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# Organocatalytic diastereo- and atropo-selective construction of eight-membered bridged (hetero)biaryls *via* asymmetric intramolecular [3 + 2] cycloaddition†

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An unprecedented and straightforward route for the asymmetric construction of privileged atroposelective bridged (hetero)biaryl eight-membered scaffolds has been accomplished through chiral phosphoric acid catalyzed asymmetric intramolecular [3 + 2] cycloaddition of innovative (hetero)biaryl aldehydes with 3-aminooxindole hydrochlorides. A class of eight-membered bridged (hetero)biaryl lactones fused to spiro [pyrrolidine-oxindole] derivatives, possessing both chiral C–C/N axes and multiple contiguous stereocenters, were obtained in good yields with excellent enantioselectivities and diastereoselectivities in one step through this direct strategy. In addition, the good scalability and derivatization of the title compounds demonstrated their synthetic utility.

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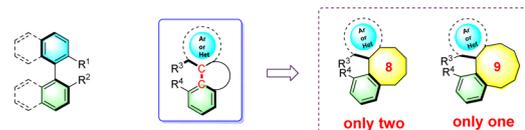
## Introduction

Atropisomeric biaryl skeletons featuring restricted rotation around a stereogenic axis constitute an important class of structural motifs found in a large variety of natural products, pharmaceutical agents, bioactive molecules and chiral ligands (Fig. 1a).<sup>1</sup> Over the past two decades, considerable research efforts have been devoted to the asymmetric construction of diverse biaryl atropisomers.<sup>2</sup> Axially chiral medium-sized bridged (hetero)biaryls, wherein the biaryl moiety is embedded in a medium-sized ring, are a unique subclass possessing more rigid structures (Fig. 1a). Notably, medium-sized bridged (hetero)biaryls are well featured in bioactive natural products (Fig. 1b). For example, spirobandakamine A<sub>1</sub> and A<sub>2</sub> exhibit strong antiprotozoal properties,<sup>3</sup> (–)-steganacin is a lignan compound known for its anti-leukemic activity,<sup>4</sup> and alkaloid (–)-rhazinilam, first isolated in 1965 from *Melodinus* Australia, has significant potential as a tubulin inhibitor.<sup>5</sup> However, in sharp contrast to the creation of common axially chiral biaryls, the enantioselective synthesis of atropisomeric medium-sized bridged (hetero)biaryls is still underdeveloped,<sup>6</sup>

reflecting the difficulties and challenges in the enantiocontrol of the biaryls within the entropically and enthalpically unfavorable formation of medium-sized rings.<sup>7</sup>

To date, only two reports for the asymmetric construction of eight-membered and one for nine-membered bridged biaryls have been documented. In seminal work, Zhao's group reported the atroposelective synthesis of eight-membered bridged heterobiaryl lactones through an NHC-catalyzed cascade reaction (Scheme 1a).<sup>8</sup> Very recently, Smith's group disclosed a process to construct eight-membered bridged biaryl lactams *via* an

### a) The research status of the atroposelective synthesis of bridged (hetero)biaryls



- ★ Axially chiral biaryls
- ★ well-developed
- ★ Axially chiral medium-sized bridged (hetero)biaryl skeletons
- ★ underdeveloped
- ★ challenges:
  - unfavorable formation of medium-sized rings
  - good enantiocontrol of (hetero)biaryl moiety
  - stereochemical control of multiple chiral elements

### b) Representative examples of axially chiral bridged biaryls in bioactive compounds



Fig. 1 Catalytic asymmetric construction of axially chiral bridged (hetero)biaryls.

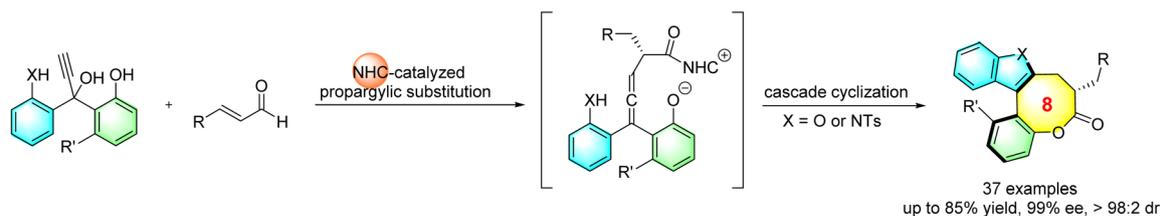
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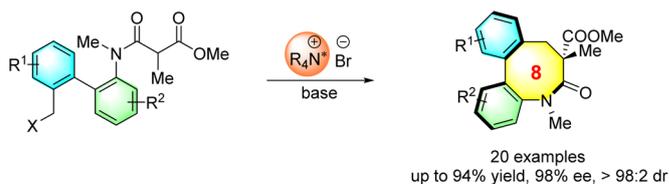
† Electronic supplementary information (ESI) available. CCDC 2234268 and 2321325. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4sc01892c>



