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Conversion of two stereocenters to one or two chiral axes: atroposelective synthesis of 2,3-diarylbenzoindoles

Central-to-axial chirality conversion provides an efficient access to axially chiral compounds. This work describes a conversion of two stereocenters to one or two chiral axes for the first time. A new class of enantiomerically enriched 2,3-diarylbenzoindoles has been synthesized efficiently using a chiral phosphoric acid catalyzed [3+2] formal cycloaddition and a mild DDQ oxidation strategy. A speculative model of the central-to-axial chirality conversion outcome is proposed based on preliminary mechanistic studies and DFT calculations. Potentially useful chiral phosphine ligand can be synthesized by this strategy smoothly.

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## Introduction

Axially chiral compounds are widely spread in natural products and bioactive molecules,<sup>1</sup> which are recognized as a type of privileged scaffolds for catalyst development, ligand design, drug discovery and materials science.<sup>2,3</sup> Many remarkable endeavors have been made to develop strategies, such as dynamic-kinetic resolution,<sup>5</sup> atroposelective coupling,<sup>6</sup> cycloaddition,<sup>7</sup> chirality conversion,<sup>8</sup> and so on,<sup>9</sup> for the construction of axial chirality.<sup>4</sup> Central-to-axial chirality conversion often provides access to axially chiral compounds that are difficult to obtain otherwise, which has been used in the asymmetric synthesis of allenes,<sup>10</sup> biaryl atropisomers<sup>8</sup> and natural products.<sup>11</sup> However, although it is an attractive strategy, only limited studies have been reported on it ever since Berson proposed this concept in 1955.<sup>8,12</sup> In 2011, Thomson reported  $\text{BF}_3\text{-Et}_2\text{O}$ -triggered aromatization of 1,4-diketones for the preparation of biphenols with excellent enantioselectivities.<sup>13a</sup> Recently, Rodriguez and Bugaut have successfully disclosed the atroposelective synthesis of 4-aryl pyridines and 3-arylfurans with excellent enantioselectivities by this strategy.<sup>13b,c</sup> Sparre developed a remote central to axial chirality conversion to prepare biaryl silanes.<sup>13d</sup> However, the previously reported

examples focus on the construction of a single stereogenic axis, and no studies have been reported on the synthesis of five-six-membered N-heterocyclic atropisomers by this strategy. Moreover, the preparation of compounds with multiple configurational axes is a challenge in asymmetric synthetic chemistry,<sup>7b,9c,14</sup> and to the best of our knowledge, the conversion of stereocenters to two axes is unprecedented.

N-Heterocyclic atropisomers are of particular interest for chemists due to the presence of a nitrogen atom that would exert steric and electronic effects during their bonding to substrates or metals; this makes these atropisomers ideal candidates for application as catalysts or ligands.<sup>3,15</sup> Compared to the well-documented preparation of six-six-membered biaryl atropisomers, the construction of five-six-membered species is still a challenge in modern asymmetric synthesis.<sup>16</sup> This is due to the fact that the increased distance between *ortho*-substituents adjacent to the axis dramatically reduces the conformational stability; this makes racemization easy to take place. Indole-based biaryl atropisomers including *N*-aryl, C(2)-aryl, and C(3)-aryl axial chirality are potential ligands and found in some natural products.<sup>17</sup> In 2010, Kitagawa reported Pd-catalyzed hydroaminocyclization to construct indole *N*-aryl axial chirality.<sup>18</sup> Later, Kamikawa, Takahashi and Ogasawara reported an enantioselective desymmetrising ring-closing metathesis strategy to prepare axially chiral indole *N*-aryl compounds.<sup>19</sup> Very recently, Shi and Tan independently reported a well-designed chiral phosphoric acid-catalyzed asymmetric synthesis of indol C(3)-aryl axial chirality;<sup>20</sup> Gu reported Pd-catalyzed dynamic kinetic intramolecular C–H cyclization to construct indol C(3)-aryl atropisomers.<sup>21</sup> However, no studies have been reported on the synthesis of indol C(2)-aryl axial chirality. On the other hand, nonchiral indol C(2)-aryl

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phosphine has been utilized as a unique ligand for Pd-catalyzed cross-coupling reaction of aryl mesylates.<sup>22</sup> Herein, we report an efficient method for the construction of benzoindole-based C(2)-aryl and C(2,3)-aryls atropisomers *via* a [3 + 2] formal cycloaddition and an oxidative central-to-axial chirality conversion reaction (Scheme 1).

