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Design and catalytic atroposelective synthesis of axially chiral isochromenone-indoles

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The catalytic atroposelective synthesis of axially chiral isochromenone-indoles has been established by the strategy of designing homophthalic anhydride-based indole derivatives as a new type of indole-based platform molecules for dynamic kinetic resolution. By this strategy, a wide range of axially chiral isochromenone-indoles were synthesized in high yields with excellent enantioselectivities (up to 98% yield, 97% ee) *via* the catalytic asymmetric sulfonylation reaction of homophthalic anhydride-based indole derivatives with aryl sulfonyl chlorides under the catalysis of chiral quaternary ammonium salt as a phase-transfer catalyst.

asymmetric organocatalysis, axial chirality, atroposelectivity, enantioselectivity, indole

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1 Introduction

Axially chiral indole-based scaffolds belong to an important class of atropisomeric heterocycles [1], which are widely found in natural products [2], bioactive molecules [3], chiral catalysts and ligands [3a,4]. Therefore, catalytic atroposelective construction of axially chiral indole-based frameworks has recently become an emerging research area [5], which has attracted intensive attention from the chemistry community (Scheme 1). As summarized in Scheme 1a, synthetic chemists have developed various strategies by asymmetric organocatalysis or metal catalysis toward the catalytic atroposelective synthesis of axially chiral (hetero) aryl indoles. As a result, a wide range of axially chiral (hetero)aryl indoles such as *N*-arylindoles [4a,6], 3-arylindoles [3a,7,8], 2-arylindoles [9], 3,3′-bisindoles [10], 2,3′-bisindoles [11] and *N*-pyrrolylindoles [3c] have been synthesized with high atroposelectivity.

However, in stark contrast, axially chiral nonaryl indoles, a class of more challenging atropisomeric heterocycles, have scarcely been investigated (Scheme 1b). Up to date, only two types of axially chiral nonaryl indoles have been synthesized in an atroposelective manner. One type is 3-alkenylindoles, which were synthesized by our group using the strategy of organocatalytic asymmetric cyclization or addition reaction of 3-alkynyl-2-indolylmethanols with nucleophiles [3b,12]; another type is 3-quinonylindoles, which were devised by Tan's group [13] using the strategy of organocatalytic asymmetric addition/oxidation reaction of indoles with quinones. Despite the progress, catalytic atroposelective synthesis of axially chiral nonaryl indoles is rather underdeveloped. Therefore, the existing challenges in this research area mainly include: (1) designing new class of axially chiral

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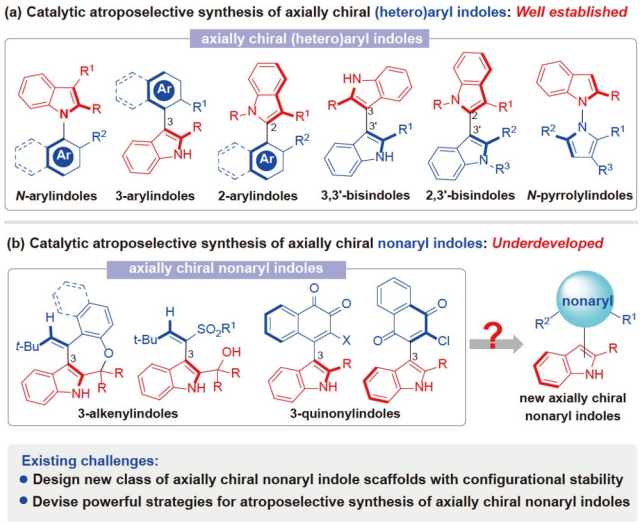
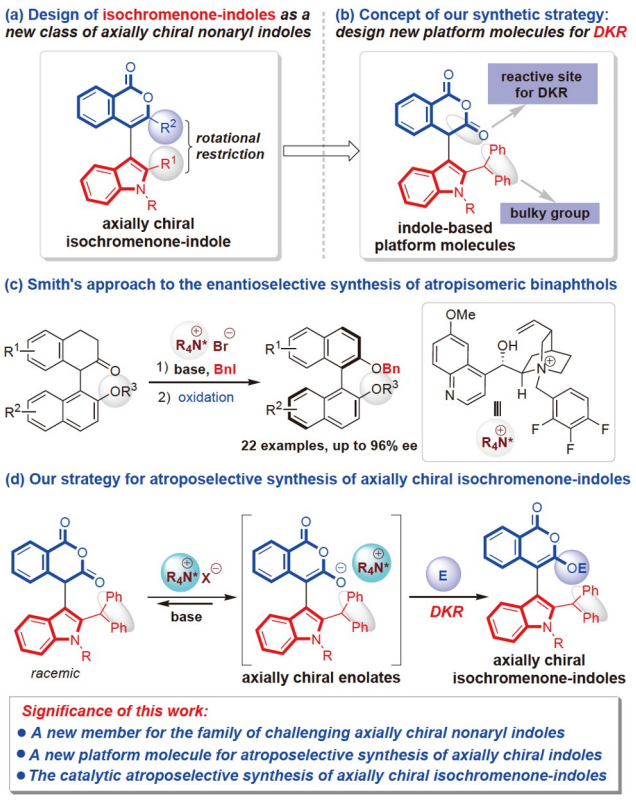


Scheme 1 Current status of catalytic atroposelective synthesis of axially chiral indoles and the existing challenges (color online).

nonaryl indole scaffolds with configurational stability; (2) devising powerful strategies for catalytic atroposelective synthesis of axially chiral nonaryl indoles.

