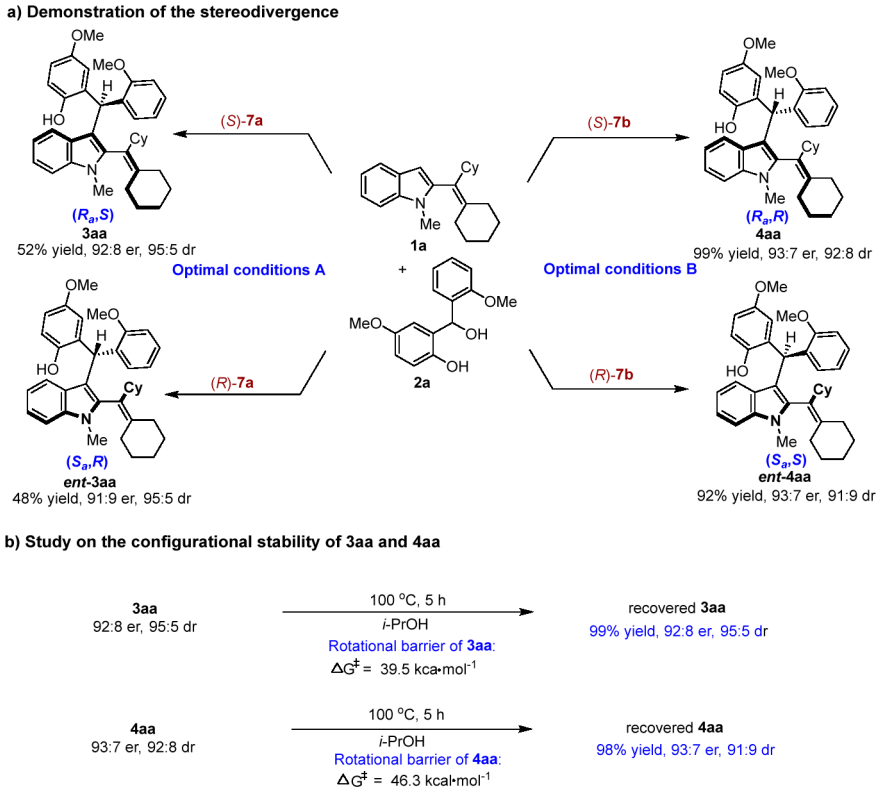
Scheme 5. Demonstration of the Stereodivergence and Study on the Configurational Stability



was transformed into the corresponding chiral phosphine ligand **9** bearing multiple chiral elements via a two-step reaction. The preliminary application of chiral ligand **9** was verified in a palladium-catalyzed enantioselective allylic alkylation reaction, which afforded chiral product **13** in a high yield of 92% with a good enantioselectivity of 87:13 er. Therefore, this result demonstrated the promising applications of this kind of 2-alkenylindole skeletons bearing both axial and central chirality in asymmetric catalysis.

To find the possible bioactivities of this class of chiral 2-alkenylindoles, a preliminary evaluation on the cytotoxicity of some selected products **3** and **4** was carried out (see the Supporting Information for details). As shown in Figure 1a, several products **3** and **4** exhibited some extent of cytotoxicity against HepG2 cancer cells, and the IC_{50} values were ranging from 20.0 to 50.4 μg/mL. Besides, the cytotoxicity of some selected products **3** and **4** against PC-3 cancer cells was also investigated (Figure 1b). Among them, product **3ac** exhibited potent cytotoxicity against PC-3 cancer cells with a very low IC_{50} value of 16.7 μg/mL. These results indicated that this class of chiral 2-alkenylindoles might find their potential applications in medicinal chemistry.

To elucidate the possible activation mode, we conducted some control experiments (Scheme 7a). When methyl-protected *o*-hydroxybenzyl alcohol **2n** was allowed to react with C3-unsubstituted 2-alkenylindole **1a** under standard conditions **A** and **B**, no reaction occurred. This indicated that the OH group in *o*-hydroxybenzyl alcohols played a crucial role in controlling the reactivity, possibly by forming hydrogen-bonding interactions with CPA. Based on the control experiments, we proposed a possible reaction pathway for this catalytic asymmetric diastereodivergent reaction. As shown in Scheme 7b, (R_a)-**1a** and (S_a)-**1a** were two enantiomers of racemic C3-unsubstituted 2-alkenylindole **1a**, and the rotational barrier of **1a** was calculated as 21.4 kcal mol^{-1}, which verified our proposal that (R_a)-**1a** and (S_a)-**1a** could rapidly transform to each other, resulting in rapid racemization for the dynamic kinetic resolution (DKR) process. Under the activation of (*S*)-**7a** via hydrogen-bonding interaction (conditions A), a fast nucleophilic addition between (R_a)-**1a** and *o*-quinone methide (*o*-QM) (generated via dehydration of *o*-hydroxybenzyl alcohol **2a**) occurred to give product (R_a,*S*)-**3aa**. When using (*S*)-**7b** as the catalyst (conditions B), diastereomer (R_a,*R*)-**4aa** was obtained, thus realizing the diastereodivergence process and the generation of two types of 2-alkenylindoles bearing both axial and central chirality. On the other hand, in the presence of CPA (*S*)-**7a** or (*S*)-**7b**, the nucleophilic addition of (S_a)-**1a** with *o*-QM was very slow and (S_a)-**1a** continuously transformed into (R_a)-**1a** via rapid racemization, resulting in the DKR process.

To explain the observed high enantioselectivity of products **3**, **4** and the diastereodivergence of this addition reaction under different reaction conditions, we performed density functional theory (DFT) calculations on the key transition states leading to four possible stereoisomers in the catalytic asymmetric diastereodivergent reactions between **1a** and **2a** under the catalysis of different CPAs (*S*)-**7a** and (*S*)-**7b**, respectively (Figure 2). As shown in Figure 2a, the Gibbs free energy barrier of transition state (R_a,*S*)-**TS1**, leading to the formation of major product (R_a,*S*)-**3aa**, was calculated as 19.4 kcal·mol^{-1}, which was the lowest energy barrier among the transition states leading to four possible stereoisomers under the catalysis of CPA (*S*)-**7a** (see Figure S4 in the Supporting Information for details). Notably, the C═O group in *o*-QM could form hydrogen-bonding interactions with CPA in (R_a,*S*)-**TS1**, demonstrating that the OH group in *o*-hydroxybenzyl

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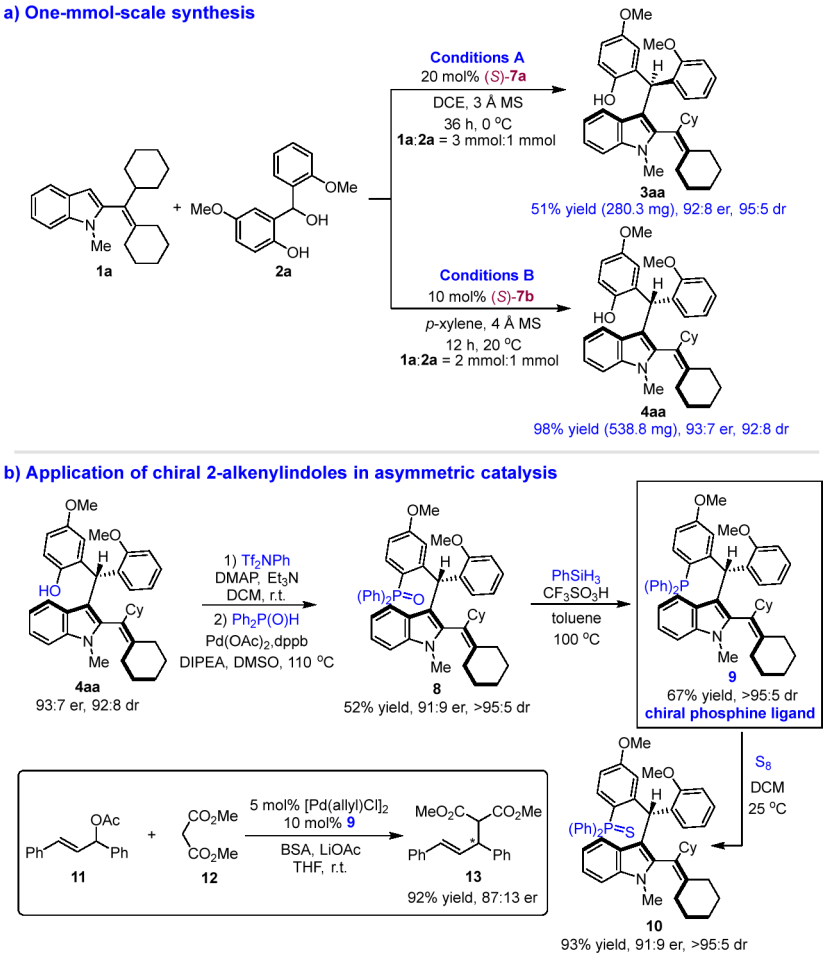
Scheme 6. Synthesis (1 mmol Scale) and Application of Axially Chiral 2-Alkenylindoles in Asymmetric Catalysis