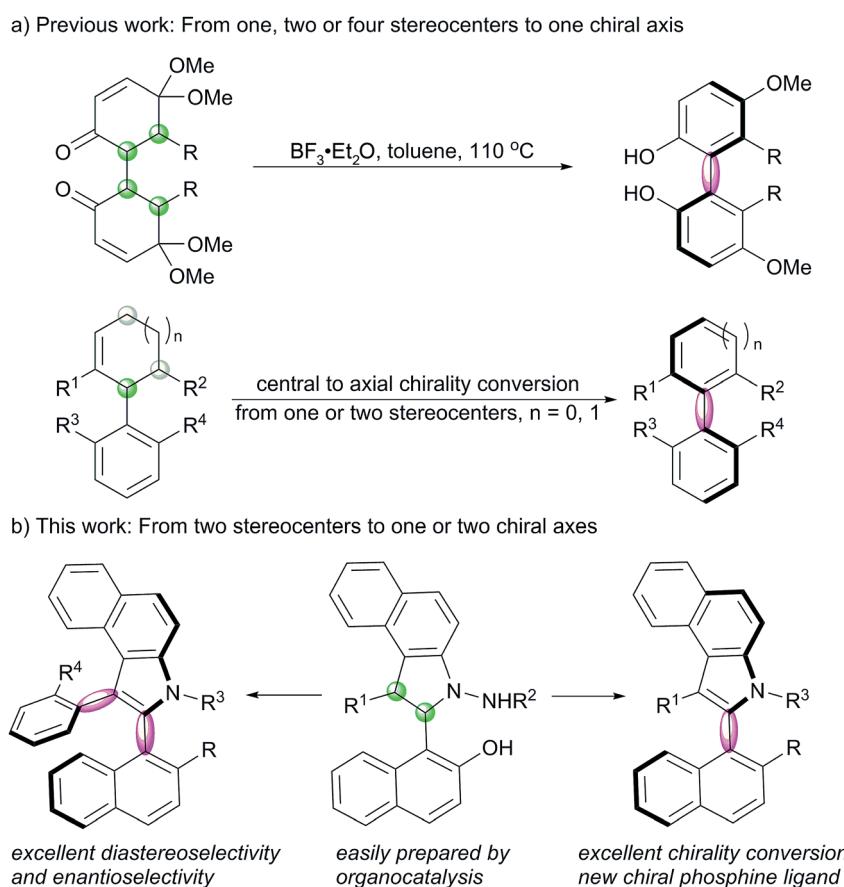
## Results and discussion

Inspired by the abovementioned elegant studies on central-to-axial chirality conversion and our previous study on the asymmetric [3 + 2] formal cycloaddition reaction,<sup>23</sup> we envisioned that an enantioselective [3 + 2] annulation of 1-styrylnaphthols with azonaphthalenes followed by oxidative aromatization would generate benzoindole (C(2) position) naphthyl atropisomers. To achieve this goal, we needed to address the following issues: (1) accomplishment of a highly diastereoselective and enantioselective [3 + 2] annulation; (2) installation of suitable groups around the C-C axis to avoid free rotation; and (3) realization of efficient chirality conversion with enantioselective and diastereoselective control *via* the development of mild oxidation conditions.

With these challenges in mind, we initially evaluated the reaction between 1-styryl naphthol (**1a**) and azonaphthalene (**2a**) in the presence of a chiral phosphoric acid. After systematic optimization of the reaction conditions,<sup>24</sup> the desired

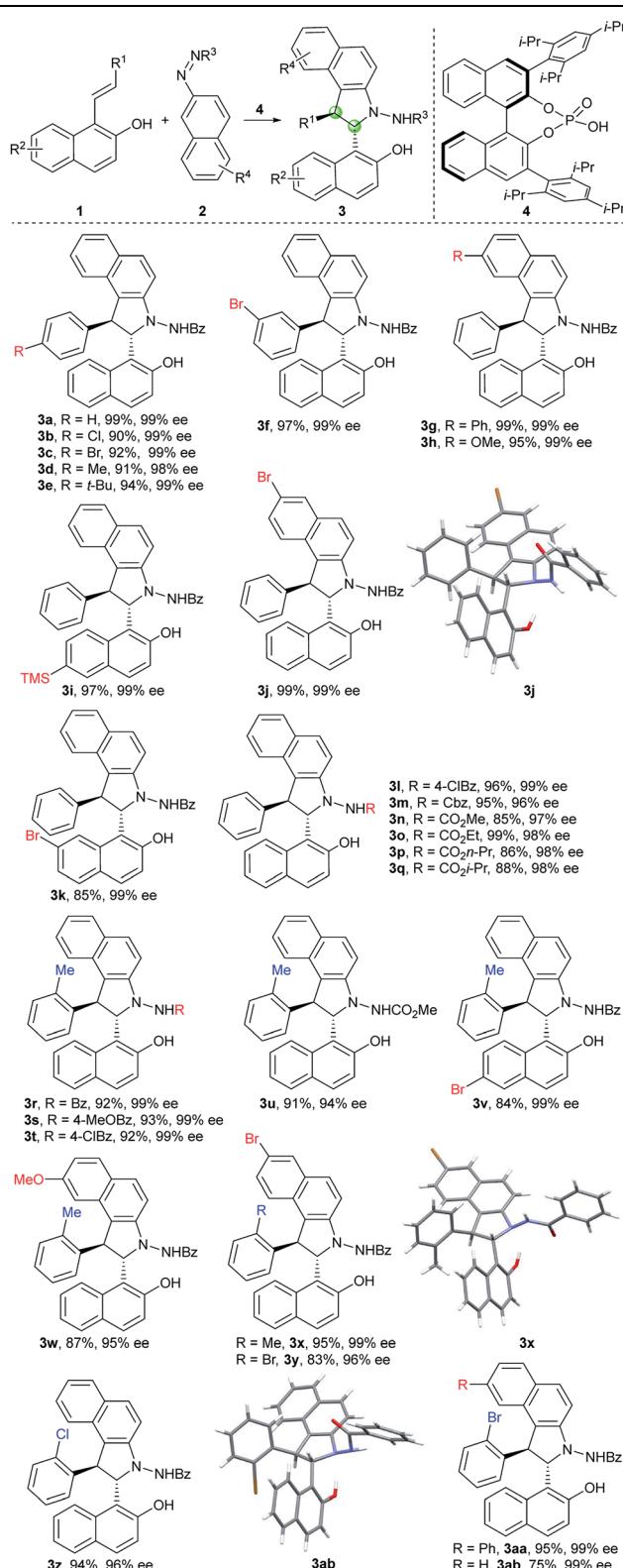
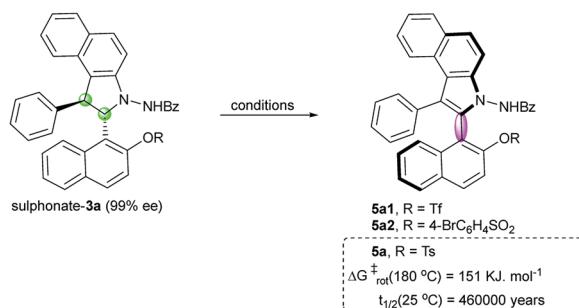
cycloaddition product **3a** was obtained in a 99% yield with exclusive diastereoselectivity and 99% ee using the chiral phosphoric acid **4** as a catalyst in  $\text{CH}_2\text{Cl}_2$  at  $-30^\circ\text{C}$  for 36 h. We then examined the substrate scope of this [3 + 2] cycloannulation. As shown in Table 1, substrates with the substituents Cl, Br, Me and *t*-Bu at the *para*-position or Br at the *meta*-position of the phenyl ring resulted in the desired products with excellent yields and enantioselectivities (**3a–f**, 98–99% ee). Substrates with substituents at the 6 or 7-position of azonaphthalene were well tolerated, and the corresponding *trans*-2,3-diarylbenzoindolines were obtained in excellent yields and enantioselectivities (**3g, h**, and **j** 99% ee). Substrates with substituents at the 6 or 7-position of the naphthol led to excellent enantioselectivities, diastereoselectivities and yields (**3i** and **k**, 99% ee). In addition, the reaction was applicable to azonaphthalene derivatives with different esters including benzyl (**3m**), methyl (**3n**), ethyl (**3o**), *n*-propyl (**3p**) and *i*-propyl (**3q**) esters. Not surprisingly, substrates with the substituents Me, Cl and Br at the *ortho*-position of the phenyl ring provided the desired products with excellent yields, diastereoselectivities and enantioselectivities (**3r–ab**, 93  $\geq$  99% ee). The exact structures of **3j**, **3x** and **3ab** were also confirmed by X-ray crystallography, and the absolute configuration was identified as (2*S*, 3*S*)-**3j**, **x**, and **ab**.<sup>25</sup>