To confront these challenges, based on our long-lasting efforts in chiral indole chemistry [14], we designed isochromenone-indoles as a new class of axially chiral nonaryl indoles and devised a powerful synthetic strategy (Scheme 2). As illustrated in Scheme 2a, the design of this new class of axially chiral nonaryl indoles is based on the consideration that isochromenone scaffold is a six-membered nonaromatic heterocyclic ring, which should have a higher rotational barrier than five-membered ring, thus benefiting the configurational stability of the axially chiral scaffold. In addition, the two bulky *ortho*-substituents around the axis would incur the rotational restriction of the axis, therefore increasing the configurational stability. As shown in Scheme 2b, the concept of our synthetic strategy is designing homophthalic anhydride-based indole derivatives as a new class of indole-based platform molecules for dynamic kinetic resolution (DKR). Specifically, in the structure of this class of platform molecules, the moiety of the carbonyl group and its α-hydrogen of homophthalic anhydrides can transform into the corresponding enolate form in the presence of a base [15], which serves as a reactive site for DKR. Moreover, the diphenylmethyl group of the indole ring can act as a bulky group to generate steric congestion around the axis.

In 2017, Smith and co-workers [16] reported an elegant approach to the enantioselective synthesis of atropisomeric binaphthols *via* a two-step reaction, which involved a counterion-directed *O*-alkylation of racemic 1-aryl-2-tetralones with benzyl iodide as an alkylation reagent in the presence of a chiral quinidine-derived ammonium salt under basic conditions and a subsequent oxidation (Scheme 2c). Based on this work, we conceived a strategy for atroposelective synthesis of axially chiral isochromenone-indoles (Scheme 2d). In detail, in the presence of a base and chiral quaternary ammonium salt as a phase-transfer catalyst (PTC), racemic homophthalic anhydride-based indole derivatives readily transform into axially chiral enolates, which would generate an ion pair with chiral ammonium. This class of axially chiral enolates then act as *O*-nucleophiles to react with a bulky electrophile (E), wherein a DKR process would occur due to the interconversion between the enolates and 1,3-diones *via* reversible protonation and deprotonation, leading to the generation of axially chiral isochromenone-indoles in an atroposelective manner. Therefore, the significance of this work lies in that it will not only offer a new member for the family of challenging axially chiral nonaryl indoles but also provide a new class of platform molecules for atroposelective synthesis of axially chiral indoles and establish the catalytic atroposelective synthesis of axially chiral isochromenone-indoles.



Scheme 2 Design of isochromenone-indoles as a new class of axially chiral nonaryl indoles and our synthetic strategy (color online).

2 Experimental

General procedure for the synthesis of products **3**: Homophthalic anhydride-based indole derivatives (0.1 mmol), aryl sufonyl chlorides (0.15 mmol), catalyst **4o** (0.005 mmol) and $KHCO_3$ (0.15 mmol) were added to a reaction tube. Then,

mesitylene (4 mL) was added to the reaction mixture, which was stirred at 15 °C for 12 h. After the completion of the reaction which was indicated by thin layer chromatography (TLC), the reaction mixture was directly purified through flash column chromatography to afford pure products **3**.

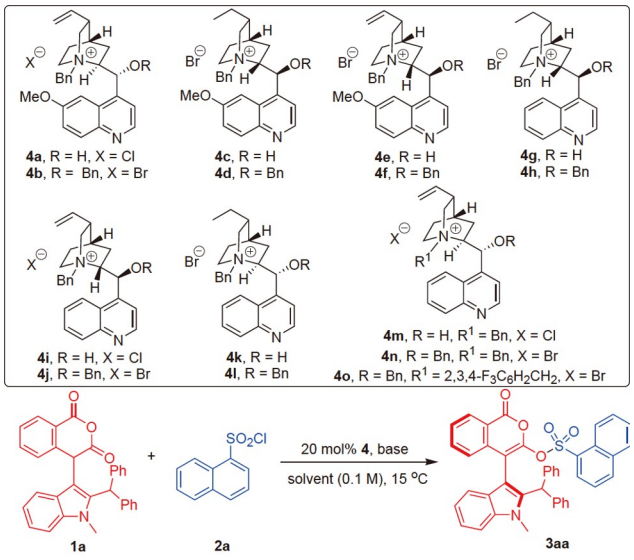
3 Results and discussion

3.1 Condition optimizations

Based on this design, we carried out the DKR reaction of homophthalic anhydride-based indole derivative **1a** by using 1-naphthalene sulfonyl chloride **2a** as a bulky electrophile using chiral phase-transfer catalyst **4a** at 15 °C in toluene in the presence of $KHCO_3$ as a base (Table 1, entry 1). As expected, this sulfonylation reaction between **1a** and **2a** smoothly occurred to afford the desired axially chiral isochromenone-indole **3aa** in a good yield of 86% albeit with a low enantioselectivity of 12% ee. Nevertheless, this preliminary result demonstrated the feasibility of our design.

