RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2024, **14**, 15591

Switchable divergent synthesis of chiral indole derivatives *via* catalytic asymmetric dearomatization of 2,3-disubstituted indoles†

Tingting Liu, Jianbin Wang, Rou Xiao and Junling Zhao *

Received 1st May 2024
Accepted 9th May 2024

DOI: 10.1039/d4ra03231d

rsc.li/rsc-advances

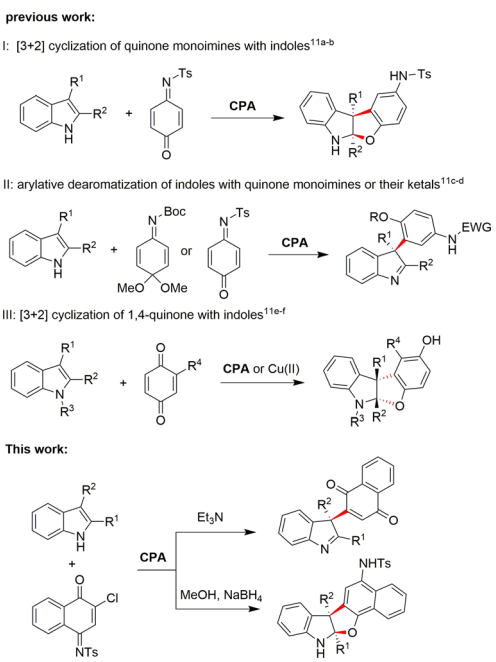
A strategy allowing the switchable divergent synthesis of chiral indole derivatives was established *via* chiral phosphoric acid-catalyzed asymmetric dearomatization of 2,3-disubstituted indoles using naphthoquinone monoimines as electrophiles. The products were switched between chiral indolenines and fused indolines according to the post-processing conditions. Both two types of products were obtained in good to high yields with generally excellent enantioselectivities. $NaBH_4$ was found to work as a promoter as well as a reductant in the cyclization process leading to fused indolines.

Introduction

The indole ring system is one of the most intriguing nitrogen-containing heterocycles because of its frequent appearance in natural products and pharmaceuticals.[1] Therefore, the synthesis of indole derivatives has garnered a lot of attention from both academic and industrial realms. The direct functionalization of the indole core is the most direct and efficient strategy to accessing indole derivatives and intensive efforts have been devoted to this end. Among which, the catalytic asymmetric dearomatization (CADA) of 3-substituted indoles[2] is particularly attractive because the resulting products are indolenines[3] or fused indolines[4] that are found in a number of natural alkaloids and bioactive molecules. In this respect, many elegant methods have been developed using various catalytic strategies, such as propargylic substitution,[5] allylic alkylation,[6] Michael addition,[7] halogenation,[8] hydrazination,[9] and arylation.[10,11]

With regard to the asymmetric arylation strategy, electrophilic quinones and their imines are excellent acceptors, and some elegant methods have been developed. As a class of privileged organocatalyst, chiral phosphoric acids (CPAs) showed the best catalytic efficiency in those transformations.[12] Zhang and co-workers[11a] reported CPA-catalyzed asymmetric arylative dearomatization/cyclization of 3-substituted indoles with 1,4-quinone monoimines, affording chiral benzofuroindolines with high yields and stereoselectivities. The 1,4-quinone monoimines used can be one-pot generated though oxidation of the corresponding phenols as reported by Zhong group, who employed a biomimetic Mn(III)/CPA relay catalysis strategy for this process.[11b] On the other hand, Shi group revealed the CADA of 2, 3-disubstituted indoles with quinone derived imine ketals or monoimines to give chiral indolenines.[11c,d] Recently, the synthesis of fused indolines *via* asymmetric [3 + 2] annulation of 1,4-quinones with indoles was also reported by Tang[11e] and Zhong,[11f] respectively (Scheme 1).

As the analogs of quinones, naphthoquinones and their derivatives often displayed similar chemical reactivity



Scheme 1 Asymmetric arylative dearomatization of indoles using quinones and their imines as electrophiles.