Then, we emphasized on the construction of an axially chiral biaryl system by the chirality conversion strategy. To avoid the



Scheme 1 Central-to-axial chirality conversion in the synthesis of atropisomers.



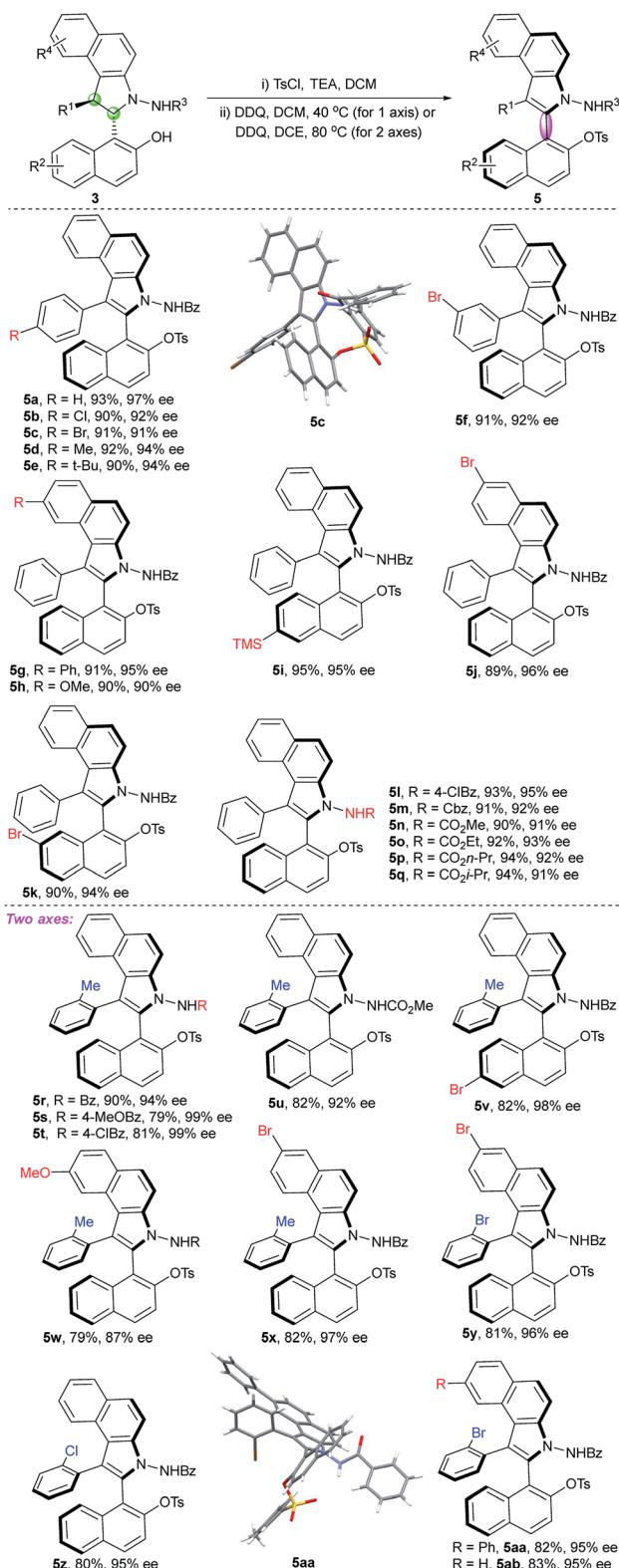
Table 1 Enantioselective [3 + 2] formal cycloaddition<sup>a</sup>Table 2 Central-to-axial chirality conversion<sup>a</sup>

Entry	5	Solvent	T (°C)	Yield <sup>b</sup> (%)	ee (%)
1 <sup>c</sup>	<b>5a1</b>	$\text{CH}_2\text{Cl}_2$	r.t.	98	7
2 <sup>c</sup>	<b>5a</b>	$\text{CH}_2\text{Cl}_2$	r.t.	98	85
3 <sup>d</sup>	<b>5a</b>	$\text{CH}_2\text{Cl}_2$	r.t.	98	90
4 <sup>d</sup>	<b>5a</b>	$\text{CH}_2\text{Cl}_2$	0	96	70
5 <sup>d</sup>	<b>5a</b>	$\text{CH}_2\text{Cl}_2$	40	97	94
6	<b>5a</b>	$\text{CH}_2\text{Cl}_2$	40	99	97
7	<b>5a</b>	DCE	60	97	96
8	<b>5a</b>	Toluene	60	97	77
9 <sup>e</sup>	<b>5a</b>	$\text{CH}_2\text{Cl}_2$	r.t.	95	45
10	<b>5a2</b>	$\text{CH}_2\text{Cl}_2$	50	97	91