To improve the atroposelectivity, a series of chiral phase-transfer catalysts **4b**–**4n**, derived from various cinchona alkaloids, were evaluated for this reaction (Table 1, entries 2–14). It was discovered that *N*-benzyl cinchonidine-derived chiral PTC **4n** bearing an *O*-benzyl group was the best catalyst to promote the DKR reaction, which delivered product **3aa** in the highest enantioselectivity of 78% ee (entry 14). Then, under the catalysis of chiral PTC **4n**, the reaction conditions were further optimized by changing bases, solvents, temperature, concentration and catalyst loading (Table S1, Supporting Information online). In brief, a series of inorganic bases were evaluated (entries 15–17), which revealed that $KHCO_3$ was still the best inorganic base with regard to the enantioselectivity and the yield (entry 14 *vs.* entries 15–17). The evaluation of representative solvents showed that these solvents were much inferior to toluene in controlling the enantioselectivity of product **3aa** (entries 18–21 *vs.* entry 14). The subsequent changing of toluene to mesitylene resulted in an increased yield of 94% with an enhanced enantioselectivity of 84% ee (entry 22). To further improve the enantioselectivity, the structure of chiral PTC **4n** was modified by changing the *N*-benzyl group to 2,3,4-trifluorobenzyl group, and this chiral PTC **4o** displayed higher catalytic activity than **4n** in facilitating the reaction to give product **3aa** in a better enantioselectivity of 90% ee (entry 23 *vs.* entry 22). In addition, lowering the reaction concentration from 0.1 to 0.025 M led to a slight increase of the enantioselectivity (entry 24). Finally, when the catalyst loading was reduced from 20 mol% to 5 mol%, axially chiral isochromenone-indole **3aa** could still be generated in an excellent enantioselectivity of 92% ee with a high yield of 80% (entry 25). So, these conditions were chosen as the optimal conditions for this DKR reaction.

Table 1 Screening of catalysts and optimization of reaction conditions [a)]



Entry	Cat.	Solvent	Base	Yield (%) [b)]	ee (%) [c)]
1	**4a**	toluene	$KHCO_3$	86	12
2	**4b**	toluene	$KHCO_3$	79	<5
3	**4c**	toluene	$KHCO_3$	71	−11
4	**4d**	toluene	$KHCO_3$	54	−20
5	**4e**	toluene	$KHCO_3$	74	−6
6	**4f**	toluene	$KHCO_3$	72	−28
7	**4g**	toluene	$KHCO_3$	91	−48
8	**4h**	toluene	$KHCO_3$	77	−38
9	**4i**	toluene	$KHCO_3$	9	−62
10	**4j**	toluene	$KHCO_3$	90	−76
11	**4k**	toluene	$KHCO_3$	56	48
12	**4l**	toluene	$KHCO_3$	80	30
13	**4m**	toluene	$KHCO_3$	77	43
14	**4n**	toluene	$KHCO_3$	89	78
15	**4n**	toluene	Cs_2CO_3	73	20
16	**4n**	toluene	K_2CO_3	85	76
17	**4n**	toluene	KOH	80	78
18	**4n**	MeCN	$KHCO_3$	55	<5
19	**4n**	acetone	$KHCO_3$	82	12
20	**4n**	AcOEt	$KHCO_3$	79	10
21	**4n**	THF	$KHCO_3$	40	66
22	**4n**	mesitylene	$KHCO_3$	94	84
23	**4o**	mesitylene	$KHCO_3$	94	90
24 [d)]	**4o**	mesitylene	$KHCO_3$	80	92
25 [d), e)]	**4o**	mesitylene	$KHCO_3$	80	92

a) Unless otherwise indicated, the reaction was carried out on a 0.1 mmol scale in the presence of 20 mol% **4** with a base (1.5 equiv.) in a solvent (0.1 M) at 15 °C for 12 h; b) isolated yield; c) the ee value was determined by high performance liquid chromatography (HPLC); d) the reaction concentration was 0.025 M; e) catalyzed by 5 mol% **4o**.