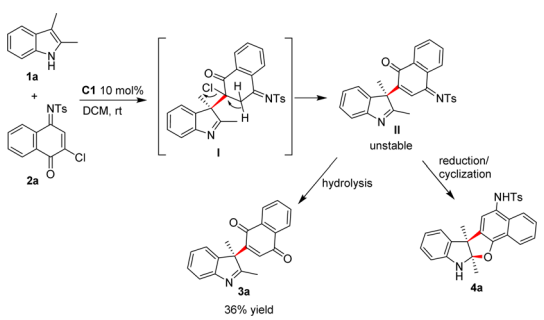
School of Pharmaceutical Sciences (Shenzhen), Shenzhen Campus of Sun Yat-sen University, Shenzhen, 518107, P. R. China. E-mail: zhaojling3@mail.sysu.edu.cn

† Electronic supplementary information (ESI) available. CCDC 2344473. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ra03231d

compared to that of quinones. However, that is not the case with respect to the CADA of indoles, and no successful example was given using naphthoquinones or their imines as electrophiles so far. This fact suggested that there might be challenges need to be overcome when naphthoquinones were used. This was exemplified by the CPA-catalyzed asymmetric [3 + 2] annulation of 1,4-quinones with indoles. Probably due to its relatively lower electrophilicity, no reaction occurred with 1,4-quinone being replaced by 1,4-napthoquinone as reported by Zhong.[11f] As our continuing interest in the asymmetric functionalization of indoles,[13] here we presented our recent study on the CADA of 2,3-disubstituted indoles using naphthoquinone monoimines as electrophiles.

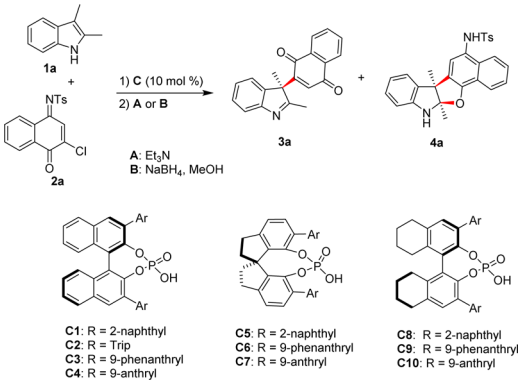
We started our investigation by reacting 2,3-dimethylindole (**1a**) with naphthoquinone monoimine (**2a**) in dichloromethane (DCM) at room temperature with 10 mol% **C1** as a catalyst. Not surprisingly, a mixture of hard-to-separate products was produced. Fortunately, we isolated the dechlorinated indolenine derivative **3a** in a low yield, and found out that the other products were slowly transformed to **3a** during the separation process. These results suggested that unstable intermediates were generated during this dearomatization process. Based on the above results, we assumed that the dearomatization of **1a** produced intermediate **I**, which underwent dehydrochlorination to give intermediate **II**. **II** was sensitive to moisture and hydrolyzation occurred during the purification process to give **3a**. Based on this assumption, the addition of a base might accelerate the process leading to **3a**, while the reduction of carbonyl group in **II** might afford indoline derivative **4a**. Thus, a switchable divergent synthesis of chiral indole derivatives might be established by simply regulating post-processing conditions (Scheme 2).

To confirm our hypothesis, trimethylamine was added to the above reaction mixture after completion by TLC (Method **A**), and the yield of **3a** was increased to 95%. On the other hand, indoline derivative **4a** was formed smoothly in 80% yield following the treatment of $NaBH_4$ (Method **B**). However, products with low enantioselectivities were observed in both cases (Table 1, entries 1 and 2). The reaction leading to **3a** was chosen as a model reaction and a range of CPAs were subsequently examined to improve the stereocontrol of this transformation. As shown in Table 1, it was found that both the substituents and



Scheme 2 Design of the switchable divergent synthesis of chiral indole derivatives.