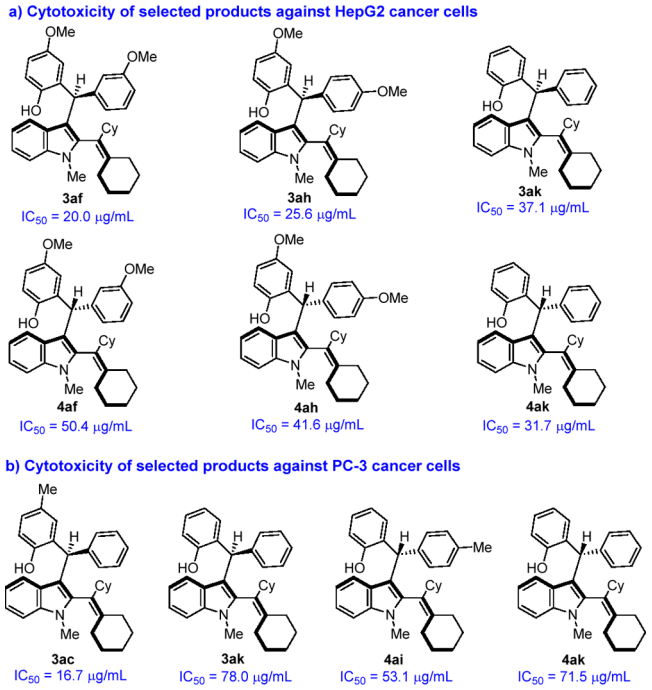


Figure 1. Chiral 2-alkenylindoles **3** and **4** with promising anticancer activity

alcohol **2a** played a crucial role in controlling the reactivity, which was consistent with the control experiments.

To explain the observed absolute configuration and good enantioselectivity of product (R_a,*S*)-**3aa**, we compared the key transition states (R_a,*S*)-**TS1** and (S_a,*R*)-**TS1**, which ultimately led to the formation of two enantiomers of **3aa**. The energy difference between (R_a,*S*)-**TS1** and (S_a,*R*)-**TS1** was calculated as 1.7 kcal mol^{-1}, which was in accordance with the observed er value (92:8). Moreover, the origin of the energy difference leading to the observed enantioselectivity of **3aa** was studied by energy decomposition analysis and noncovalent interaction (NCI) plots (see Figures S5 and S6 in the Supporting Information for details). Energy decomposition analysis indicated that the energy difference between (R_a,*S*)-**TS1** and (S_a,*R*)-**TS1** could be mainly attributed to the difference of distortion energies of the substrates and the catalyst. Structure analysis in Figure 2a indicated that the planar carbon center of C3-unsubstituted 2-alkenylindole **1a** (∠C5C6C7H8 = 179.2°) and *o*-QM (∠C1C2H4C3 = 180.0°) as well as the angle in *o*-QM (∠C1C2C3 = 127.7°) were ready to distort to pyramidal structures during the nucleophilic addition. The dihedral angles of these two carbon centers in (R_a,*S*)-**TS1** (∠C5C6C7H8 = 157.1° and ∠C1C2H4C3 = 156.2°) and the angle of *o*-QM (∠C1C2C3 = 127.6°) were bigger than those in (S_a,*R*)-**TS1** (∠C5C6C7H8 = 152.9°, ∠C1C2H4C3 = 145.1°, ∠C1C2C3 = 122.2°), indicating more structural distortions in (S_a,*R*)-**TS1** than those in (R_a,*S*)-**TS1**. Besides, the hydrogen bond between the oxygen atom and the

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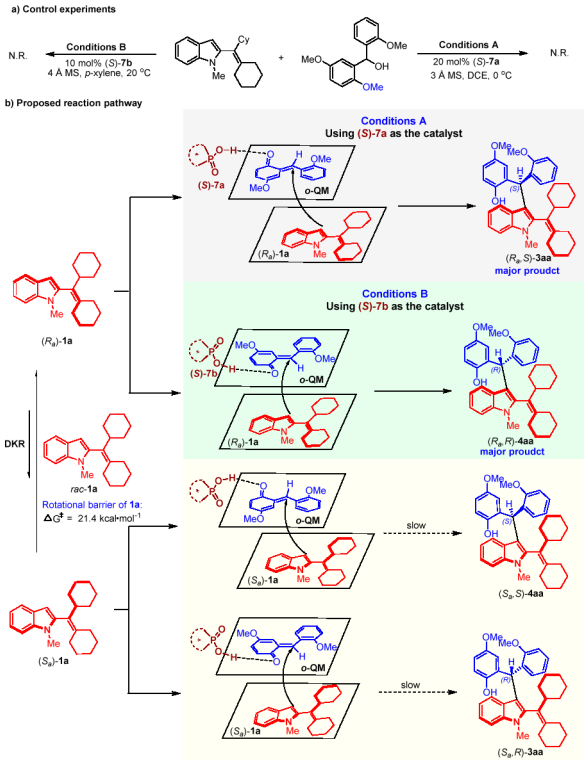
Scheme 7. Control Experiments and Proposed Reaction Pathway



hydrogen atom of CPA (*S*)-**7a** in (R_a,*S*)-**TS1** (b1 = 1.416 Å) was considerably shorter than that in (S_a,*R*)-**TS1** (b1 = 1.449 Å), further indicating the bigger structural distortion in (S_a,*R*)-**TS1**. These results well explain the observed absolute configuration and good enantioselectivity of the major enantiomer of product **3aa**. Moreover, the energy barrier of (R_a,*S*)-**TS1** was much lower than those of (R_a,*R*)-**TS1** and (S_a,*S*)-**TS1**, which corresponded to the formation of minor diastereomers (R_a,*R*)-**4aa** and (S_a,*S*)-**4aa**. So, these calculation results also explained the observed high diastereoselectivity of **3aa** in the presence of CPA (*S*)-**7a**.