3.2 Investigation on the substrate scope

After establishing the optimal reaction conditions, the substrate scope of homophthalic anhydride-based indole derivatives **1** was studied by the sulfonylation reaction with 1-naphthalene sulfonyl chloride **2a**. As illustrated in Table 2, a series of substrates **1b**–**1g** bearing electronically different *para*-, *meta*- or *ortho*-substituted phenyl groups (Ar) could successfully undergo the catalytic asymmetric sulfonylation reaction, delivering axially chiral isochromenone-indoles **3ba**–**3ga** in high yields (73%–95%) with excellent enantioselectivities (92%–97% ee). In addition, a variety of homophthalic anhydride-based indole derivatives **1h**–**1n** bearing either electron-donating or electron-withdrawing R groups at C4–C7 positions of the indole ring could serve as suitable substrates to give the corresponding products **3ha**–**3na** in moderate to good yields (66%–95%) with high enantioselectivities (90%–96% ee). In addition, substrate **1o** bearing a free NH group on the indole ring could be utilized in this reaction to give product **3oa** in a good yield of 80% with an excellent enantioselectivity of 92% ee. Moreover, this protocol was also applicable to substrates **1p**–**1x** bearing various R^2 substituents at different positions (C5′–C8′) of the isochromenone moiety, affording axially chiral isochromenone-indoles **3pa**–**3xa** in generally good yields (73%–98%) with high enantioselectivities (92%–96% ee). Notably, substrate **1s** bearing a diphenylphosphine oxide functionality at the C6′ position could serve as an effective substrate for this reaction, generating product **3sa** in a good yield of 89% with an excellent enantioselectivity of 92% ee.

Then, the substrate scope with respect to aryl sulfonyl chlorides **2** was explored. As illustrated in Table 3, both 1-naphthalene sulfonyl chloride **2a** and 2-naphthalene sulfonyl chloride **2b** could serve as effective substrates for this sulfonylation reaction, which generated axially chiral isochromenone-indoles **3aa**–**3ab** in good yields with high enantioselectivities. Moreover, a series of phenyl sulfonyl chlorides **2c**–**2g** bearing electronically different substituents at either *ortho*-, *meta*- or *para*-position of the phenyl ring could successfully participate in this reaction, offering axially chiral isochromenone-indoles **3ac**–**3ag** in overall high yields (90%–94%) with good enantioselectivities (85%–94% ee).

3.3 Investigation on the configurational stability

To get some information on this new class of axially chiral scaffolds, we investigated the configurational stability and the rotational barrier of isochromenone-indole **3aa**. As showed in Scheme 3, compound **3aa** with 92% ee was stirred in isopropanol at 110 °C for 9 h, but no erosion of the enantioselectivity was observed for the recovered **3aa**. This result demonstrated that this class of axially chiral isochromenone-indole scaffolds have a high configurational stability. In addition, the rotational barrier of compound **3aa** was theoretically calculated as 39.67 kcal mol^{-1}, which is much higher than the energy barrier (24 kcal mol^{-1}) required for isolating the two atropisomers of axially chiral compounds [17]. So, the high rotational barrier of compound **3aa** is in accordance with the experimentally observed configurational stability of this compound. In addition, the absolute configuration of axially chiral product **3aa** (>99% ee after recrystallization) was determined to be (S_a) by single-crystal X-ray diffraction analysis [18]. Thus, the absolute configurations of other axially chiral isochromenone-indole **3** were assigned to be (S_a) by analogy with **3aa**.

3.4 Investigation on the reaction mechanism

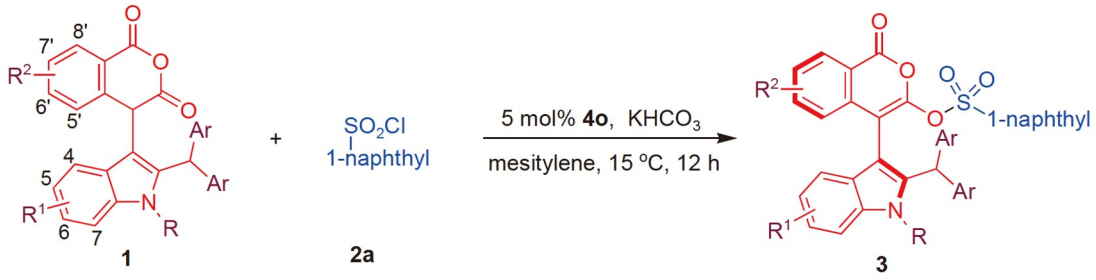
Based on the experimental results, we suggested a possible reaction pathway for the DKR process leading to the generation of axially chiral product (S_a)-**3aa** (Scheme 4). In the presence of $KHCO_3$ as a base and chiral quaternary ammonium salt **4o** as a chiral PTC, racemic homophthalic anhydride-based indole **1a** with central chirality was easily transform into a pair of axially chiral enolates **A** and **B**, which generated the corresponding ion pairs with chiral ammonium, respectively. Notably, there was an interconversion between axially chiral enolates **A**–**B** and racemic homophthalic anhydride-based indole **1a** *via* reversible protonation and deprotonation. In principle, axially chiral enolates **A** and **B** can act as *O*-nucleophiles to undergo sulfonylation reaction with 1-naphthalene sulfonyl chloride **2a** to generate the two atropisomers of isochromenone-indole **3aa**. However, because axially chiral enolate **A** react with **2a** much faster than axially chiral enolate **B**, enolate **B** continuously transformed into enolate **A** *via* the interconversion with racemic substrate **1a**, therefore realizing the DKR process and leading to the generation of (S_a)-**3aa** as a major atropisomer.