Table 1 Optimization of the Reaction Conditions[a]



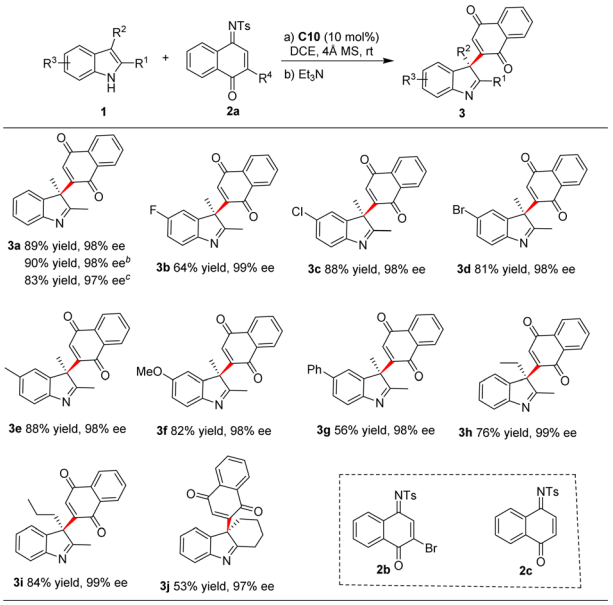
Entry	CPA	Solvent	A/B	Yield [b](%)	ee[c] (%)
1	**C1**	DCM	**A**	**3a**, 95	30
2	**C1**	DCM	**B**	**4a**, 80	33
3	**C2**	DCM	**A**	**3a**, 95	8
4	**C3**	DCM	**A**	**3a**, 95	76
5	**C4**	DCM	**A**	**3a**, 71	72
6	**C5**	DCM	**A**	**3a**, 44	22
7	**C6**	DCM	**A**	**3a**, 62	57
8	**C7**	DCM	**A**	**3a**, 46	32
9	**C8**	DCM	**A**	**3a**, 92	31
10	**C9**	DCM	**A**	**3a**, 95	82
11	**C10**	DCM	**A**	**3a**, 95	84
12	**C10**	THF	**A**	**3a**, 51	21
13	**C10**	PhMe	**A**	**3a**, 97	84
14	**C10**	DCE	**A**	**3a**, 88	94
15[d, e]	**C10**	DCE	**A**	**3a**, 89	98
16[d, e]	**C10**	DCE	**B**	**4a**, 93	99

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), **C** (0.005 mmol), solvent (0.5 mL), room temperature, 2 h, unless otherwise noted. Condition **A**: 0.1 mL Et_3N was added and the reaction was stirred in air for an extra 30 min. Condition **B**: MeOH (0.5 mL) and $NaBH_4$ (0.5 mmol) were added and the reaction was stirred for an extra 30 min. [b] Isolated yields were given. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase. All dr > 20 : 1 determined by ^1H NMR spectra analysis. [d] 20 mg 4 Å molecular sieves was added. [e] Reaction time is 6 h.

the chiral backbones of the catalysts have remarkable effects on the yield and enantioselectivity of the product. Among these catalysts tested, **C10** showed the best catalytic efficiency to give **3a** in 95% yield and 84% ee (Table 1, entry 11). The enantioselectivity of **3a** was further improved to 94% ee when 1,2-dichloroethane (DCE) was used as the reaction media (Table 1, entry 14). The best result in term of yield and ee was obtained with the addition of 4 Å molecular sieves as an additive, albeit a prolonged reaction time was needed (Table 1, entry 15). When the post-processing condition was switched to **B**: with the addition of $NaBH_4$ and MeOH, the corresponding indoline derivative **4a** was produced in 93% yield and 99% ee (Table 1, entry 16). Thus, we have developed a method for the switchable chiral indolenines/indolines synthesis by simply switching the post-processing conditions of the reaction.