In addition, Figure 2b shows the calculated transition states leading to four possible stereoisomers under the catalysis of CPA (*S*)-**7b**. Obviously, the energy barrier of (R_a,*R*)-**TS2** leading to the formation of major product (R_a,*R*)-**4aa** was lower (19.3 kcal·mol^{-1}) than those of other three transition states (see Figure S7 in the Supporting Information for details). The energy difference between the transition states (R_a,*R*)-**TS2** and (S_a,*S*)-**TS2**, leading to the generation of two enantiomers of **4aa**, was 2.2 kcal·mol^{-1}, which well explained the observed absolute configuration of major enantiomer (R_a,*R*)-**4aa** and its good enantioselectivity of 93:7 er. Similarly, the origin of the energy difference leading to the observed enantioselectivity of **4aa** was also investigated by energy decomposition analysis (see Figure S8 in the Supporting Information for details). Energy decomposition analysis indicated that the energy difference between (R_a,*R*)-**TS2** and (S_a,*S*)-**TS2** mainly comes from the difference of interaction energies between the substrates and CPA (*S*)-**7b**. As shown in Figure 2b, three C−H···O (b3 = 2.209 Å, b4 = 2.321 Å, b5 = 2.540 Å) and four C−H···π interactions (b6 = 2.920 Å, b7 = 2.853 Å, b8 = 2.755 Å, b9 = 3.128 Å) between the substrates [(R_a)-**1a** and *o*-QM] and CPA (*S*)-**7b** were observed in (R_a,*R*)-**TS2**. In contrast, only one C−H···O (b3 = 2.513 Å) and two C−H···π interactions (b4 = 2.530 Å, b5 = 2.427 Å) were observed in (S_a,*S*)-**TS2**, indicating that the interactions between the substrates and CPA (*S*)-**7b** in (S_a,*S*)-**TS2** were weaker than those in (R_a,*R*)-**TS2**. These noncovalent interactions could also be visualized from the NCI plots (see Figure S9 in the Supporting Information for details). These results well explained the observed absolute configuration and good enantioselectivity of the major product (R_a,*R*)-**4aa**. Evidently, under the catalysis of CPA (*S*)-**7b**, the energy barrier of (R_a,*R*)-**TS2** was much lower than those of (R_a,*S*)-

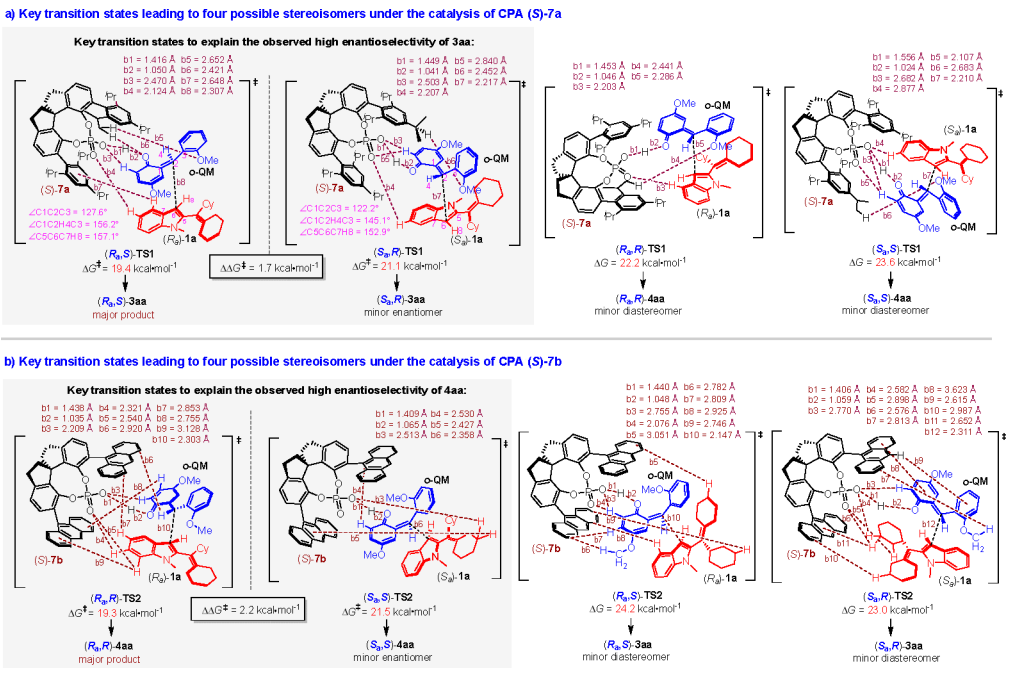


Figure 2. Key transition states to explain the enantioselectivity and diastereodivergence of the products.

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Precis. Chem. 2024, 2, 208−220

TS2 and (S_a,*R*)-**TS2** corresponding to the generation of minor diastereomers (R_a,*S*)-**3aa** and (S_a,*R*)-**3aa**, which explained the observed high diastereoselectivity of **4aa** in the presence of CPA (*S*)-**7b**. Therefore, the theoretical calculations provided an in-depth understanding of the origin of the observed stereoselectivity and diastereodivergence of the products under different reaction conditions.

CONCLUSIONS

In summary, we have established the first catalytic asymmetric diastereodivergent synthesis of 2-alkenylindoles bearing both axial chirality and central chirality via CPA-catalyzed addition reactions of C3-unsubstituted 2-alkenylindoles with *o*-hydroxybenzyl alcohols. Using this approach, two series of 2-alkenylindoles bearing multiple chiral elements were synthesized in a diastereodivergent fashion with moderate to high yields and excellent stereoselectivities. Moreover, such 2-alkenylindoles bearing both axial and central chirality could be converted into new chiral ligand, and several 2-alkenylindole products displayed potent anticancer activities, which demonstrated their promising applications in asymmetric catalysis and medicinal chemistry. Besides, theoretical calculations have been performed on the key transition states leading to different stereoisomers, which provided an in-depth understanding of this catalytic asymmetric diastereodivergent reaction. Therefore, this work has not only established the first catalytic atroposelective synthesis of axially chiral 2-alkenylindoles with potential applications, but also provided a new strategy for diastereodivergent construction of indole-based scaffolds bearing both axial and central chirality, thus offering an efficient tactic toward settling the challenges in developing catalytic asymmetric diastereodivergent reactions for the synthesis of chiral compounds bearing both axial and central chirality.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/prechem.4c00008.

Experimental procedures, spectroscopic data for all new compounds, theoretical calculations (PDF)

X-ray crystallographic data for **3aa** (CIF)

X-ray crystallographic data for *rac*-**4ak** (CIF)

Accession Codes

CCDC 2326447 (**3aa**) and CCDC 2326448 (*rac*-**4ak**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Abram, M.; Jakubiec, M.; Kamiński, K. Chirality as an Important Factor for the Development of New Antiepileptic Drugs. *ChemMedChem.* **2019**, *14*, 1744−1761.

(2) Bogaerts, J.; Aerts, R.; Vermeyen, T.; Johannessen, C.; Herrebout, W.; Batista, J. M. Tackling Stereochemistry in Drug