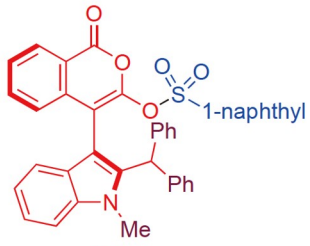
3.5 Lager-scale synthesis and investigation on the utility

In order to demonstrate the utility of this catalytic asymmetric sulfonylation reaction in synthesizing axially chiral indole derivatives, a one-mmol-scale reaction of **1l** with **2a** was carried out, which smoothly gave rise to axially chiral isochromenone-indole **3la** in a good yield of 67% with a high enantioselectivity of 90% ee (Scheme 5a). In addition, a preliminary synthetic transformation of product **3la** was performed by Suzuki coupling reaction with arylboronic acid, which afforded axially chiral indole derivative **5** in a moderate yield with retained enantioselectivity (Scheme 5b).

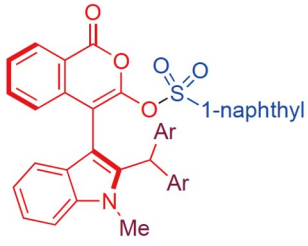
Moreover, to find the possible bioactivities of this new class of axially chiral isochromenone-indoles, we performed

Table 2 Substrate scope of homophthalic anhydride-based indole derivatives **1** [a)]



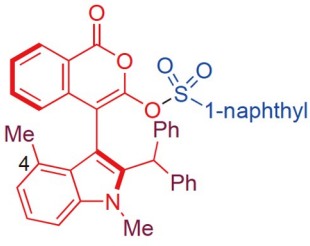


3aa
80% yield, 92% ee

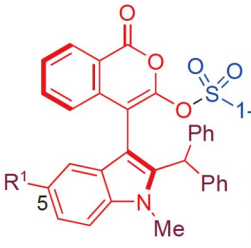


3ba-3ga

3ba, Ar = 2-OMeC$_6$H$_4$
95% yield, 97% ee
3ca, Ar = 3-OMeC$_6$H$_4$
95% yield, 95% ee
3da, Ar = 3-FC$_6$H$_4$
73% yield, 93% ee
3ea, Ar = 3-ClC$_6$H$_4$
83% yield, 93% ee
3fa, Ar = 4-OMeC$_6$H$_4$
95% yield, 95% ee
3ga, Ar = 4-ClC$_6$H$_4$
95% yield, 92% ee

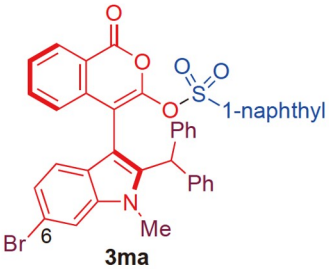


3ha
94% yield, 93% ee

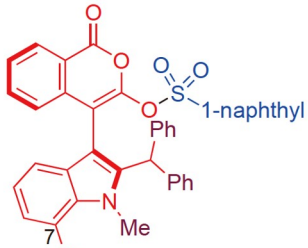


3ia-3la

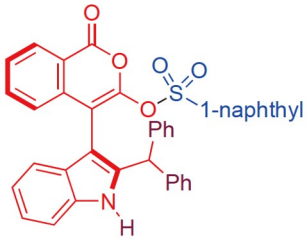
3ia, R^1 = OMe, 93% yield, 96% ee
3ja, R^1 = Me, 95% yield, 94% ee
3ka, R^1 = Cl, 95% yield, 92% ee
3la, R^1 = Br, 75% yield, 90% ee



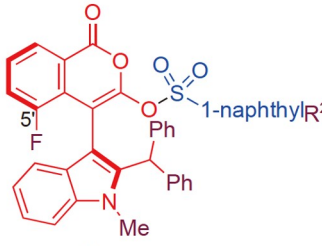
3ma
95% yield, 94% ee



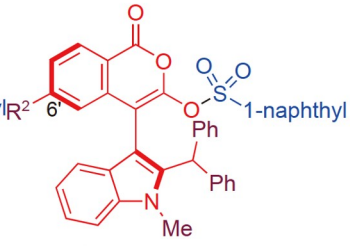
3na
66% yield, 96% ee



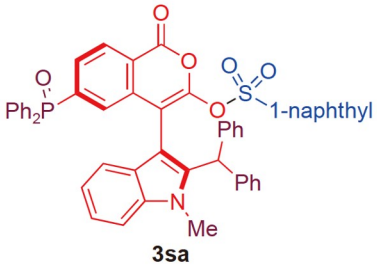
3oa
80% yield, 92% ee



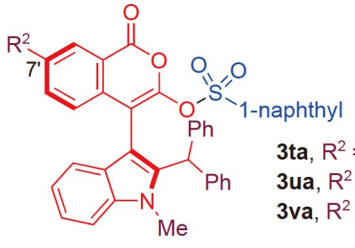
3pa
98% yield, 94% ee



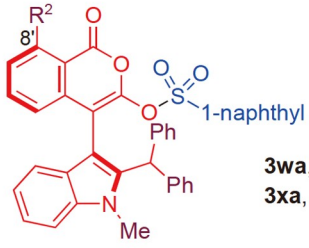
3qa, R^2 = Me, 87% yield, 96% ee
3ra, R^2 = F, 98% yield, 96% ee