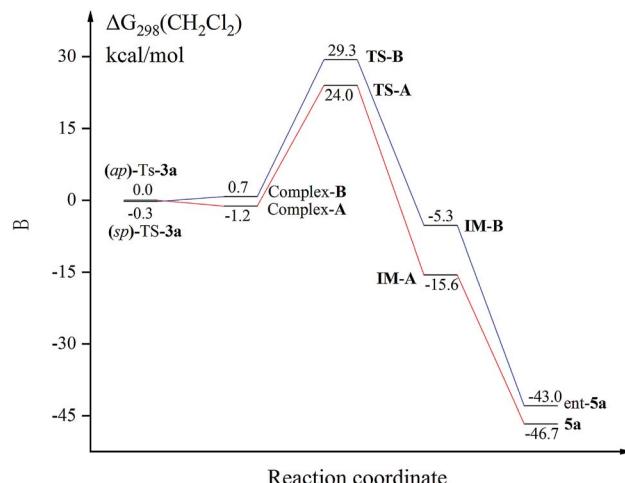
<sup>a</sup> Reactions were carried out with sulphonate-**3a** (0.2 mmol) in  $\text{CH}_2\text{Cl}_2$ , DDQ (0.4 mmol in  $\text{CH}_2\text{Cl}_2$ , 0.01 M) was added over 1 h by a syringe pump. <sup>b</sup> Isolated yields. <sup>c</sup> DDQ was added in one batch. <sup>d</sup> DDQ (0.01 M) was added dropwise over 30 min. <sup>e</sup>  $\text{MnO}_2$  (1.0 mmol) was used.

dearomatization side reactions, sulphonate derivatives were prepared from compound **3a**. Oxidation of triflate **3a** using DDQ in  $\text{CH}_2\text{Cl}_2$  at room temperature provided the desired atropisomer **5a1** in quantitative yield but with poor enantioselectivity (Table 1, entry 1). We proposed that a bulky substituent adjacent to the C-C axis may be helpful in chirality conversion and stabilizing the axial chirality. Thus, tosylate **3a** was prepared; indeed, the corresponding atropisomer **5a** was obtained with a significant increase in enantioselectivity (85% ee, entry 2) under the same reaction conditions. Satisfyingly, a measurable increase in enantioselectivity was observed by the slow addition of DDQ to  $\text{CH}_2\text{Cl}_2$  (entry 3 vs. entry 2). Interestingly, the reaction temperature also plays an important role in this chirality conversion: higher reaction temperature leads to higher enantioselectivity (entries 3–5). The best result (97% ee) was obtained at 40 °C by the slow addition of DDQ (entry 6). Moreover, other solvents, such as DCE and toluene, were tested. DCE provided similar result at 60 °C (entry 7), whereas toluene led to only 77% ee (entry 8). Another oxidant *i.e.*  $\text{MnO}_2$  led to poor enantioselectivity (entry 9). In addition to the tosyl group, 4-bromobenzenesulfonyl is a suitable group for the construction of a stable atropisomer (entry 10). To investigate the configurational stability of these new atropisomers, thermal racemization was conducted.<sup>24</sup> Compound **5a** displays excellent stability with a barrier to rotation of 151 kJ mol<sup>-1</sup>, and the half-life time of racemization was determined to be 460 000 years at 25 °C.

Table 3 Scope of the central-to-axial chirality conversion<sup>a</sup>



<sup>a</sup> Reactions were carried out under the optimal conditions for 3a-q (Table 1, entry 6); for 3r-ab, DCE was used as the solvent at 80 °C; isolated yield by two steps: all dr > 20 : 1 for 5r-5ab.



**Fig. 1** Energy profile of the DDQ-mediated central-to-axial chirality conversion

Once the optimized conditions were identified (Table 2, entry 6), other substrates were examined. As shown in Table 3, the substrates **3a–q** were well tolerated in this central-to-axial chirality conversion process, and the corresponding five-six-membered atropisomers were obtained with excellent yields and enantioselectivities (**5a–q**). The absolute configuration of **5a–q** was assigned as *aR* on the basis of the X-ray crystallographic structure of **5c**.<sup>25</sup> The substrates **3r–ab** were also used to obtain vicinal biaryl benzoindole atropisomers bearing two stereogenic axes. Gratifyingly, the desired products **5r–x** containing the *ortho*-methyl group were obtained with excellent diastereoselectivities (all > 20 : 1) and enantioselectivities (87–99% ee) under the newly developed optimal reaction conditions with higher reaction temperature in DCE (Table 3). Not only methyl substituent at the *ortho*-position of the phenyl ring, but also chloride and bromide were suitable groups for the reaction and produced axially chiral products (**5y**, **5z**, **5aa**, and **5ab**) with excellent diastereoselectivities and enantioselectivities. The second chiral axis of compound **5x** also displayed good stability with a barrier to rotation of 126.6 kJ mol<sup>−1</sup>, and the half-life time of racemization was determined to be 28 years at 25 °C.<sup>24</sup> Note that all halogen-substituted substrates were suitable for the conversion, exhibiting highly impressive performance (**5b**, **c**, **f**, **i**, **k**, **v**, and **x–ab**), which are appropriate substrates for synthetic transformations through cross-coupling reactions. The absolute configuration of **5r–ab** was assigned as (*2aR*, *3aS*) on the basis of the X-ray crystallographic structure of **5aa**.<sup>25</sup>