Molecules with Vibrational Optical Activity. *Pharmaceuticals* **2021**, *14*, 877−901.
(3) *Foye's Principles of Medicinal Chemistry*, 7th ed.; Lemke, T. L., Williams, D. A., Roche, V. F., Zito, S. W., Eds.; Lippincott Williams & Wilkins, Wolters Kluwer: Baltimore, 2013.
(4) Waldeck, B. Biological Significance of the Enantiomeric Purity of Drugs. *Chirality* **1993**, *5*, 350−355.
(5) Wei, L.; Zhu, Q.; Xu, S.-M.; Chang, X.; Wang, C.-J. Stereodivergent Synthesis of α,α-Disubstituted α-Amino Acids via Synergistic Cu/Ir Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1508−1513.
(6) Jiang, X.; Boehm, P.; Hartwig, J. F. Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1239−1242.
(7) Xu, S.-M.; Wei, L.; Shen, C.; Xiao, L.; Tao, H.-Y.; Wang, C.-J. Stereodivergent Assembly of Tetrahydro-γ-Carbolines via Synergistic Catalytic Asymmetric Cascade Reaction. *Nat. Commun.* **2019**, *10*, 5553−5563.
(8) Zhang, M.-M.; Wang, Y.-N.; Wang, B.-C.; Chen, X.-W.; Lu, L.-Q.; Xiao, W.-J. Synergetic Iridium and Amine Catalysis Enables Asymmetric [4 + 2] Cycloadditions of Vinyl Aminoalcohols with Carbonyls. *Nat. Commun.* **2019**, *10*, 2716−2724.
(9) Singha, S.; Serrano, E.; Mondal, S.; Daniliuc, C. G.; Glorius, F. Diastereodivergent Synthesis of Enantioenriched α,β-Disubstituted γ-Butyrolactones via Cooperative N-Heterocyclic Carbene and Ir Catalysis. *Nat. Catal.* **2020**, *3*, 48−54.
(10) Peng, Y.; Huo, X.; Luo, Y.; Wu, L.; Zhang, W. Enantio- and Diastereodivergent Synthesis of Spirocycles through Dual-Metal-Catalyzed [3 + 2] Annulation of 2-Vinyloxiranes with Nucleophilic Dipoles. *Angew. Chem., Int. Ed.* **2021**, *60*, 24941−24949.
(11) Lin, L.; Feng, X. Catalytic Strategies for Diastereodivergent Synthesis. *Chem.—Eur. J.* **2017**, *23*, 6464−6482.
(12) Krautwald, S.; Carreira, E. M. Stereodivergence in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5627−5639.
(13) Zhan, G.; Du, W.; Chen, Y.-C. Switchable Divergent Asymmetric Synthesis via Organocatalysis. *Chem. Soc. Rev.* **2017**, *46*, 1675−1692.
(14) Beletskaya, I. P.; Nájera, C.; Yus, M. Stereodivergent Catalysis. *Chem. Rev.* **2018**, *118*, 5080−5200.
(15) Nájera, C.; Foubelo, F.; Sansano, J. M.; Yus, M. Stereodivergent Routes in Organic Synthesis: Carbohydrates, Amino Acids, Alkaloids and Terpenes. *Org. Biomol. Chem.* **2020**, *18*, 1232−1278.
(16) Huo, X.; Li, G.; Wang, X.; Zhang, W. Bimetallic Catalysis in Stereodivergent Synthesis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202210086.
(17) krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehydes. *Science* **2013**, *340*, 1065−1068.
(18) Huo, X.; He, R.; Zhang, X.; Zhang, W. An Ir/Zn Dual Catalysis for Enantio- and Diastereodivergent α-Allylation of α-Hydroxyketones. *J. Am. Chem. Soc.* **2016**, *138*, 11093−10096.
(19) Rong, Z.-Q.; Wang, M.; Chow, C. H. E.; Zhao, Y. A Catalyst-Enabled Diastereodivergent Aza-Diels-Alder Reaction: Complementarity of N-Heterocyclic Carbenes and Chiral Amines. *Chem.—Eur. J.* **2016**, *22*, 9483−9487.
(20) Kim, B.; Kim, Y.; Lee, S. Y. Stereodivergent Carbon-Carbon Bond Formation between Iminium and Enolate Intermediates by Synergistic Organocatalysis. *J. Am. Chem. Soc.* **2021**, *143*, 73−79.
(21) He, Z.; Peng, L.; Guo, C. Catalytic Stereodivergent Total Synthesis of Amathaspiramide D. *Nat. Synth.* **2022**, *1*, 393−400.
(22) Hu, Y.; Huang, J.-Y.; Yan, R.-J.; Chen, Z.-C.; OuYang, Q.; Du, W.; Chen, Y.-C. Diastereodivergent cis- and trans-Fused [4 + 2] Annulations of Cyclic 1,3-Dienes and 1-Azadienes via Ligand-Controlled Palladium Catalysis. *Chem. Sci.* **2023**, *14*, 1896−1901.
(23) Xiao, L.; Wei, L.; Wang, C. Stereodivergent Synthesis of Enantioenriched γ-Butyrolactones Bearing Two Vicinal Stereocenters Enabled by Synergistic Copper and Iridium Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 24930−24940.
(24) Wen, Y.; Zhang, Z.; Li, S.; Song, J.; Gong, L. Stereodivergent Propargylic Alkylation of Enals via Cooperative NHC and Copper Catalysis. *Nat. Commun.* **2022**, *13*, 1344−1353.
(25) Zhu, M.; Wang, P.; Zhang, Q.; Tang, W.; Zi, W. Diastereodivergent Aldol-Type Coupling of Alkoxyallenes with Pentafluorophenyl Esters Enabled by Synergistic Palladium/Chiral Lewis Base Catalysis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202207621.
(26) Hu, Q.; He, Z.; Peng, L.; Guo, C. Combining Nickel and Squaramide Catalysis for the Stereodivergent α-Propargylation of Oxindoles. *Nat. Synth.* **2022**, *1*, 322−331.
(27) Shen, G.; He, F.; Xie, W.; Gu, H.; Yang, X. Diastereodivergent Asymmetric [4 + 2] Cycloaddition of In Situ Generated Ortho-Quinone Methides and Allenyl Ketones Enabled by Chiral Phosphoric Acid Catalysis. *ACS Catal.* **2023**, *13*, 12472−12480.
(28) Wen, Y.; Yang, F.; Li, S.; Yao, X.; Song, J.; Gong, L. Diastereodivergent Desymmetric Annulation to Access Spirooxindoles: Chemical Probes for Mitosis. *J. Am. Chem. Soc.* **2023**, *145*, 4199−4207.
(29) Wang, J.; Zheng, S.; Rajkumar, S.; Xie, J.; Yu, N.; Peng, Q.; Yang, X. Chiral Phosphoric Acid-Catalyzed Stereodivergent Synthesis of Trisubstituted Allenes and Computational Mechanistic Studies. *Nat. Commun.* **2020**, *11*, 5527−5538.
(30) Zhang, J.; Huo, X.; Xiao, J.; Zhao, L.; Ma, S.; Zhang, W. Enantio- and Diastereodivergent Construction of 1,3-Nonadjacent Stereocenters Bearing Axial and Central Chirality through Synergistic Pd/Cu Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 12622−12632.
(31) Zhang, H.-H.; Li, T.-Z.; Liu, S.-J.; Shi, F. Catalytic Asymmetric Synthesis of Atropisomers Bearing Multiple Chiral Elements: An Emerging Field. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202311053.
(32) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534−547.
(33) Liao, G.; Zhou, T.; Yao, Q.; Shi, B.-F. Recent Advances in the Synthesis of Axially Chiral Biaryls via Transition Metal-Catalysed Asymmetric C-H Functionalization. *Chem. Commun.* **2019**, *55*, 8514−8523.
(34) Bonne, D.; Rodriguez, J. Enantioselective Syntheses of Atropisomers Featuring a Five-membered Ring. *Chem. Commun.* **2017**, *53*, 12385−12393.
(35) Bonne, D.; Rodriguez, J. A Bird's Eye View of Atropisomers Featuring a Five-Membered Ring. *Eur. J. Org. Chem.* **2018**, *2018*, 2417−2431.
(36) Zhang, S.; Liao, G.; Shi, B.-F. Enantioselective Synthesis of Atropoisomers Featuring Pentatomic Heteroaromatics. *Chin. J. Org. Chem.* **2019**, *39*, 1522−1528.
(37) Da, B.; Xiang, S.; Li, S.; Tan, B. Chiral Phosphoric Acid Catalyzed Asymmetric Synthesis of Axially Chiral Compounds. *Chin. J. Chem.* **2021**, *39*, 1787−1796.
(38) Carmona, J.; Rodríguez-Franco, C.; Fernández, R.; Hornillos, V.; Lassaletta, J. M. Atroposelective Transformation of Axially Chiral (Hetero)Biaryls. From Desymmetrization to Modern Resolution Strategies. *Chem. Soc. Rev.* **2021**, *50*, 2968−2983.
(39) Cheng, J. K.; Xiang, S.-H.; Li, S.; Ye, L.; Tan, B. Recent Advances in Catalytic Asymmetric Construction of Atropisomers. *Chem. Rev.* **2021**, *121*, 4805−4902.
(40) Liu, C.-X.; Zhang, W.-W.; Yin, S.-Y.; Gu, Q.; You, S.-L. Synthesis of Atropisomers by Transition-Metal-Catalyzed Asymmetric C-H Functionalization Reactions. *J. Am. Chem. Soc.* **2021**, *143*, 14025−14040.
(41) Wu, Y.-J.; Liao, G.; Shi, B.-F. Stereoselective Construction of Atropisomers Featuring a C-N Chiral Axis. *Green. Synth. Catal.* **2022**, *3*, 117−136.
(42) Rodríguez-Salamanca, P.; Fernández, R.; Hornillos, V.; Lassaletta, J. M. Asymmetric Synthesis of Axially Chiral C-N Atropisomers. *Chem.—Eur. J.* **2022**, *28*, No. e202104442.
(43) Qin, W.; Liu, Y.; Yan, H. Enantioselective Synthesis of Atropisomers via Vinylidene Ortho-Quinone Methides (VQMs). *Acc. Chem. Res.* **2022**, *55*, 2780−2795.