3sa
89% yield, 92% ee



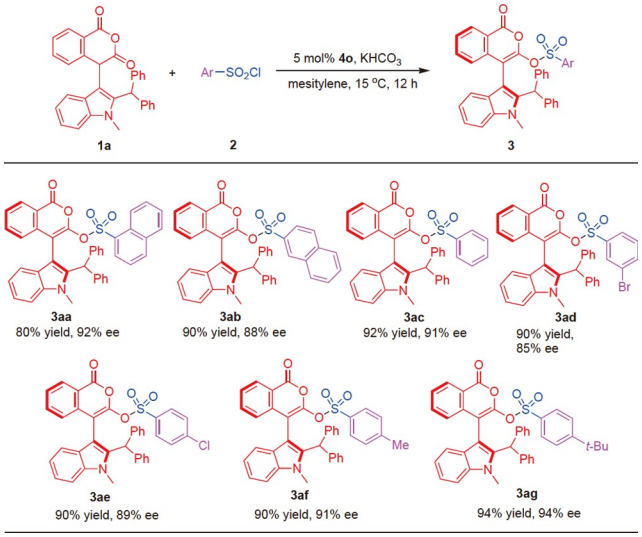
3ta, R^2 = OMe, 73% yield, 95% ee
3ua, R^2 = Me, 98% yield, 94% ee
3va, R^2 = F, 77% yield, 96% ee



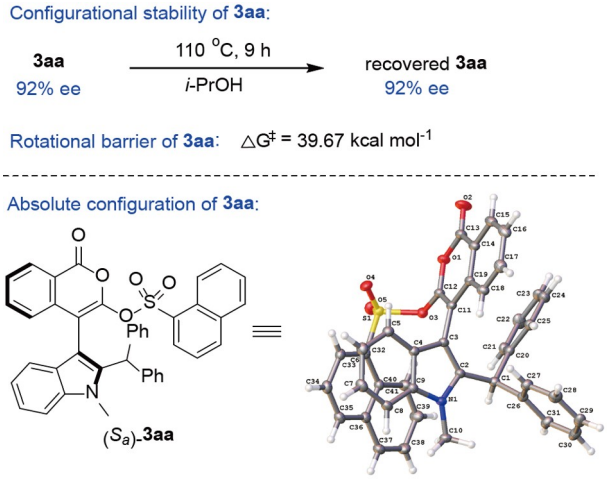
3wa, R^2 = Me, 88% yield, 95% ee
3xa, R^2 = F, 89% yield, 95% ee

a) Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), **4o** (5 mol%), $KHCO_3$ (1.5 equiv.), mesitylene (4 mL), 15 °C for 12 h. Isolated yields were provided, and ee values were determined by HPLC.

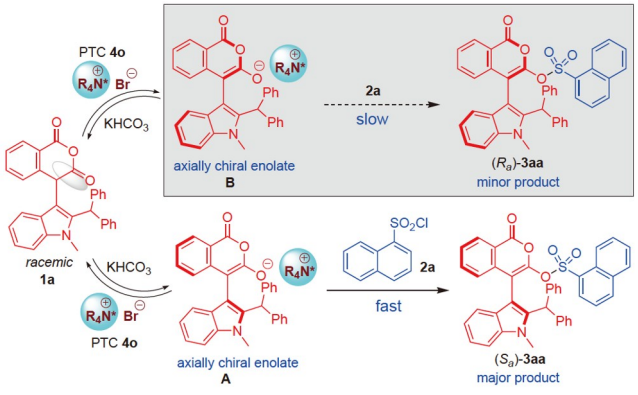
Table 3 Substrate scope of aryl sulfonyl chlorides **2**[a)]



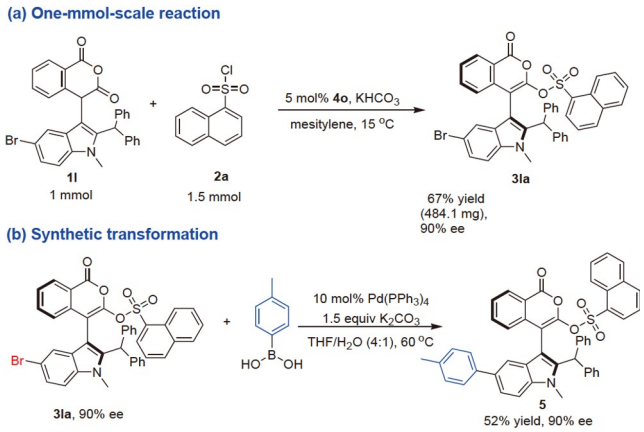
a) Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), **4o** (5 mol%), $KHCO_3$ (1.5 equiv.), mesitylene (4 mL), 15 °C for 12 h. Isolated yields were provided, and ee values were determined by HPLC.