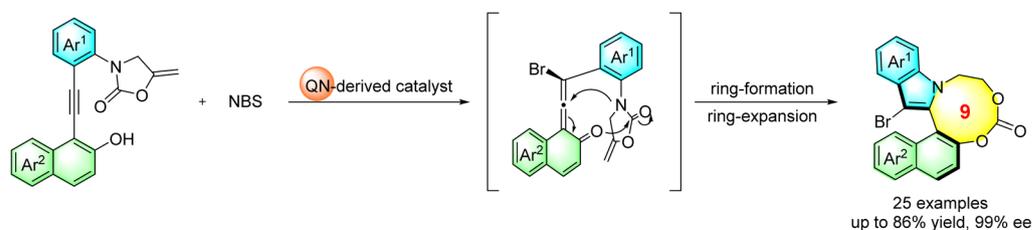
a) **Zhao's work:** organocatalytic cascade cyclization to bridged heterobiaryl with 8-membered lactone (C-C axial and one central chirality)



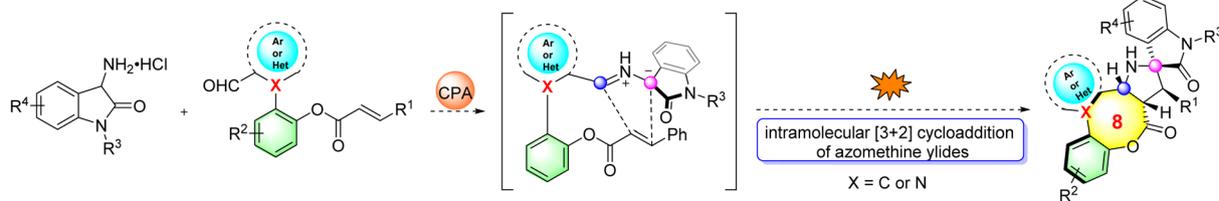
b) **Smith's work:** counterion catalyzed C-alkylation to bridged biaryl with 8-membered lactam (C-C axial and one central chirality)



c) **Yan's work:** organocatalytic ring-formation and expansion to bridged heterobiaryl with 9-membered carbonate (C-C axial chirality)



d) **This work:** intramolecular [3+2] cycloaddition to bridged (hetero)biaryl with 8-membered lactone (C-C/N axial and four contiguous central chirality)



Scheme 1 Current research on axially chiral medium-sized bridged (hetero)biaryls.

asymmetric intramolecular counterion-directed C-alkylation reaction (Scheme 1b).<sup>9</sup> Meanwhile, Yan's group reported a quinine-thiourea-catalyzed nucleophilic cyclization to access axially chiral bridged nine-membered heterobiaryl carbonates through vinylidene *ortho*-quinone methide (VQM) intermediates (Scheme 1c).<sup>10</sup> It should be noted that both the C-C chiral axis and one single chiral center were created in the former two reports, while catalytic methods of the enantioselective synthesis of medium-sized atropisomeric bridged (hetero)biaryls containing a C-C or C-N stereogenic axis and multiple contiguous stereocenters in one step have not been realized to date. As is known, significant challenges exist in the preparation of this kind of skeleton, such as the development of new strategies, the design of reasonable substrates and good enantio- and diastereocontrol of multiple chiral elements, which hindered the development of this topic.<sup>11</sup>

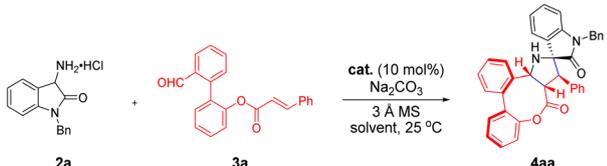
Organocatalytic 1,3-dipolar cycloaddition involving azomethine ylides and electron-deficient unsaturated bonds is capable of furnishing biologically relevant nitrogenous five-membered heterocycles in asymmetric syntheses.<sup>12</sup> Despite great advances achieved in organocatalytic asymmetric intermolecular [3 + 2]

cycloaddition reactions, the corresponding intramolecular variants have barely been developed since the pioneering work by Gong in 2010.<sup>13</sup> Inspired by the above-mentioned study and our previous work,<sup>14</sup> herein, we report an organocatalytic intramolecular [3 + 2] cycloaddition process with *in situ* generation of azomethine ylides from 3-aminooxindole hydrochlorides and newly designed (hetero)biaryl aldehydes (Scheme 1d), which not only provides a straightforward asymmetric approach for the atroposelective synthesis of medium-membered bridged (hetero)biaryls, but also affords an array of structurally congested eight-membered bridged (hetero)biaryl lactones fused to spiro[pyrrolidine-oxindole] scaffolds bearing both C-C/C-N axial chirality and four contiguous chiral centers.