https://doi.org/10.1021/prechem.4c00008
Precis. Chem. 2024, 2, 208−220

(44) Cheng, J. K.; Xiang, S.-H.; Tan, B. Organocatalytic Enantioselective Synthesis of Axially Chiral Molecules: Development of Strategies and Skeletons. *Acc. Chem. Res.* **2022**, *55*, 2920−2937.
(45) Feng, J.; Lu, C.-J.; Liu, R.-R. Catalytic Asymmetric Synthesis of Atropisomers Featuring an Aza Axis. *Acc. Chem. Res.* **2023**, *56*, 2537−2554.
(46) Norton, R.; Wells, R. A Series of Chiral Polybrominated Biindoles from the Marine Blue-green Alga Rivularia Firma. Application of Carbon-13 NMR Spin-lattice Relaxation Data and Carbon-13-proton Coupling Constants to Structure Elucidation. *J. Am. Chem. Soc.* **1982**, *104*, 3628−3635.
(47) Ito, C.; Thoyama, Y.; Omura, M.; Kajiura, I.; Furukawa, H. Alkaloidal Constituents of Murraya koenigii. Isolation and Structural Elucidation of Novel Binary Carbazolequinones and Carbazole Alkaloids. *Chem. Pharm. Bull.* **1993**, *41*, 2096−2100.
(48) Zhang, Q.; Mándi, A.; Li, S.; Chen, Y.; Zhang, W.; Tian, X.; Zhang, H.; Li, H.; Zhang, W.; Zhang, S.; Ju, J.; Kurtán, T.; Zhang, C. N-N-Coupled Indolo-sesquiterpene Atropo-Diastereomers from a Marine-Derived Actinomycete. *Eur. J. Org. Chem.* **2012**, *2012*, 5256−5262.
(49) Jiang, F.; Chen, K.-W.; Wu, P.; Zhang, Y.-C.; Jiao, Y.; Shi, F. A Strategy for Synthesizing Axially Chiral Naphthyl-Indoles: Catalytic Asymmetric Addition Reactions of Racemic Substrates. *Angew. Chem., Int. Ed.* **2019**, *58*, 15104−15110.
(50) Wang, C.-S.; Li, T.-Z.; Liu, S.-J.; Zhang, Y.-C.; Deng, S.; Jiao, Y.; Shi, F. Axially Chiral Aryl-Alkene-Indole Framework: A Nascent Member of the Atropisomeric Family and Its Catalytic Asymmetric Construction. *Chin. J. Chem.* **2020**, *38*, 543−552.
(51) Chen, K.-W.; Chen, Z.-H.; Yang, S.; Wu, S.-F.; Zhang, Y.-C.; Shi, F. Organocatalytic Atroposelective Synthesis of N-N Axially Chiral Indoles and Pyrroles by De Novo Ring Formation. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202116829.
(52) Baumann, T.; Brückner, R. Atropselective Dibrominations of a 1,1′-Disubstituted 2,2′-Biindolyl with Diverging Point-to-Axial Asymmetric Inductions. Deriving 2,2′-Biindolyl-3,3′-Diphosphane Ligands for Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 4714−4719.
(53) Xia, W.; An, Q.-J.; Xiang, S.-H.; Li, S.; Wang, Y.-B.; Tan, B. Chiral Phosphoric Acid Catalyzed Atroposelective C-H Amination of Arenes. *Angew. Chem., Int. Ed.* **2020**, *59*, 6775−6779.
(54) He, T.; Peng, L.; Li, S.; Hu, F.; Xie, C.; Huang, S.; Jia, S.; Qin, W.; Yan, H. Chiral Naphthyl-C2-Indole as Scaffold for Phosphine Organocatalysis: Application in Asymmetric Formal [4 + 2] Cycloaddition Reactions. *Org. Lett.* **2020**, *22*, 6966−6971.
(55) Liu, S.-J.; Chen, Z.-H.; Chen, J.-Y.; Ni, S.-F.; Zhang, Y.-C.; Shi, F. Rational Design of Axially Chiral Styrene-Based Organocatalysts and Their Application in Catalytic Asymmetric [2 + 4] Cyclizations. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202112226.
(56) Li, T.-Z.; Liu, S.-J.; Tan, W.; Shi, F. Catalytic Asymmetric Construction of Axially Chiral Indole-Based Frameworks: An Emerging Area. *Chem.—Eur. J.* **2020**, *26*, 15779−15792.
(57) Zhang, H.-H.; Shi, F. Organocatalytic Atroposelective Synthesis of Indole Derivatives Bearing Axial Chirality: Strategies and Applications. *Acc. Chem. Res.* **2022**, *55*, 2562−2580.
(58) Ototake, N.; Morimoto, Y.; Mokuya, A.; Fukaya, H.; Shida, Y.; Kitagawa, O. Catalytic Enantioselective Synthesis of Atropisomeric Indoles with an N-C Chiral Axis. *Chem.—Eur. J.* **2010**, *16*, 6752−6755.
(59) Wang, L.; Zhong, J.; Lin, X. Atroposelective Phosphoric Acid Catalyzed Three-Component Cascade Reaction: Enantioselective Synthesis of Axially Chiral N-Arylindoles. *Angew. Chem., Int. Ed.* **2019**, *58*, 15824−15828.
(60) Zhang, J.; Xu, Q.; Wu, J.; Fan, J.; Xie, M. Construction of N-C Axial Chirality through Atroposelective C-H Olefination of N-Arylindoles by Palladium/Amino Acid Cooperative Catalysis. *Org. Lett.* **2019**, *21*, 6361−6365.
(61) Sun, L.; Chen, H.; Liu, B.; Chang, J.; Kong, L.; Wang, F.; Lan, Y.; Li, X. Rhodium-Catalyzed Atroposelective Construction of Indoles via C-H Bond Activation. *Angew. Chem., Int. Ed.* **2021**, *60*, 8391−8395.
(62) Kim, A.; Kim, A.; Park, S.; Kim, S.; Jo, H.; Ok, K. M.; Lee, S. K.; Song, J.; Kwon, Y. Catalytic and Enantioselective Control of the C-N Stereogenic Axis via the Pictet-Spengler Reaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 12279−12283.
(63) Ren, Q.; Cao, T.; He, C.; Yang, M.; Liu, H.; Wang, L. Highly Atroposelective Rhodium(II)-Catalyzed N-H Bond Insertion: Access to Axially Chiral N-Arylindolocarbazoles. *ACS Catal.* **2021**, *11*, 6135−6140.
(64) Wang, Z.-S.; Zhu, L.-J.; Li, C.-T.; Liu, B.-Y.; Hong, X.; Ye, L.-W. Synthesis of Axially Chiral N-Arylindoles via Atroposelective Cyclization of Ynamides Catalyzed by Chiral Brønsted Acids. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202201436.
(65) Corti, V.; Thøgersen, M. K.; Enemærke, V. J.; Rezayee, N. M.; Barløse, C. L.; Jørgensen, K. A. Construction of C-N Atropisomers by Aminocatalytic Enantioselective Addition of Indole-2-Carboxaldehydes to *o*-Quinone Derivatives. *Chem.—Eur. J.* **2022**, *28*, No. e202202395.
(66) Li, Y.; Liou, Y.-C.; Chen, X.; Ackermann, L. Thioether-Enabled Palladium-Catalyzed Atroposelective C-H Olefination for N-C and C-C Axial Chirality. *Chem. Sci.* **2022**, *13*, 4088−4094.
(67) Wang, Y.; Zhou, X.; Shan, W.; Liao, R.; Deng, Y.; Peng, F.; Shao, Z. Construction of Axially Chiral Indoles by Cycloaddition-Isomerization via Atroposelective Phosphoric Acid and Silver Sequential Catalysis. *ACS. Catal.* **2022**, *12*, 8094−8130.
(68) Wang, P.; Huang, Y.; Jing, J.; Wang, F.; Li, X. Rhodium(III)-Catalyzed Atroposelective Synthesis of C-N Axially Chiral Naphthylamines and Variants via C-H Activation. *Org. Lett.* **2022**, *24*, 2531−2535.
(69) Niu, C.; Zhou, Y.; Chen, Q.; Zhu, Y.; Tang, S.; Yu, Z.; Sun, J. Atroposelective Synthesis of N-Arylindoles via Enantioselective N-H Bond Insertion. *Org. Lett.* **2022**, *24*, 7428−7433.
(70) Kim, A.; Lee, C.; Song, J.; Lee, S. K.; Kwon, Y. All-Round Catalytic and Atroposelective Strategy via Dynamic Kinetic Resolution for N-/2-/3-Arylindoles. *Nat. Commun.* **2023**, *14*, 5502−5512.
(71) Zhang, Z.-J.; Li, S.-W.; Oliveira, J. A.; Li, Y.; Chen, X.; Zhang, S.-Q.; Xu, L.-C.; Rogge, T.; Hong, X.; Ackermann, L. Data-Driven Design of New Chiral Carboxylic Acid for Construction of Indoles with C-Central and C-N Axial Chirality via Cobalt Catalysis. *Nat. Commun.* **2023**, *14*, 3149−3157.
(72) Zhang, P.; Guo, C.-Q.; Yao, W.; Lu, C.-J.; Li, Y.; Paton, R. S.; Liu, R.-R. Pd-Catalyzed Asymmetric Amination of Enamines: Expedient Synthesis of Structurally Diverse N-C Atropisomers. *ACS Catal.* **2023**, *13*, 7680−7690.
(73) Zhang, M.; Zhao, P.; Wu, D.; Qiu, Z.; Zhao, C.; Zhang, W.; Li, F.; Zhou, J.; Liu, L. Brønsted Acid-Catalyzed Reaction of N-Arylnaphthalen-2-Amines with Quinone Esters for the Construction of Carbazole and C-N Axially Chiral Carbazole Derivatives. *J. Org. Chem.* **2023**, *88*, 2841−2850.
(74) Wang, L.; Yuan, W.-K.; Wang, Z.-K.; Luo, J.; Zhou, T.; Shi, B.-F. Synthesis of C-N Axial Chirality N-Arylindoles via Pd(II)-Catalyzed Free Amine-Directed Atroposelective C-H Olefination. *Chin. J. Chem.* **2023**, *41*, 2788−2792.
(75) Thönnißen, V.; Atodiresei, I. L.; Patureau, F. W. Atroposelective Nenitzescu Indole Synthesis. *Chem.—Eur. J.* **2023**, *29*, No. e202300279.
(76) Rodriguez-Salamanca, P.; de Gonzalo, G.; Carmona, J. A.; Lopez-Serrano, J.; Iglesias-Sigüenza, J.; Fernandez, R.; Lassaletta, J. M.; Hornillos, V. Biocatalytic Atroposelective Synthesis of Axially Chiral N-Arylindoles via Dynamic Kinetic Resolution. *ACS Catal.* **2023**, *13*, 659−664.
(77) Zhang, H.-H.; Wang, C.-S.; Li, C.; Mei, G.-J.; Li, Y.; Shi, F. Design and Enantioselective Construction of Axially Chiral Naphthyl-Indole Skeletons. *Angew. Chem., Int. Ed.* **2017**, *56*, 116−121.
(78) Qi, L.-W.; Mao, J.-H.; Zhang, J.; Tan, B. Organocatalytic Asymmetric Arylation of Indoles Enabled by Azo Groups. *Nat. Chem.* **2018**, *10*, 58−64.