Scheme 3 Investigation on the configurational stability of **3aa** and its absolute configuration (color online).



Scheme 4 Suggested reaction pathway for the DKR process (color online).



Scheme 5 One-mmol-scale reaction and synthetic transformation (color online).

the investigation on the antitumor activity of some selected axially chiral products **3** by evaluating their cytotoxicity against the PC-3 cancer cell line (see Table S2 for details). As shown in Figure 1, several axially chiral isochromenone-indoles **3** exhibited some extent of cytotoxicity against PC-3 cancer cells, with half maximal inhibitory concentration (IC_{50}) values ranging from 47.59 to 161.3 μg mL^{-1}. So, these results indicated that this class of axially chiral indole derivatives have potential antitumor activities, which might find their future applications in medicinal chemistry.

3.6 Investigation on the alkylation reaction of homophthalic anhydride-based indole derivatives1

To examine the possibility of atroposelective synthesis of axially chiral isochromenone-indoles by alkylation reaction instead of sulfonylation reaction, we carried out the investigation on the catalytic asymmetric alkylation reaction of homophthalic anhydride-based indole derivatives **1**.

Initially, we carried out the alkylation reaction of homophthalic anhydride-based indole derivative **1a** with benzyl bromide **6a** as an alkylation reagent under the optimal reaction conditions for the sulfonylation reaction (Scheme 6). Unfortunately, this alkylation reaction between **1a** and **6a** could not occur under such conditions. Then, a variety of reaction parameters such as solvents, inorganic bases, chiral phase-transfer catalysts **4a**–**4z**, temperature, molar ratio and concentration were carefully modulated (see Table S4 for details). Nevertheless, in most cases, the enantioselectivity of this alkylation reaction could be hardly controlled. After evaluating these conditions, the alkylation product **7aa** could be obtained in a moderate yield of 57% but with an extremely low enantioselectivity of 9% ee (Scheme 6).

Then, to further investigate the possibility conditions for controlling the enantioselectivity of this alkylation reaction, we modified the structure of alkylation reagents **6** in the alkylation reaction with homophthalic anhydride-based

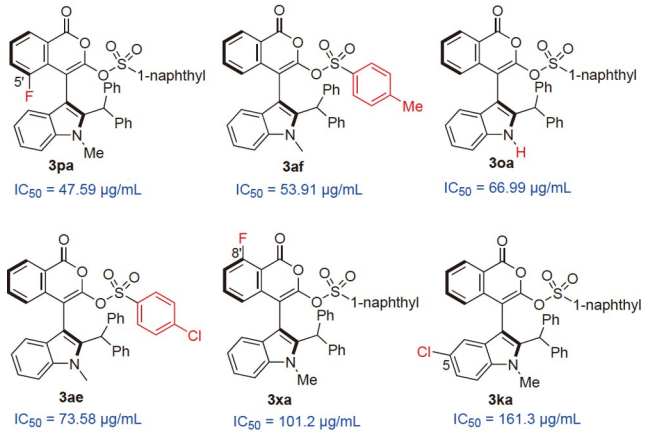
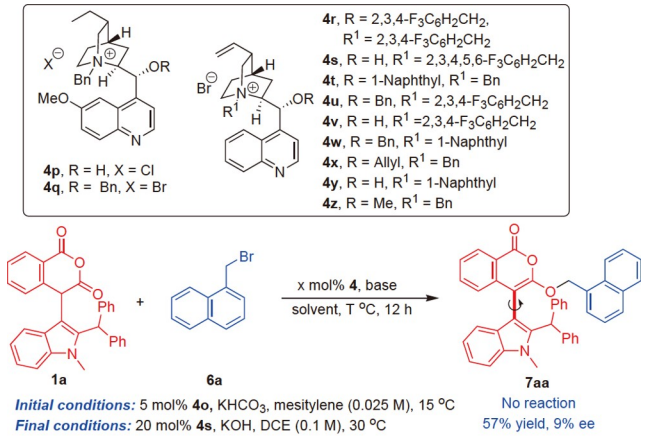


Figure 1 Investigation on the antitumor activity of axially chiral isochromenone-indoles (color online).