## Results and discussion

As shown in Table 1, we commenced our study with 3-amino oxindole hydrochloride **2a** and biaryl aldehyde **3a** as model substrates in the presence of an appropriate inorganic base and 3 Å molecular sieves (MSs) to conduct the intramolecular [3 + 2] cycloaddition reaction in dichloromethane at room temperature



Table 1 Optimization of reaction conditions<sup>a</sup>


**2a**, **3a** → **4aa**  
 cat. (10 mol%), Na<sub>2</sub>CO<sub>3</sub>, 3 Å MS, solvent, 25 °C

**1a**, Ar = CH<sub>3</sub>  
**1b**, Ar = 2-naphthyl  
**1c**, Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>  
**1d**, Ar = 2,4,6-(i-Pr)<sub>3</sub>-C<sub>6</sub>H<sub>2</sub>  
**1e**, Ar = 9-phenanthryl

Entry	Cat.	Solvent	T [h]	Yield <sup>b</sup> [%]	dr <sup>c</sup>	ee <sup>d</sup> [%]
1	DPP	DCM	10	46	>20 : 1	—
2	<b>1a</b>	DCM	12	4	>20 : 1	79
3	<b>1b</b>	DCM	48	31	>20 : 1	95
4	<b>1c</b>	DCM	16	17	>20 : 1	96
5	<b>1d</b>	DCM	16	47	>20 : 1	96
6	<b>1e</b>	DCM	24	64	>20 : 1	98
7 <sup>e</sup>	<b>1e</b>	DCM	28	44	>20 : 1	98
8 <sup>f</sup>	<b>1e</b>	DCM	36	40	>20 : 1	97
9	<b>1e</b>	CHCl <sub>3</sub>	48	24	>20 : 1	97
10	<b>1e</b>	THF	36	37	>20 : 1	97
11	<b>1e</b>	Tol.	48	65	>20 : 1	98
12	<b>1e</b>	Et <sub>2</sub> O	48	92	>20 : 1	98
13	<b>1e</b>	DCE	40	40	>20 : 1	98