We next conducted DFT studies to gain insight into the reaction mechanism and the origin of the high levels of chirality conversion observed. Tosylation of **3a** provided the compound **Ts-3a** as a 73 : 27 mixture of the conformational diastereoisomers (*sp*)-**Ts-3a** and (*ap*)-**Ts-3a** at 25 °C. There exists an equilibrium between two rotamers because different ratios of them can be observed by <sup>1</sup>H NMR at various temperatures.<sup>24,26</sup> The rotational barrier was determined to be 80.8 kJ mol<sup>-1</sup> via the 1D-EXSY experiment in C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub> at 40 °C.<sup>24</sup> Selective 1D NOE and 2D NOESY of **Ts-3a** have indicated that

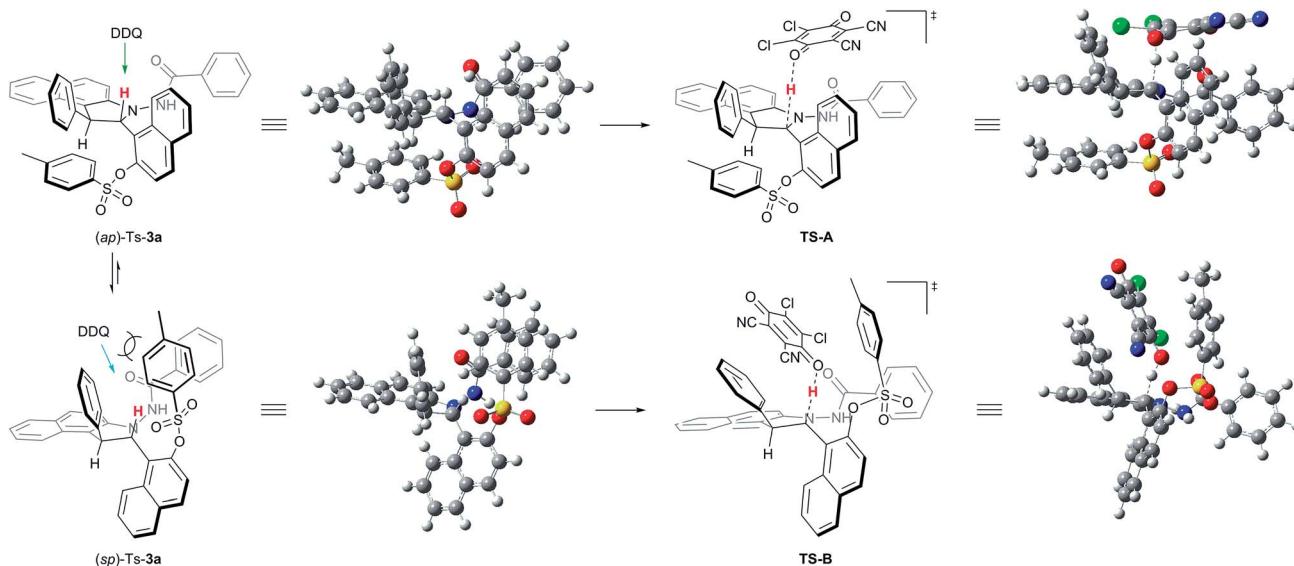
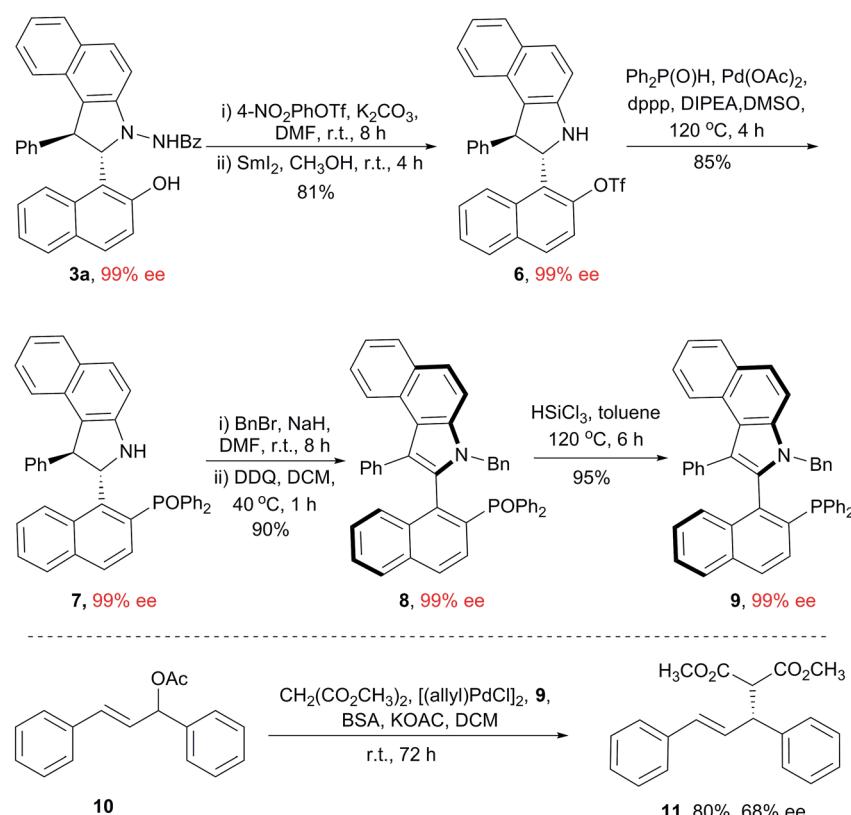


Fig. 2 3D structures of the substrates and transition states.