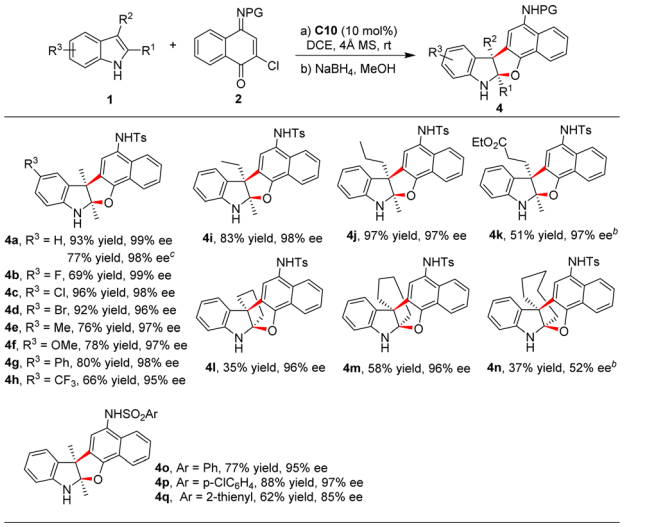
With the optimal reaction conditions determined, we first studied the scope of the reaction leading to chiral indolenine

Table 2 Substrate scope for the synthesis of chiral indolenines[a]



[a] Reactions conditions: **1** (0.05 mmol), **2** (0.075 mmol), **C10** (0.005 mmol), 20 mg 4 Å molecular sieves, DCE (0.5 mL), room temperature, 6–46 h. After completion, 0.1 mL Et_3N was added, and the reaction mixture was stirred in air for 30 min. Isolated yields are given. Enantiomeric excess was determined by HPLC on a chiral stationary phase. [b] **2b** was used as an electrophile. [c] **2c** was used as an electrophile.

Table 3 Substrate scope for the synthesis of fused indolines[a]



[a] Reactions conditions: **1** (0.05 mmol), **2** (0.075 mmol), **C10** (0.005 mmol), 20 mg 4 Å molecular sieves, DCE (0.5 mL), room temperature, 4–79 h. After completion, 0.5 mL MeOH and 0.5 mmol $NaBH_4$ (in portions) was added, and the reaction mixture was stirred for 30 min. Isolated yields are given. Enantiomeric excess was determined by HPLC on a chiral stationary phase. dr > 20 : 1 in all cases. [b] Without the addition of molecular sieves. [c] **2c** was used as an electrophile.

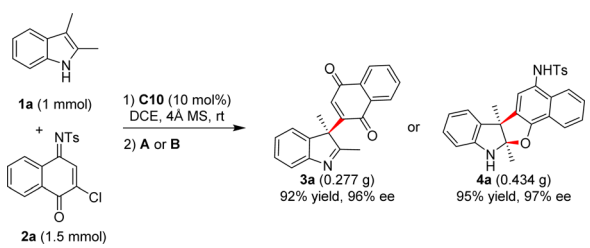
derivatives **3**, and the results were presented in Table 2. It was revealed that substituents variations on the benzene position of indoles were well tolerated, producing the corresponding products in good to high yields (53–90%) with excellent enantioselectivities (97–99% ee). Then, we turned our attention to the reaction using other naphthoquinone monoimines. The reaction proceeded smoothly when brominated substrate **2b** was used, expectedly, debromination occurred to produce **3a** in comparably high yield and ee. The reaction of unsubstituted imine **2c** was also examined. In this case, the intermediate should be a naphthol derivative **III** which tend to undergo cyclization to give fused indoline **4a**. However, high yield of **3a** was still obtained following the addition of Et_3N. This result suggested that the cyclization process was much slower than expected and oxidation/hydrolyzation occurred quickly under basic condition.[14]

Then, the scope for the synthesis of fused indoline derivatives **4** was examined (Table 3). The reaction between various 2,3-disubstituted indoles and naphthoquinone monoimines were investigated under the standard conditions, and the results indicated that the change of post-processing conditions has little effect on the efficiency of this reaction, affording the corresponding fused indolines **4** smoothly with good outcomes. It seems that $NaBH_4$ played multiple roles in this reaction: (1) as a reducing agent, (2) as a "promoter" to accelerate the cyclization process.[15] This point was further confirmed by the reaction of **2c**. In this case, cyclization product **4a** was not observed in the absence of $NaBH_4$, while high yield (77%) of **4a** was obtained in just 10 minutes following the addition of this reagent.[14]