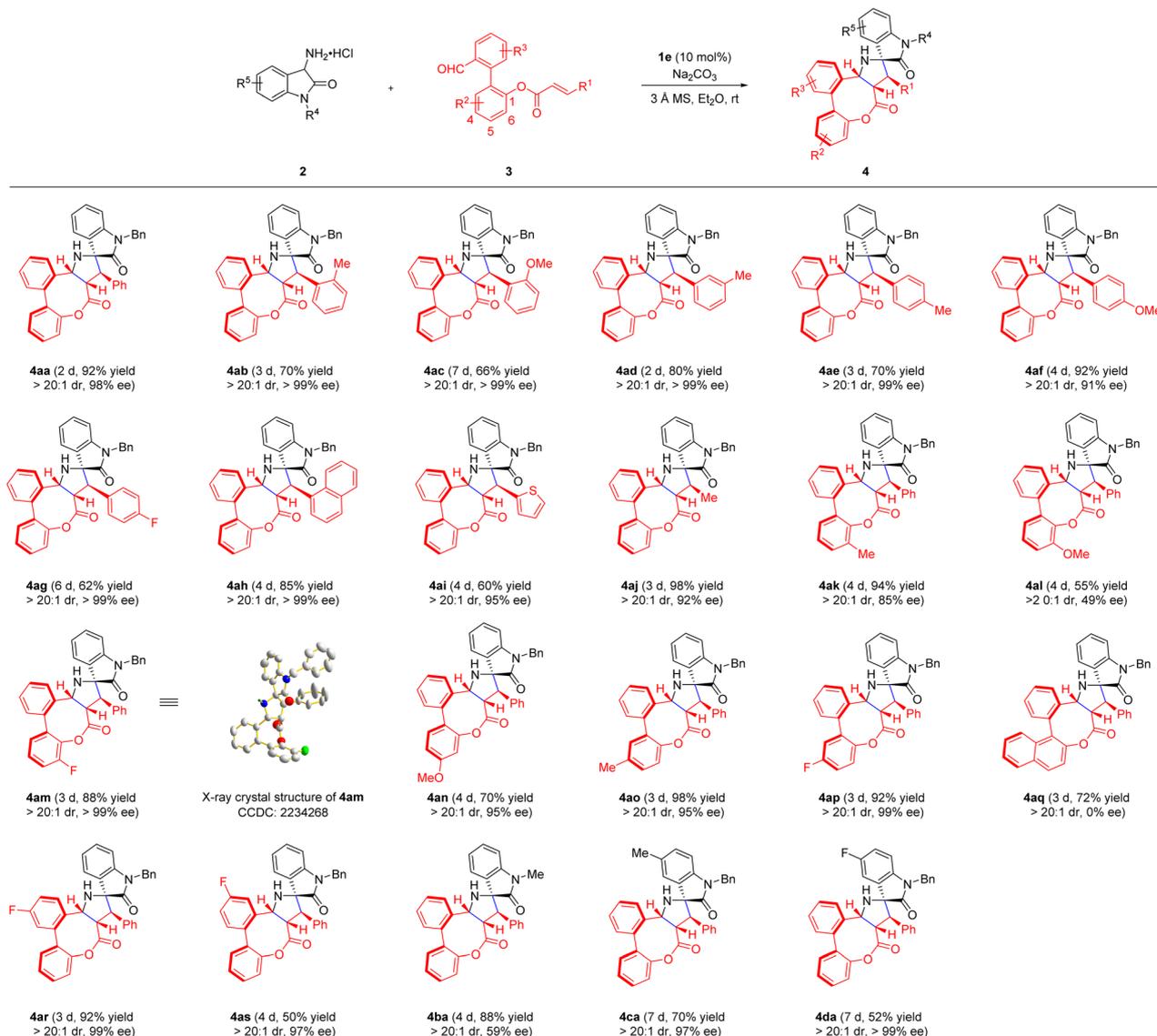
<sup>a</sup> The reaction was carried out on a 0.1 mmol scale with Na<sub>2</sub>CO<sub>3</sub> (1.5 equiv.), 3 Å MS (100 mg), cat. (10 mol%) in 1.0 mL solvent at 25 °C under nitrogen, and the ratio of **2a/3a** was 1.5/1. <sup>b</sup> Isolated yield. <sup>c</sup> The dr was determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>d</sup> The ee was determined by chiral HPLC. <sup>e</sup> In the presence of 1.2 equiv. Na<sub>2</sub>CO<sub>3</sub>. <sup>f</sup> No base.

with 10 mol% diphenyl phosphate (DPP). To our delight, the cycloaddition reaction proceeded smoothly to give the desired product **4aa** in 46% yield, which is consistent with our design (entry 1). Encouraged by this preliminary result, we turned our attention to the asymmetric version by examining an array of BINOL-derived chiral phosphoric acids (CPAs) with different substituents and steric environments (entries 2–6). Among them, the catalyst **1e** bearing a 9-phenanthryl group at 3,3'-positions was found to be the optimal choice to afford the target product **4aa** with a stereogenic axis and multiple stereogenic centers in 64% yield and excellent diastereoselectivity and enantioselectivity (>20 : 1 dr, 98% ee, entry 6). In addition, the amount of base was then evaluated, considering that an additional equivalent of inorganic base may have an effect on the formation of dipoles. The reactivity and efficiency of the reaction gradually decreased, when the amount of base was 1.2 equiv. or without the base, although excellent enantioselectivities and diastereoselectivities were maintained (entries 7 and 8). Subsequently, attempts to further improve the reactivity through screening of solvents (entries 9–13) proved to be effective, providing encouraging results and identifying Et<sub>2</sub>O as the best solvent for this reaction to furnish the product in 92% yield with excellent diastereo- and enantio-selectivity (>20 : 1 dr, 98% ee, entry 12).