*ap*-Ts-3a is the minor conformer.<sup>24</sup> Hence, the fundamental step of the process would be the deprotonation of the central chiral substrate (*ap*)-Ts-3a((*sp*)-Ts-3a), leading to the cationic intermediate **IM-A** (**IM-B**), wherein a central-to-axial chirality conversion simultaneously occurred. Upon *in situ* elimination of the other proton, the product **5a** (ent-**5a**) was generated. All

calculations were performed with Gaussian 09. The geometries of all intermediates and transition states were optimized at the B3LYP-D3/6-1G(d) level, and energies were calculated at the M06-2X-D3/6-311++G(d,p) level with the solvation effect.<sup>24</sup> Indeed, the potential energy of (*sp*)-Ts-3a was found to be lower than that of (*ap*)-Ts-3a by 0.3 kcal mol<sup>-1</sup>; thus, DDQ first



Scheme 2 Synthesis and application of the phosphine ligand 9.

coordinated with (*sp*)-Ts-**3a** to form a charge-transfer complex (Fig. 1).<sup>24</sup> The steric effect between DDQ and Ts group in (*sp*)-Ts-**3a** is observable (Fig. 2). The charge transfer in the hydride transfer transition states **TS-A** was favored by 5.3 kcal mol<sup>-1</sup> over **TS-B**. Moreover, the potential energy of the intermediate **IM-A** was found to be clearly lower than that of the intermediate **IM-B** by 10.3 kcal mol<sup>-1</sup>. These results indicate that the hydride transfer is the rate-determining step of the overall transformation, in agreement with the studies reported in the literature.<sup>27</sup>

To demonstrate the utility of this method, a scale-up experiment was carried out. The desired product **5a** (2 mmol scale) was successfully prepared without losing any efficiency and enantioselectivity. The replacement of the Ts group with the more reactive Tf group was achieved by conventional transformation, and then, Pd-catalyzed coupling of this modified compound with Ph<sub>2</sub>P(O)H provided a diphenyl phosphine oxide product (Scheme S2†).<sup>24</sup> Unfortunately, a measurable decrease in the ee value (from 99% ee to 92% ee) has been observed when the Ts group was removed, suggesting that a bulky group in the naphthyl moiety also plays an important role in the configurational stability of this scaffold.

Based on the central-to-axial chirality conversion strategy, we designed a new synthetic route for the preparation of benzoindole-based C(2)-naphthyl phosphine ligands. As shown in Scheme 2, compound **7**, bearing a bulky diphenyl phosphine oxide group, was prepared smoothly from **3a**, and the enantioselectivity was retained (99% ee). Direct oxidation of **7** provided a nearly racemic benzoindolenaphthyl atropisomer (<5% ee); this indicated that the *N*-substituent was also crucial for this axial chirality. Thus, benzylation of **7** was conducted, and then, oxidation under our abovementioned optimized conditions resulted in the desired product **8** in a 90% yield with 99% ee. Finally, the reduction of **8** with HSiCl<sub>3</sub> resulted in the formation of the new benzoindolenaphthyl phosphine ligand **9** (99% ee). The utility of this ligand was primarily demonstrated by an asymmetric allylation reaction between (*E*)-1,3-diphenylallyl acetate and dimethyl malonate. The desired product **11** was obtained in an 80% yield with 68% ee.

## Conclusions

In summary, we developed the first construction of newly 2,3-diarylbenzoindoles in high yields and enantioselectivities using an efficient stepwise strategy, including chiral phosphoric acid-catalyzed [3 + 2] formal cycloaddition of 1-styrylnaphthols with azonaphthalenes and a DDQ-oxidized central-to-axial chirality conversion reaction. This constitutes the first stereoselective conversion of two stereocenters to two axes. Preliminary, mechanistic studies and DFT calculations indicate that the hydride transfer is the rate-determining step, and the more stable conformational atropdiastereomer is prone to undergo oxidation to form the more stable iminium cation during the central-to-axial chirality conversion reaction. Moreover, new chiral phosphine compounds can be prepared efficiently by this strategy, which is attractive for the development of novel catalysts or ligands. However, further investigations on the

development of this new chiral phosphine ligand and its application in some asymmetric reactions are underway.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- (a) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (b) M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193; (c) B. Chen, X. Liu, Y.-J. Hu, D.-M. Zhang, L. Deng, J. Lu, L. Min, W.-C. Ye and C.-C. Li, *Chem. Sci.*, 2017, **8**, 4961; (d) R. W. Hoffmann, H.-G. Schmalz, U. Koert and G. K. Pierens, *Chem. Sci.*, 2019, **10**, 943; (e) J. Hu, F. Sarrami, H. Li, G. Zhang, K. A. Stubbs, E. Lacey, S. G. Stewart, A. Karton, A. M. Piggott and Y.-H. Chooi, *Chem. Sci.*, 2019, **10**, 1457.
- (a) Y. Wang, A. Urbasand and Q. Li, *J. Am. Chem. Soc.*, 2012, **134**, 3342; (b) Y.-N. Ma, S.-X. Liand and S.-D. Yang, *Acc. Chem. Res.*, 2017, **50**, 1480; (c) P. W. Glunz, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 53.
- (a) W. Fuand and W. Tang, *ACS Catal.*, 2016, **6**, 4814; (b) P. Kočovský, Š. Vyskočil and M. Smrčina, *Chem. Rev.*, 2003, **103**, 3213; (c) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029.
- For reviews, see: (a) J. Wencel-Delord, A. Panossian, F. R. Lerouxand and F. Colobert, *Chem. Soc. Rev.*, 2015, **44**, 3418; (b) G. Bencivenni, *Synlett*, 2015, **26**, 1915; (c) E. Kumarasamy, R. Raghunathan, M. P. Sibiand and J. Sivaguru, *Chem. Rev.*, 2015, **115**, 11239; (d) D. Zhang and Q. Wang, *Coord. Chem. Rev.*, 2015, **286**, 1; (e) P. Loxq, E. Manoury, R. Poli, E. Deydierand and A. Labande, *Coord. Chem. Rev.*, 2016, **308**, 131; (f) Y.-B. Wang and B. Tan, *Acc. Chem. Res.*, 2018, **51**, 534; (g) B. Zilate, A. Castrogiovanni and C. Sparr, *ACS Catal.*, 2018, **8**, 2981.
- (a) J. Clayden, S. P. Fletcher, J. J. W. McDoualland and S. J. M. Rowbottom, *J. Am. Chem. Soc.*, 2009, **131**, 5331; (b) J. L. Gustafson, D. Lim and S. J. Miller, *Science*, 2010, **328**, 1251; (c) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.*, 2013, **135**, 3964; (d) A. Ros, B. Estepa, P. Ramirez-Lopez, E. Alvarez, R. Fernandez and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2013, **135**, 15730; (e) V. Bhat, S. Wang, B. M. Stoltz and