https://doi.org/10.1021/prechem.4c00008
Precis. Chem. 2024, 2, 208−220

(79) Bisag, G. D.; Pecorari, D.; Mazzanti, A.; Bernardi, L.; Fochi, M.; Bencivenni, G.; Bertuzzi, G.; Corti, V. Central-to-Axial Chirality Conversion Approach Designed on Organocatalytic Enantioselective Povarov Cycloadditions: First Access to Configurationally Stable Indole-Quinoline Atropisomers. *Chem.—Eur. J.* **2019**, *25*, 15694−15701.
(80) Ding, W.-Y.; Yu, P.; An, Q.-J.; Bay, K. L.; Xiang, S.-H.; Li, S.; Chen, Y.; Houk, K. N.; Tan, B. DFT-Guided Phosphoric-Acid-Catalyzed Atroposelective Arene Functionalization of Nitrosonaphthalene. *Chem.* **2020**, *6*, 2046−2059.
(81) Mao, J.-H.; Wang, Y.-B.; Yang, L.; Xiang, S.-H.; Wu, Q.-H.; Cui, Y.; Lu, Q.; Lv, J.; Li, S.; Tan, B. Organocatalyst-Controlled Site-Selective Arene C-H Functionalization. *Nat. Chem.* **2021**, *13*, 982−991.
(82) Xu, W.-L.; Zhao, W.-M.; Zhang, R.-X.; Chen, J.; Zhou, L. Organocatalytic Cycloaddition-Elimination Cascade for Atroposelective Construction of Heterobiaryls. *Chem. Sci.* **2021**, *12*, 14920−14926.
(83) Yang, H.; Sun, H.-R.; He, R.-Q.; Yu, L.; Hu, W.; Chen, J.; Yang, S.; Zhang, G.-G.; Zhou, L. Organocatalytic Cycloaddition of Alkynylindoles with Azonaphthalenes for Atroposelective Construction of Indole-Based Biaryls. *Nat. Commun.* **2022**, *13*, 632−640.
(84) Wu, P.; Yu, L.; Gao, C.-H.; Cheng, Q.; Deng, S.; Jiao, Y.; Tan, W.; Shi, F. Design and Synthesis of Axially Chiral Aryl-Pyrroloindoles via the Strategy of Organocatalytic Asymmetric [2 + 3] Cyclization. *Fundam. Res.* **2023**, *3*, 237−l248.
(85) Xia, Y.; Liu, M.; Qian, C.; Li, P.; Dong, M.; Li, W. Asymmetric Organocatalytic [3 + 2] Annulation of Propargylic Alcohols with Indolylnaphthalenols: Synergistic Construction of Axial and Central Chirality. *Org. Chem. Front.* **2022**, *10*, 30−34.
(86) Woldegiorgis, A. G.; Gu, H.; Lin, X. Atroposelective Synthesis of Axially Chiral Styrenes Connecting an Axially Chiral Naphthyl-Indole Moiety Using Chiral Phosphoric Acid Catalysis. *Org. Lett.* **2023**, *25*, 2068−2072.
(87) Liu, Y.-W.; Chen, Y.-H.; Cheng, J. K.; Xiang, S.-H.; Tan, B. Enantioselective Synthesis of 3-Arylindole Atropisomers via Organocatalytic Indolization of Iminoquinones. *Chem. Synth.* **2023**, *3*, 11−18.
(88) He, C.; Hou, M.; Zhu, Z.; Gu, Z. Enantioselective Synthesis of Indole-Based Biaryl Atropisomers via Palladium-Catalyzed Dynamic Kinetic Intramolecular C-H Cyclization. *ACS Catal.* **2017**, *7*, 5316−5320.
(89) Xi, C.-C.; Zhao, X.-J.; Tian, J.-M.; Chen, Z.-M.; Zhang, K.; Zhang, F.-M.; Tu, Y.-Q.; Dong, J.-W. Atroposelective Synthesis of Axially Chiral 3-Arylindoles by Copper-Catalyzed Asymmetric Cross-Coupling of Indoles with Quinones and Naphthoquinones. *Org. Lett.* **2020**, *22*, 4995−5000.
(90) Shaaban, S.; Li, H.; Otte, F.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. Enantioselective Synthesis of Five-Membered-Ring Atropisomers with a Chiral Rh(III) Complex. *Org. Lett.* **2020**, *22*, 9199−9202.
(91) Li, X.; Zhao, L.; Qi, Z.; Li, X. Construction of Atropisomeric 3-Arylindoles via Enantioselective Cacchi Reaction. *Org. Lett.* **2021**, *23*, 5901−5905.
(92) Wang, C.-S.; Wei, L.; Fu, C.; Wang, X.-H.; Wang, C.-J. Asymmetric Synthesis of Axially Chiral Naphthyl-C3-Indoles via a Palladium-Catalyzed Cacchi Reaction. *Org. Lett.* **2021**, *23*, 7401−7406.
(93) Surgenor, R. R.; Liu, X.; Keenlyside, M. J. H.; Myers, W.; Smith, M. D. Enantioselective Synthesis of Atropisomeric Indoles via Iron-Catalysed Oxidative Cross-Coupling. *Nat. Chem.* **2023**, *15*, 357−365.
(94) Rodríguez-Franco, C.; Ros, A.; Merino, P.; Fernández, R.; Lassaletta, J. M.; Hornillos, V. Dynamic Kinetic Resolution of Indole-Based Sulfenylated Heterobiaryls by Rhodium-Catalyzed Atroposelective Reductive Aldol Reaction. *ACS Catal.* **2023**, *13*, 12134−12141.
(95) Hu, Y.-L.; Wang, Z.; Yang, H.; Chen, J.; Wu, Z.-B.; Lei, Y.; Zhou, L. Conversion of Two Stereocenters to One or Two Chiral Axes: Atroposelective Synthesis of 2,3-Diarylbenzoindoles. *Chem. Sci.* **2019**, *10*, 6777−6784.