With the optimized reaction conditions established, we next set out to investigate the scope and generality of the intramolecular [3 + 2] cycloaddition strategy (Scheme 2). Initially, biaryl aldehydes **3** featuring diverse substituents, easily prepared *via* classic Pd-catalyzed Suzuki–Miyaura cross coupling reactions from readily available starting materials, were examined by reacting with substrate **2a** under the standard conditions. In detail, substituents, including electron-donating (–Me and –OMe) and electron-withdrawing (–F) groups, were well tolerated at different positions (*ortho*, *meta* and *para* positions) of the aromatic R<sup>1</sup> group, affording the corresponding products **4aa–4ag** in good to excellent yields (62–92%) with consistently high diastereo- and enantio-selectivities (all >20 : 1 dr, 91–>99% ee). Meanwhile, the R<sup>1</sup> group could be switched to heteroaryl or 1-naphthalene groups, which generally afforded products with good results (**4ai** and **4ah**; 60% and 85% yields, 95% and >99% ee, respectively, all >20 : 1 dr). Notably, biaryl aldehyde **3j** bearing a methyl functional group also performed well, delivering the expected product **4aj** in 98% yield and 92% ee. In addition, we evaluated the scope with respect to the biaryl moiety under the optimized reaction conditions (**4ak–4as**). It is noteworthy that diverse substrates (**3k** and **3m–3p**) proceeded smoothly with **2a** to furnish desired atroposelective bridged biaryls, maintaining moderate to good yields and excellent ee values in this catalysis system. Among them, the absolute configuration of product **4am** was determined by X-ray crystallographic analysis. However, when the C6 position of the biaryl moiety was the methoxy group, **4al** could be applied in the current transformation, but in relatively lower yield and diminished enantioselectivity, perhaps due to the presence of bulky methoxyl. The result shows that the steric hindrance of substituents at the C6 position has a significant impact on both the efficiency and the stereoselectivity of the process. Moreover, biaryl aldehyde **3q** containing the naphthalene group gives a racemic product under the standard conditions, and the reason might be that the larger naphthalene group adversely affects hydrogen-bonding interaction between the hydroxyl of catalyst **1e** and the carbonyl group of the part of dipolarophile in organizing the transition state. Gratifyingly, biaryl aldehydes **3r** and **3s** bearing substituents at the *para*- and *meta*-positions of the formyl were well accommodated, and desired products were successfully generated with high enantioselective excess.

Next, the substrate scope for the organocatalytic asymmetric [3 + 2] cycloaddition of various 3-amino oxindole hydrochlorides **2** with biaryl aldehyde **3a** was explored. Firstly, we probed the influence of the N-protecting group of the oxindole ring, and the result indicated that an alkyl group such as an N-Me-substituted reactant was fully compatible with the reaction, resulting in the anticipated product **4ba** in good yield, albeit with lower enantioselectivity compared to model substrate **2a**. It might be that N-Bn-substituted substrate **2a** has π–π interaction with chiral phosphoric acid catalyst **1e**, thereby achieving better stereochemical control. Ultimately, when incorporating electron-donating or electron-withdrawing substituents at the C5-position of the amino-oxindole benzene ring, the related products **4ca** and **4da** were also uneventfully obtained with excellent stereocontrol in good yields, respectively.