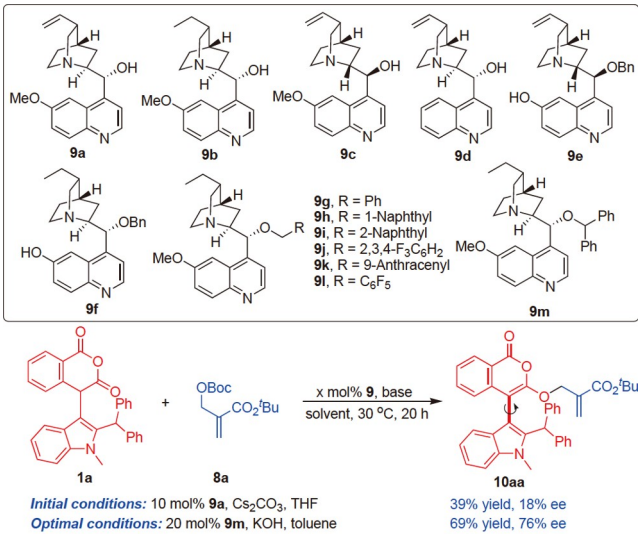


Scheme 6 Catalysts and model reaction employed for conditions optimization using benzyl bromide **6a** as an alkylation reagent (color online).

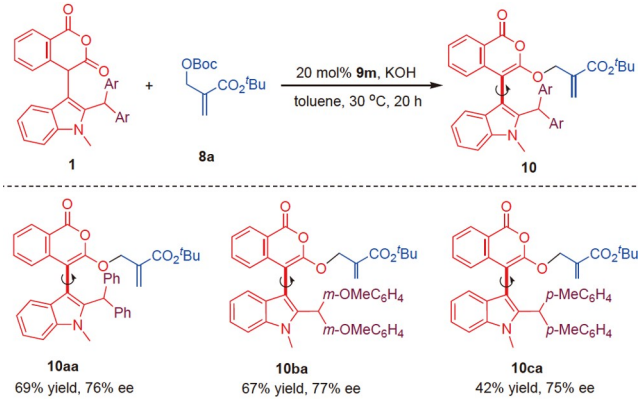
indole derivative **1a**. However, in these cases, none of other alkylation reagents **6** displayed higher reactivity and better enantio-control than benzyl bromide **6a** as an alkylation reagent (see Table S5 for details). These results implied that the synthesis of axially chiral isochromenone-indoles **7** in an enantioselective manner *via* the catalytic asymmetric alkylation reaction with benzyl halides **6** as alkylation reagents was very difficult.

At last, we conceived whether the enantioselective synthesis of axially chiral isochromenone-indoles could be achieved by other catalytic asymmetric alkylation reactions instead of using benzyl halides **6** as alkylation reagents. Based on this consideration, we decided to use Morita-Baylis-Hillman (MBH) carbonates as alkylation reagents because MBH carbonates belong to a class of highly reactive electrophiles under the catalysis of chiral Lewis bases, which have been widely applied in catalytic asymmetric alkylation reactions. Therefore, we carried out the alkylation reaction between homophthalic anhydride-based indole derivative **1a** and MBH carbonate **8a** under the catalysis of chiral Lewis base **9a** at 30 °C in tetrahydrofuran (THF) in the presence of Cs_2CO_3 as a base (Scheme 7). As expected, this alkylation reaction occurred to afford the desired axially chiral isochromenone-indole **10aa** although the yield and the enantioselectivity were low (39% yield, 18% ee). To improve the yield and the enantioselectivity, we carefully optimized the reaction conditions by evaluating the solvents, chiral Lewis bases **9a**–**9m**, inorganic bases, molar ratio and reaction concentration (Table S6). Finally, the optimal conditions for this alkylation reaction were obtained (Scheme 7), which could deliver axially chiral isochromenone-indole **10aa** in a moderate yield of 69% with a good enantioselectivity of 76% ee.

Based on the optimal reaction conditions, this catalytic asymmetric alkylation reaction was further explored in a few examples by using MBH carbonate **8a** as the alkylation reagent. As illustrated in Scheme 8, several substrates **1** bearing different phenyl groups (Ar) successfully underwent the catalytic asymmetric alkylation reaction with **8a**, delivering axially chiral isochromenone-indoles **10** in moderate



Scheme 7 Catalysts and model reaction employed for conditions optimization using MBH carbonate **8a** as an alkylation reagent (color online).



Scheme 8 Synthesis of axially chiral isochromenone-indoles **10** by the alkylation reaction with MBH carbonate **8a** (color online).

yields (42%–69%) with good enantioselectivities (75%–77% ee).

4 Conclusions

In summary, we have designed isochromenone-indoles as a new class of axially chiral nonaryl indoles and established the catalytic atroposelective synthesis of axially chiral isochromenone-indoles by the strategy of designing homophthalic anhydride-based indole derivatives as a new type of indole-based platform molecules for dynamic kinetic resolution. By this strategy, a wide range of axially chiral isochromenone-indoles were synthesized in high yields with excellent enantioselectivities (up to 98% yield, 97% ee) *via* the catalytic asymmetric sulfonylation reaction of homophthalic anhydride-based indole derivatives with aryl sulfonyl chlorides under the catalysis of chiral quaternary ammonium salt as a phase-transfer catalyst. This approach has not only offered a new member for the family of challenging axially chiral nonaryl indoles with configurational stability, but also provided a powerful strategy for catalytic atroposelective synthesis of axially chiral nonaryl indoles.

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Conflict of interest The authors declare no conflict of interest.

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18 CCDC 2173719 (**3aa**) contains the Supporting Information