(96) Peng, L.; Li, K.; Xie, C.; Li, S.; Xu, D.; Qin, W.; Yan, H. Organocatalytic Asymmetric Annulation of Ortho-Alkynylanilines: Synthesis of Axially Chiral Naphthyl-C2-Indoles. *Angew. Chem., Int. Ed.* **2019**, *58*, 17199−17204.
(97) He, Y.-P.; Wu, H.; Wang, Q.; Zhu, J. Palladium-Catalyzed Enantioselective Cacchi Reaction: Asymmetric Synthesis of Axially Chiral 2,3-Disubstituted Indoles. *Angew. Chem., Int. Ed.* **2020**, *59*, 2105−2109.
(98) Xu, D.; Huang, S.; Hu, F.; Peng, L.; Jia, S.; Mao, H.; Gong, X.; Li, F.; Qin, W.; Yan, H. *CCS Chem.* **2022**, *4*, 2686−2697.
(99) Jia, S.; Tian, Y.; Li, X.; Wang, P.; Lan, Y.; Yan, H. Atroposelective Construction of Nine-Membered Carbonate-Bridged Biaryls. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202206501.
(100) Yin, S.-Y.; Pan, C.; Zhang, W.-W.; Liu, C.-X.; Zhao, F.; Gu, Q.; You, S.-L. *Org. Lett.* **2022**, *24*, 3620−3625.
(101) Liu, J.; Li, Q.; Shao, Y.; Sun, J. Atroposelective Synthesis of Axially Chiral C2-Arylindoles via Rhodium-Catalyzed Asymmetric C-H Bond Insertion. *Org. Lett.* **2022**, *24*, 4670−4674.
(102) Yu, L.; Liu, J.; Xiang, S.; Lu, T.; Ma, P.; Zhao, Q. Silver-Catalyzed Direct Nucleophilic Cyclization: Enantioselective De Novo Synthesis of C-C Axially Chiral 2-Arylindoles. *Org. Lett.* **2023**, *25*, 522−527.
(103) Bao, W.; Chen, Y.-H.; Liu, Y.-W.; Xiang, S.-H.; Tan, B. Atroposelective Synthesis of 2-Arylindoles via Chiral Phosphoric Acid-Catalyzed Direct Amination of Indoles. *Chin. J. Chem.* **2024**, *42*, 731−735.
(104) Ma, C.; Jiang, F.; Sheng, F.-T.; Jiao, Y.; Mei, G.-J.; Shi, F. Design and Catalytic Asymmetric Construction of Axially Chiral 3,3′-Bisindole Skeletons. *Angew. Chem., Int. Ed.* **2019**, *58*, 3014−3020.
(105) Sheng, F.-T.; Li, Z.-M.; Zhang, Y.-Z.; Sun, L.-X.; Zhang, Y.-C.; Tan, W.; Shi, F. Atroposelective Synthesis of 3,3′-Bisindoles Bearing Axial and Central Chirality: Using Isatin-Derived Imines as Electrophiles. *Chin. J. Chem.* **2020**, *38*, 583−589.
(106) Chen, K.-W.; Wang, Z.-S.; Wu, P.; Yan, X.-Y.; Zhang, S.; Zhang, Y.-C.; Shi, F. Catalytic Asymmetric Synthesis of 3,3′-Bisindoles Bearing Single Axial Chirality. *J. Org. Chem.* **2020**, *85*, 10152−10166.
(107) Sheng, F.-T.; Yang, S.; Wu, S.-F.; Zhang, Y.-C.; Shi, F. Catalytic Asymmetric Synthesis of Axially Chiral 3,3′-Bisindoles by Direct Coupling of Indole Rings. *Chin. J. Chem.* **2022**, *40*, 2151−2160.
(108) Wang, H.-Q.; Wu, S.-F.; Yang, J.-R.; Zhang, Y.-C.; Shi, F. Design and Organocatalytic Asymmetric Synthesis of Indolyl-Pyrroloindoles Bearing Both Axial and Central Chirality. *J. Org. Chem.* **2023**, *88*, 7684−7702.
(109) Tian, M.; Bai, D.; Zheng, G.; Chang, J.; Li, X. Rh(III)-Catalyzed Asymmetric Synthesis of Axially Chiral Biindolyls by Merging C-H Activation and Nucleophilic Cyclization. *J. Am. Chem. Soc.* **2019**, *141*, 9527−9532.
(110) He, X.-L.; Zhao, H.-R.; Song, X.; Jiang, B.; Du, W.; Chen, Y.-C. Asymmetric Barton-Zard Reaction To Access 3-Pyrrole-Containing Axially Chiral Skeletons. *ACS Catal.* **2019**, *9*, 4374−4381.
(111) Zhang, P.; Xu, Q.; Wang, X.-M.; Feng, J.; Lu, C.-J.; Li, Y.; Liu, R.-R. Enantioselective Synthesis of N-N Bisindole Atropisomers. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202212101.
(112) Chen, Z.-H.; Li, T.-Z.; Wang, N.-Y.; Ma, X.-F.; Ni, S.-F.; Zhang, Y.-C.; Shi, F. Organocatalytic Enantioselective Synthesis of Axially Chiral N,N′-Bisindoles. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202300419.
(113) Wang, L.-Y.; Miao, J.; Zhao, Y.; Yang, B.-M. Chiral Acid-Catalyzed Atroposelective Indolization Enables Access to 1,1′-Indole-Pyrroles and Bisindoles Bearing a Chiral N-N Axis. *Org. Lett.* **2023**, *25*, 1553−1557.
(114) Yao, W.; Lu, C.-J.; Zhan, L.-W.; Wu, Y.; Feng, J.; Liu, R.-R. Enantioselective Synthesis of N-N Atropisomers by Palladium-Catalyzed C-H Functionalization of Pyrroles. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202218871.
(115) Yin, S.-Y.; Zhou, Q.; Liu, C.-X.; Gu, Q.; You, S.-L. Enantioselective Synthesis of N-N Biaryl Atropisomers through