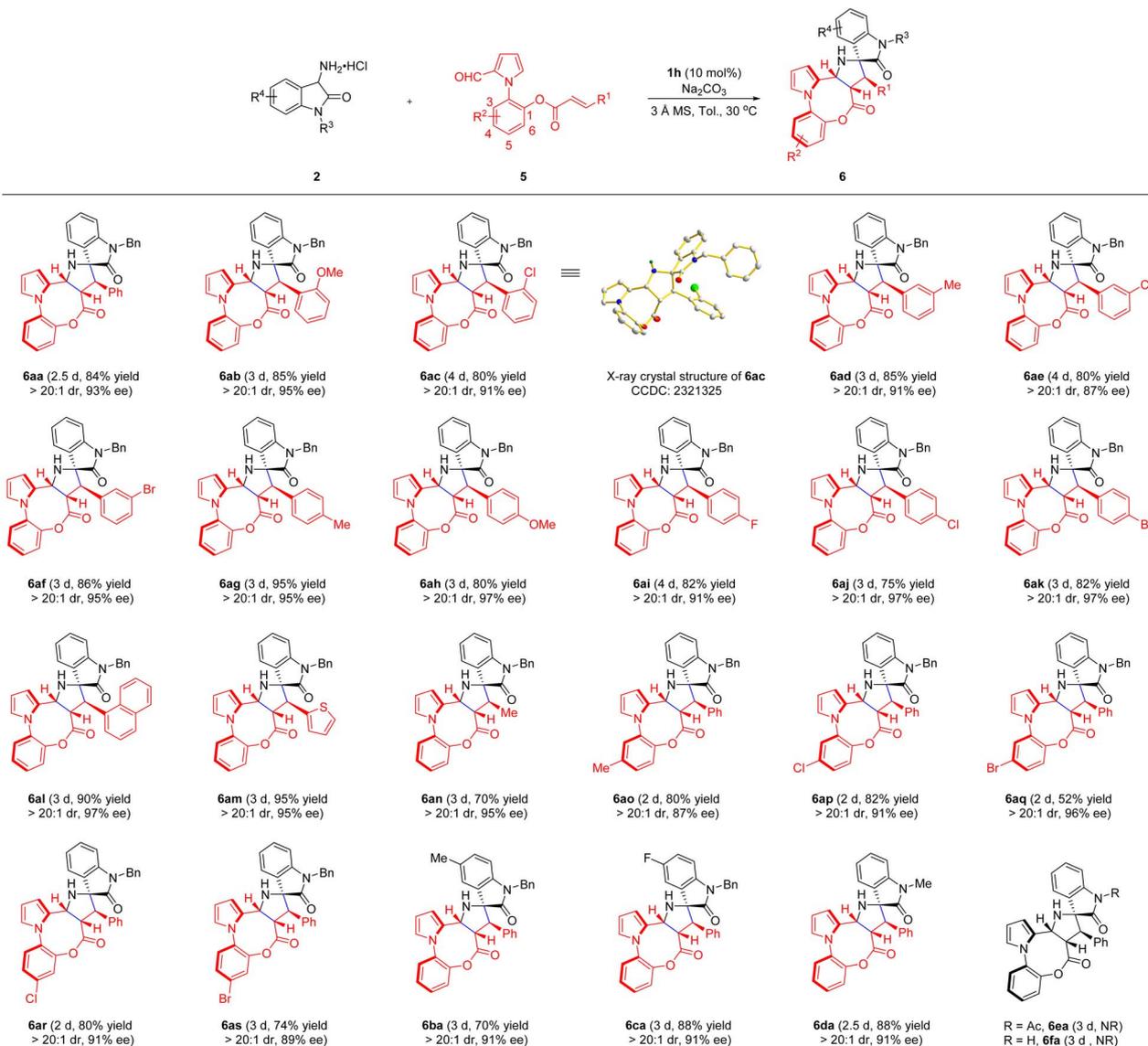
Scheme 2 Substrate scope of **2** and **3**. Reaction conditions: the reactions were conducted with **2** (0.3 mmol),  $\text{Na}_2\text{CO}_3$  (0.3 mmol), 3 Å MS (200 mg), **1e** (10 mol%) and **3** (0.2 mmol) in  $\text{Et}_2\text{O}$  (2.0 mL) at 25 °C under nitrogen. Yields of the isolated products are given. The dr was determined by  $^1\text{H}$  NMR of the crude reaction mixture. The ee was determined by chiral HPLC.

In addition, in parallel with atropisomers bearing a C–C axis, C–N axially chiral frameworks also frequently occur in natural products, pharmaceuticals and ligands with widespread applications.<sup>15</sup> However, the construction of enantioenriched C–N atropisomers remains rare due to a lower rotation barrier and higher rotational degree of freedom around C–N bonds in comparison to the corresponding C–C bonds.<sup>16</sup> Therefore, the enantioselective synthesis of C–N axially chiral skeletons containing additional stereogenic elements is more challenging.<sup>17</sup> Inspired by the above results, we envisage that further expanding this methodology to the preparation of C–N axially chiral eight-membered bridged heterobiaryls with four stereogenic centers by fine-tuning of substrates may be possible. Hence, *N*-aryl-2-formylpyrroles **5** were successfully prepared through the key Clauson–Kaas reaction and subsequent transformations. As shown in ESI Table 1,<sup>†</sup> a preliminary

investigation was performed by reacting newly designed heterobiaryl aldehyde **5a** and 3-amino oxindole hydrochloride **2a** in the presence of DPP, affording the desired product **6aa** in 66% yield. Subsequently, the optimized reaction conditions were discovered *via* screening of diverse CPAs, solvents, reactant concentrations and bases. Under these conditions, the corresponding product **6aa** was obtained in 84% yield and 93% ee.

Then, we investigated the substrate scope with regard to the substitution pattern of *N*-aryl-2-formylpyrroles **5**. As highlighted in Scheme 3, newly designed and simply synthesized substrates bearing alkyl groups (**5d** and **5g**), alkoxy groups (**5b** and **5h**) and halogen groups (**5c**, **5e**, **5f**, **5i**, **5j**, and **5k**) on the benzene ring of substituent  $\text{R}^1$  worked efficiently, generating the structurally varied products **6ab–6ak** in 75–95% yields with 87–97% ee and >20:1 dr in all cases, which indicated that the substitution position and electronic feature affected neither the yield nor the