S. C. Virgil, *J. Am. Chem. Soc.*, 2013, **135**, 16829; (f) S. Lu, S. B. Poh and Y. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 11041; (g) J. Wang, M.-W. Chen, Y. Ji, S.-B. Hu and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2016, **138**, 10413; (h) C. Yu, H. Huang, X. Li, Y. Zhang and W. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 6956; (i) P. Ramirez-Lopez, A. Ros, A. Romero-Arenas, J. Iglesias-Sigüenza, R. Fernandez and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2016, **138**, 12053; (j) Y. Liu, Y.-L. S. Tse, F. Y. Kwong and Y.-Y. Yeung, *ACS Catal.*, 2017, **7**, 4435; (k) J. D. Jolliffe, R. J. Armstrong and M. D. Smith, *Nat. Chem.*, 2017, **9**, 558.

6 (a) T. Shimada, Y.-H. Cho and T. Hayashi, *J. Am. Chem. Soc.*, 2002, **124**, 13396; (b) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess and L. Kürti, *J. Am. Chem. Soc.*, 2013, **135**, 7414; (c) J. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2014, **53**, 13244; (d) Y.-H. Chen, D.-J. Cheng, J. Zhang, Y. Wang, X.-Y. Liu and B. Tan, *J. Am. Chem. Soc.*, 2015, **137**, 15062; (e) S. Narute, R. Parnes, F. D. Toste and D. Pappo, *J. Am. Chem. Soc.*, 2016, **138**, 16553; (f) M. Moliterno, R. Cari, A. Puglisi, A. Antenucci, C. Sperandio, E. Moretti, A. Di Sabato, R. Salvio and M. Bella, *Angew. Chem., Int. Ed.*, 2016, **55**, 6525; (g) J.-Z. Wang, J. Zhou, C. Xu, H. Sun, L. Kürti and Q.-L. Xu, *J. Am. Chem. Soc.*, 2016, **138**, 5202; (h) H. Gao, Q.-L. Xu, C. Keene, M. Yousufuddin, D. H. Ess and L. Kürti, *Angew. Chem., Int. Ed.*, 2016, **55**, 566; (i) J. Feng, B. Li, Y. He and Z. Gu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2186; (j) Y.-H. Chen, L.-W. Qi, F. Fang and B. Tan, *Angew. Chem., Int. Ed.*, 2017, **56**, 16308; (k) Y.-S. Jang, Ł. Woźniak, J. Pedroni and N. Cramer, *Angew. Chem., Int. Ed.*, 2018, **57**, 12901.

7 (a) A. Gutnov, B. Heller, C. Fischer, H. J. Drexler, A. Spannenberg, B. Sundermann and C. Sundermann, *Angew. Chem., Int. Ed.*, 2004, **43**, 3795; (b) T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, *J. Am. Chem. Soc.*, 2004, **126**, 8382; (c) K. Tanaka, G. Nishida, A. Wada and K. Noguchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 6510; (d) G. Nishida, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem., Int. Ed.*, 2007, **46**, 3951; (e) M. Auge, A. Feraldi-Xypolia, M. Barbazanges, C. Aubert, L. Fensterbank, V. Gandon, E. Kolodziej and C. Ollivier, *Org. Lett.*, 2015, **17**, 3754; (f) Y. Kwon, A. J. Chinn, B. Kim and J. S. Miller, *Angew. Chem., Int. Ed.*, 2018, **57**, 6251; (g) Y. Liu, X. Wu, S. Li, L. Xue, C. Shan and Z. Z. H. Yan, *Angew. Chem., Int. Ed.*, 2018, **57**, 6491; (h) S.-C. Zheng, Q. Wangand and J. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 1494.

8 (a) A. I. Meyers and D. G. Wetzlauer, *J. Am. Chem. Soc.*, 1984, **106**, 1135; (b) A. Straub and A. Goehrt, *Angew. Chem., Int. Ed.*, 1996, **35**, 2662; (c) Y. Nishii, K. Wakasugi, K. Koga and Y. Tanabe, *J. Am. Chem. Soc.*, 2004, **126**, 5358; (d) A. V. Vorogushin, W. D. Wulff and H.-J. Hansen, *J. Am. Chem. Soc.*, 2002, **124**, 6512.

9 (a) A. Link and C. Sparr, *Angew. Chem., Int. Ed.*, 2014, **53**, 5458; (b) R. J. Armstrong and M. D. Smith, *Angew. Chem., Int. Ed.*, 2014, **53**, 12822; (c) D. Lotter, M. Neuburger, M. Rickhaus, D. Häussinger and C. Sparr, *Angew. Chem., Int. Ed.*, 2016, **55**, 2920; (d) J.-W. Zhang, J.-H. Xu, D.-J. Cheng, C. Shi, X.-Y. Liu and B. Tan, *Nat. Commun.*, 2016, **7**, 10677; (e) L. Zhang, J. Zhang, J. Ma, D.-J. Cheng and B. Tan, *J. Am. Chem. Soc.*, 2017, **139**, 1714; (f) Q.-J. Yao, S. Zhang, B.-B. Zhan and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2017, **56**, 6617; (g) K. Zhao, L. Duan, S. Xu, J. Jiang and Y. F. Z. Gu, *Chem.*, 2018, **4**, 599; (h) T. Yang, X. Guo, Q. Yin and X. Zhang, *Chem. Sci.*, 2019, **10**, 2473.