https://doi.org/10.1021/prechem.4c00008
Precis. Chem. 2024, 2, 208−220

Iridium(I)-Catalyzed C-H Alkylation with Acrylates. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202305067.
(116) Wang, C.-S.; Xiong, Q.; Xu, H.; Yang, H.-R.; Dang, Y.; Dong, X.-Q.; Wang, C.-J. Organocatalytic Atroposelective Synthesis of Axially Chiral N,N′-Pyrrolylindoles via De Novo Indole Formation. *Chem. Sci.* **2023**, *14*, 12091−12097.
(117) Wang, J.-Y.; Sun, M.; Yu, X.-Y.; Zhang, Y.-C.; Tan, W.; Shi, F. Atroposelective Construction of Axially Chiral Alkene-Indole Scaffolds via Catalytic Enantioselective Addition Reaction of 3-Alkynyl-2-Indolylmethanols. *Chin. J. Chem.* **2021**, *39*, 2163−2171.
(118) Wang, F.; Jing, J.; Zhao, Y.; Zhu, X.; Zhang, X.-P.; Zhao, L.; Hu, P.; Deng, W.-Q.; Li, X. Rhodium-Catalyzed C-H Activation-Based Construction of Axially and Centrally Chiral Indenes through Two Discrete Insertions. *Angew. Chem., Int. Ed.* **2021**, *60*, 16628−16633.
(119) Wu, Y.-X.; Liu, Q.; Zhang, Q.; Ye, Z.; He, Y. Asymmetric Allylic Substitution-Isomerization for Accessing Axially Chiral Vinylindoles by Intramolecular $\pi \ldots \pi$ Stacking Interactions. *Cell Reports Physical Science* **2022**, *3*, 101005−101016.
(120) Mi, R.; Chen, H.; Zhou, X.; Li, N.; Ji, D.; Wang, F.; Lan, Y.; Li, X. Rhodium-Catalyzed Atroposelective Access to Axially Chiral Olefins via C-H Bond Activation and Directing Group Migration. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202111860.
(121) Ji, D.; Jing, J.; Wang, Y.; Qi, Z.; Wang, F.; Zhang, X.; Wang, Y.; Li, X. Palladium-Catalyzed Asymmetric Hydrophosphination of Internal Alkynes: Atroposelective Access to Phosphine-Functionalized Olefins. *Chem.* **2022**, *8*, 3346−3362.
(122) Zhan, L.-W.; Lu, C.-J.; Feng, J.; Liu, R.-R. Atroposelective Synthesis of C-N Vinylindole Atropisomers by Palladium-Catalyzed Asymmetric Hydroarylation of 1-Alkynylindoles. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202312930.
(123) Zhang, L.; Wu, Qi.; Ren, M.; Zhang, H.; Zhang, X.; Liu, J.; Fu, Z. N-Heterocyclic Carbene-Catalyzed Atroposelective Synthesis of 5-Indo-1-yl Pyran-2-ones with an N-C Axis from Enals. *Adv. Synth.Catal.* **2023**, *365*, 3467−3472.
(124) Mei, G.-J.; Shi, F. Indolylmethanols as Reactants in Catalytic Asymmetric Reactions. *J. Org. Chem.* **2017**, *82*, 7695−7707.
(125) Zhang, H.-H.; Shi, F. Advances in Catalytic Asymmetric Reactions Using 2-Indolylmethanols as Platform Molecules. *Chin. J. Org. Chem.* **2022**, *42*, 3351−3372.
(126) Shi, Y.-C.; Yan, X.-Y.; Wu, P.; Jiang, S.; Xu, R.; Tan, W.; Shi, F. Design and Application of *m*-Hydroxybenzyl Alcohols in Regioselective [3 + 3] Cycloadditions of 2-Indolymethanols. *Chin. J. Chem.* **2023**, *41*, 27−36.
(127) Zhang, Y.-C.; Jiang, F.; Shi, F. Organocatalytic Asymmetric Synthesis of Indole-Based Chiral Heterocycles: Strategies, Reactions, and Outreach. *Acc. Chem. Res.* **2020**, *53*, 425−446.
(128) Hang, Q.-Q.; Wu, S.-F.; Yang, S.; Wang, X.; Zhong, Z.; Zhang, Y.-C.; Shi, F. Design and Catalytic Atroposelective Synthesis of Axially Chiral Isochromenone-Indoles. *Sci. China Chem.* **2022**, *65*, 1929−1937.
(129) Zhang, J.-Y.; Chen, J.-Y.; Gao, C.-H.; Yu, L.; Ni, S.-F.; Tan, W.; Shi, F. Asymmetric [4+n] Cycloadditions of Indolyldimethanols for the Synthesis of Enantioenriched Indole-Fused Rings. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202305450.
(130) Wang, J.-Y.; Gao, C.-H.; Ma, C.; Wu, X.-Y.; Ni, S.-F.; Tan, W.; Shi, F. Design and Catalytic Asymmetric Synthesis of Furan-Indole Compounds Bearing both Axial and Central Chirality. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202316454.
(131) Wang, H.-Q.; Yang, S.; Zhang, Y.-C.; Shi, F. Advances in Catalytic Asymmetric Reactions Involving *o*-Hydroxybenzyl Alcohols. *Chin. J. Org. Chem.* **2023**, *43*, 974−999.
(132) Yang, S.; Wang, N.-Y.; Hang, Q.; Zhang, Y.-C.; Shi, F. Advances in Catalytic Asymmetric Reactions Involving *o*-Hydroxyphenyl Substituted *p*-Quinone Methides. *Acta Chim. Sinica* **2023**, *81*, 793−808.
(133) Dorsch, C.; Schneider, C. Asymmetric Brønsted Acid Catalyzed Cycloadditions of Ortho-Quinone Methides and Related Compounds. *Synthesis* **2022**, *54*, 3125−3141.
(134) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758.
(135) Terada, M. Binaphthol-Derived Phosphoric Acid as a Versatile Catalyst for Enantioselective Carbon-Carbon Bond Forming Reactions. *Chem. Commun.* **2008**, *2008*, 4097−4112.
(136) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, *2010*, 1929−1982.
(137) Yu, J.; Shi, F.; Gong, L.-Z. Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles. *Acc. Chem. Res.* **2011**, *44*, 1156−1171.
(138) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153.
(139) Xia, Z.-L.; Xu-Xu, Q.-F.; Zheng, C.; You, S.-L. Chiral Phosphoric Acid-Catalyzed Asymmetric Dearomatization Reactions. *Chem. Soc. Rev.* **2020**, *49*, 286−300.
(140) Lin, X.; Wang, L.; Han, Z.; Chen, Z. Chiral Spirocyclic Phosphoric Acids and Their Growing Applications. *Chin. J. Chem.* **2021**, *39*, 802−824.
(141) Cheng, J. K.; Xiang, S.-H.; Tan, B. Imidodiphosphorimidates (IDPis): Catalyst Motifs with Unprecedented Reactivity and Selectivity. *Chin. J. Chem.* **2023**, *41*, 685−694.
(142) CCDC 2326447 for **3aa**, CCDC 2326448 for *rac*-**4ak**; see the Supporting Information for details.

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Precis. Chem. 2024, 2, 208−220