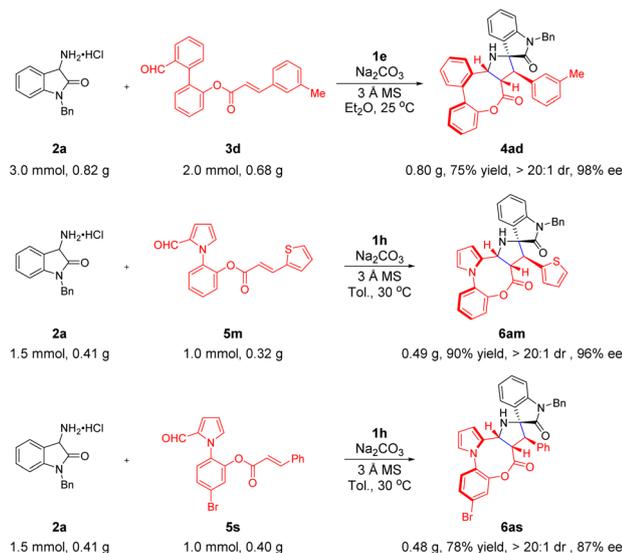
**Scheme 3** Substrate scope of **2** and **5**. Reaction conditions: the reactions were conducted with **2** (0.3 mmol),  $\text{Na}_2\text{CO}_3$  (0.3 mmol), 3 Å MS (200 mg), **1h** (10 mol%) and **5** (0.2 mmol) in toluene (4.0 mL) at 30 °C under nitrogen. Yields of the isolated products are given. The dr was determined by  $^1\text{H}$  NMR of the crude reaction mixture. The ee was determined by chiral HPLC.

diastereo- and enantio-selectivity. Among them, the absolute configuration of product **6ac** was determined by X-ray crystallographic analysis. Particularly, both the introduced naphthyl and thienyl groups on the  $\text{R}^1$  moiety also participated well in this transformation, delivering the corresponding products **6al** and **6am** in 90% and 95% isolated yields with 97% ee and 95% ee, respectively. In addition to aryl and heteroaryl groups, the substrate with an aliphatic substituent (–Me) at this position was accommodated as well, furnishing the desired product **6an** in good yield and excellent enantioselectivity. After that, pleasingly, different substituents at the C4 or C5 positions of the  $\text{R}^2$  group, such as methyl, chlorine and bromine, were all compatible with this reaction to give optically pure products **6ao–6as**. In parallel, the influence of various substituents on 3-amino oxindole hydrochlorides **2** was then studied. Those substrates containing methyl and fluorine groups incorporated

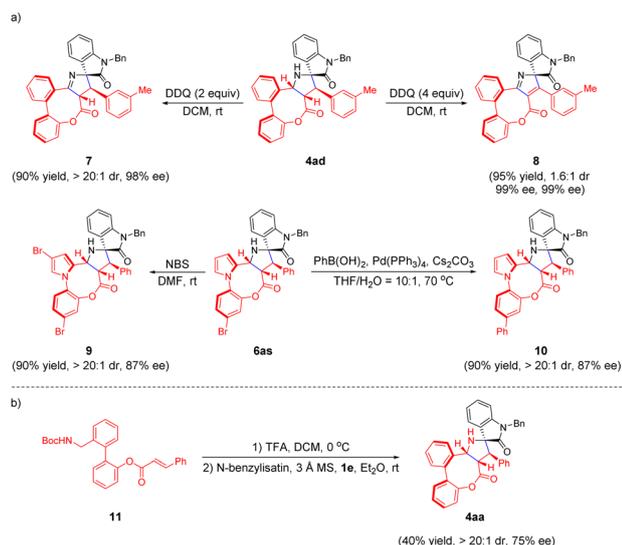
on the C5 position of the oxindole ring underwent the reaction smoothly under standard conditions, producing the products **6ba** and **6ca** in both 91% ee with 70% and 88% yields, respectively. Moreover, replacing the N–Bn of **2a** with other electron-donating groups, such as N–Me, could also successfully afford product **6da** with excellent yield, diastereo- and enantio-selectivity. In contrast, substrates **5** without a N-protecting group or with an electron-withdrawing group at the N1 position were not applicable at the current stage probably due to the poor nucleophilicity of the 3-amino group.