10 (a) T. Konoike and Y. Araki, *Tetrahedron Lett.*, 1992, **33**, 5093; (b) C. Schultz-Fademrecht, B. Wibbeling, R. Fröhlich and D. Hoppe, *Org. Lett.*, 2001, **3**, 1221; (c) S. Wu, X. Huang, W. Wu, P. Li, C. Fu and S. Ma, *Nat. Commun.*, 2015, **6**, 7946.

11 (a) R. A. Gibbs and W. H. Okamura, *J. Am. Chem. Soc.*, 1988, **110**, 4062; (b) T. Qin, S. L. Skraba-Joiner, Z. G. Khalil, R. P. Johnson, R. J. Capon and J. A. Porco, *Nat. Chem.*, 2015, **7**, 234.

12 J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, 1955, **77**, 450.

13 (a) F. Guo, L. C. Konkol and R. J. Thomson, *J. Am. Chem. Soc.*, 2011, **133**, 18; (b) O. Quinonero, M. Jean, N. Vanthuyne, C. Roussel, D. Bonne, T. Constantieux, C. Bressy, X. Bugaut and J. Rodriguez, *Angew. Chem., Int. Ed.*, 2016, **55**, 1401; (c) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne and J. Rodriguez, *J. Am. Chem. Soc.*, 2017, **139**, 2140; (d) A. Link and C. Sparr, *Angew. Chem., Int. Ed.*, 2018, **57**, 7136.

14 (a) K. T. Barrett, A. J. Metrano, P. R. Rablen and S. J. Miller, *Nature*, 2014, **509**, 71; (b) K. Tanaka, A. Kamisawa, T. Suda, K. Noguchi and M. Hirano, *J. Am. Chem. Soc.*, 2007, **129**, 12078; (c) D. Lotter, A. Castrogiovanni, M. Neuburger and C. Sparr, *ACS Cent. Sci.*, 2018, **4**, 656; (d) Y. Tan, S. Jia, F. Hu, Y. Liu, L. Peng, D. Li and H. Yan, *J. Am. Chem. Soc.*, 2018, **140**, 16893.

15 (a) S. Mishra, J. Liu and A. Aponick, *J. Am. Chem. Soc.*, 2017, **139**, 3352; (b) M. Pappopula and A. Aponick, *Angew. Chem., Int. Ed.*, 2015, **54**, 15827; (c) M. Pappopula, F. S. P. Cardoso, B. O. Garrett and A. Aponick, *Angew. Chem., Int. Ed.*, 2015, **54**, 15202; (d) B. Song, T. Knauber and L. J. Goofsen, *Angew. Chem., Int. Ed.*, 2013, **52**, 2954.

16 (a) D. Bonne and J. Rodriguez, *Eur. J. Org. Chem.*, 2018, **2018**, 2417; (b) D. Bonne and J. Rodriguez, *Chem. Commun.*, 2017, **53**, 12385.

17 (a) R. S. Nortonand and R. J. Wells, *J. Am. Chem. Soc.*, 1982, **104**, 3628; (b) T. Benincori, O. Piccolo, S. Rizzo and F. Sannicolò, *J. Org. Chem.*, 2000, **65**, 8340; (c) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth and W. Lobin, *J. Am. Chem. Soc.*, 2001, **123**, 2703.

18 (a) N. Ototake, Y. Morimoto, A. Mokuya, H. Fukaya, Y. Shida and O. Kitagawa, *Chem.-Eur. J.*, 2010, **16**, 6752; (b) Y. Morimoto, S. Shimizu, A. Mokuya, N. Ototake, A. Saito and O. Kitagawa, *Tetrahedron*, 2016, **72**, 5221.

19 K. Kamikawa, S. Arae, W.-Y. Wu, C. Nakamura, T. Takahashi and M. Ogasawara, *Chem.-Eur. J.*, 2015, **21**, 4954.

20 (a) L.-W. Qi, J.-H. Mao, J. Zhang and B. Tan, *Nat. Chem.*, 2018, **10**, 58; (b) H.-H. Zhang, C.-S. Wang, C. Li, G.-J. Mei, Y. Li and F. Shi, *Angew. Chem., Int. Ed.*, 2017, **56**, 116; (c) C. Ma, F. Jiang, F.-T. Sheng, Y. Jiao, G.-J. Mei and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 3014.

21 C. He, M. Hou, Z. Zhu and Z. Gu, *ACS Catal.*, 2017, **7**, 5316.



22 (a) C. M. So, C. P. Lau, A. S. C. Chan and F. Y. Kwong, *J. Org. Chem.*, 2008, **73**, 7731; (b) C. M. So, z. Zhou, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2008, **47**, 6402; (c) C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2008, **47**, 8059.

23 W. Feng, H. Yang, Z. Wang, B.-B. Gou, J. Chen and L. Zhou, *Org. Lett.*, 2018, **20**, 2929.

24 See ESI for details.†

25 CCDC 1884267 (**3j**), 1891943 (**3x**), 1905908 (**3ab**), 1882145 (**5c**) and 1905131 (**5aa**) contain the supplementary crystallographic data for this paper.†

26 N. Di Iorio, G. Filippini, A. Mazzanti, P. Righi and G. Bencivenni, *Org. Lett.*, 2017, **19**, 6692.

27 (a) H. H. Jung and P. E. Floreancig, *Tetrahedron*, 2009, **65**, 10830; (b) O. R. Luca, T. Wang, S. J. Konezny, V. S. Batista and R. H. Crabtree, *New J. Chem.*, 2011, **35**, 998; (c) X. Guo, H. Zipse and H. Mayr, *J. Am. Chem. Soc.*, 2014, **136**, 13863; (d) C. A. Morales-Rivera, P. E. Floreancig and P. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 17935.