To further demonstrate the synthetic practicality of this formal intramolecular [3 + 2] cycloaddition process (Scheme 4), the reaction of substrates **2a** and **3d** was conducted on a gram scale under the optimized conditions, producing the expected product **4ad** in 75% yield with a similar level of enantioselectivity and diastereoselectivity observed for a lower-scale

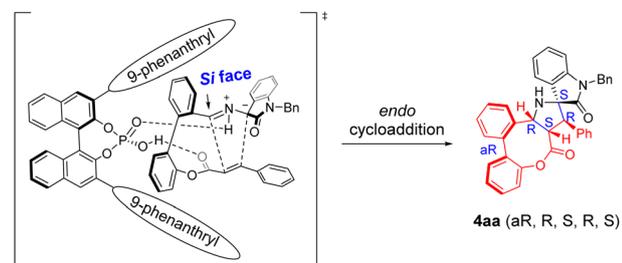




Scheme 4 The scale-up experiments.



Scheme 5 Synthetic transformations and umpolung intramolecular 1,3-dipolar cycloaddition reaction.



Scheme 6 Proposed transition state.

reaction. Subsequently, the 1.0 mmol scale reaction of **5m** and **5s** with **2a** proceeded smoothly, achieving the atropisomers **6am** and **6as** in good yields with 96% ee and 87% ee, respectively.

In addition, facile derivatization of the eight-membered bridged (hetero)biaryl lactones was carried out to showcase the potential application value of this protocol (Scheme 5a). The compound **4ad** underwent dehydrogenative oxidation in the presence of 2.0 equiv. DDQ to provide 2*H*-pyrrole product **7** smoothly in 90% yield with high diastereoselectivity and enantioselectivity retained. Moreover, when **4ad** was treated with 4.0 equiv. DDQ, the corresponding product **8** was achieved in 1.6 : 1 dr with 99% ee and 99% ee. The regioselective mono-bromination of **6as** with NBS in DMF at room temperature afforded the compound **9** in 90% yield and 87% ee. Meanwhile, compound **10** could also be obtained in 90% yield, >20 : 1 dr and 87% ee, through a Pd-catalyzed Suzuki–Miyaura cross coupling reaction. Later, inspired by previous work,<sup>13b</sup> we explored the feasibility of the umpolung intramolecular 1,3-dipolar cycloaddition reaction of *N*-Boc biaryl benzylamine **11** and *N*-benzylisatin in the presence of catalyst **1e** in Et<sub>2</sub>O at room temperature, affording compound **4aa** in 40% yield with 75% ee (Scheme 5b).

Combining the experimental results of our work with previous reports on chiral phosphoric acid catalysis, the plausible mode of dual activation was proposed and is depicted in Scheme 6 to interpret the observed outcome of stereocontrol. The high degree of diastereocontrol is attributed to the stereospecificity and stereoselectivity of [3 + 2] cycloaddition involving azomethine ylide<sup>18</sup> together with the trend of eight-membered bridged biaryls to form a stable boat conformation.<sup>7f,19</sup> On the other hand, chiral phosphoric acid (**1e**), a bifunctional catalyst, has hydrogen-bonding interaction with the reaction partner in this transformation. The hydroxyl of catalyst **1e** is believed to act as a Brønsted acid to activate the carbonyl group of the part of dipolarophile, while the P=O moiety acts as a Brønsted base to activate the part of 1,3-dipole. In the meantime, the transition state undergoes intramolecular [3 + 2] cycloaddition from the Re face to afford the final product bearing multiple stereogenic elements with excellent enantioselectivity.

## Conclusions

In summary, we have successfully disclosed a chiral phosphoric acid catalyzed asymmetric intramolecular [3 + 2] cycloaddition reaction of (hetero)biaryl aldehydes bearing an unsaturated double bond with 3-amino oxindole hydrochlorides, which led to the efficient construction of highly enantiomerically enriched medium-membered bridged (hetero)biaryls. The reaction proceeded smoothly under mild conditions, which uneventfully delivered a wide range of atroposelective eight-membered bridged (hetero)biaryl lactones fused to spiro[pyrrolidine-oxindole] scaffolds containing both a C–C/C–N chiral axis and four contiguous stereocenters in good yields with high diastereoselectivities and enantioselectivities. In addition, further structural modifications demonstrated the promising utility of this methodology. Notably, only a single catalyst was used to realize stereochemical control of both central chirality and axial chirality. Therefore, this work provides a firm foundation for constructing other axially chiral bridged (hetero)biaryls bearing



a larger-sized ring and further related studies are currently being conducted in our laboratory.

## Data availability

General information, detailed experimental procedures, characterization data for compounds, and NMR and HPLC spectra are available in the ESI.†

## Author contributions

Y. W. performed the experiments and analyzed the experimental data. B. W., Y. H., X. B., X. W., S. W. and J. Q. conceptualized and directed the project. B. W. and Y. W. wrote the manuscript with proofreading from all authors.

## Conflicts of interest

There are no conflicts to declare.

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