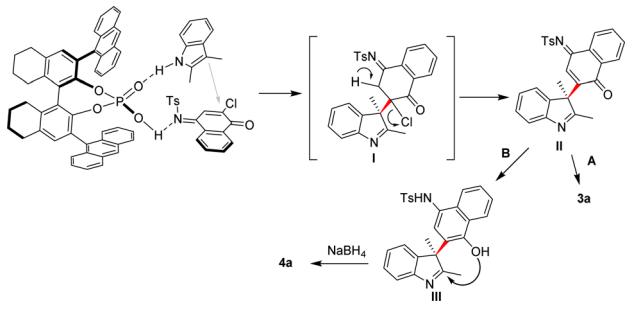
The absolute configurations of the newly formed chiral centers in **4a** were assigned as 2*R*, 3*S* by X-ray analysis of its methylated product **5** (for details, see the ESI†).[16] According to this observation, the chiral quaternary center in **3** has a *S* configuration. That is because the synthesis of these two types of chiral indole derivatives originated from the same asymmetric dearomatization reaction and the only difference is the post-processing procedure which will not influence the configuration of the existing quaternary chiral center at the C3-position of indole nucleus.

The synthetic potential of this reaction was also explored. When the model reactions were up scaled to 1 mmol under the standard conditions, high yields of **3a** or **4a** were obtained, respectively, with slightly decreased enanioselectivities (Scheme 3).

Finally, the possible reaction mechanism was proposed to explain the stereochemistry of this reaction. As shown in Scheme 4, both substrates were activated through hydrogen bonding interaction with the catalyst, and **1a** attack **2a** from the



Scheme 3 Scale-up reactions for the syntheses of **3a** and **4a**.



Scheme 4 Possible reaction mechanism.

bottom to give indolenine intermediate **I** bearing a quaternary chiral centre in *S* configuration. The addition of $NaBH_4$ produced **III** which underwent cyclization to give **4a**, Re face attack was favoured during this process to generate the second quaternary chiral centre in *R* configuration.

Conclusions

In conclusion, we have developed a protocol allowing the switchable divergent synthesis of chiral indolenines/fused indolines *via* a CPA-catalyzed dearomatization of 2,3-disubstituted indoles with naphthoquinone monoimines. Unlike their quinone-derived counterparts, the reaction of naphthoquinone monoimines with indoles produced unstable intermediates which can be readily transformed to different products by simply using different post-processing conditions. In the case for the synthesis of fused indolines, $NaBH_4$ was used as a reducing agent as well as a promoter in the cyclization process.

Author contributions

J. Z. conceived and directed the project. T. L., J. W. and R. X. conducted the experimental work and data analysis. J. Z. wrote the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant 21971264) for financial support of this program.

Notes and references

1 (*a*) R. J. Sundberg, in *The Chemistry of Indoles*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Academic Press, New York, 1996; (*b*) K. S. Ryan and C. L. Drennan, *Chem. Biol.*, 2009, **16**, 351; (*c*) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, Biomedical importance of indoles, *Molecules*, 2013, **18**, 6620–6662; (*d*) M. Z. Zhang, Q. Chen and G. F. Yang, A review on recent developments of indole-containing antiviral agents, *Eur. J. Med. Chem.*, 2015, **89**, 421–441; (*e*) Y. C. Wan, Y. H. Li, C. X. Yan, M. Yan and Z. L. Tang, Indole: A privileged scaffold for the design of anti-cancer agents, *Eur. J. Med. Chem.*, 2019, **183**, 111691.

2 For reviews, see: (*a*) C. X. Zhuo, W. Zhang and S. L. You, Catalytic Asymmetric Dearomatization Reactions, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662–12686; (*b*) Y.-C. Zhang, F. Jiang and F. Shi, Organocatalytic asymmetric synthesis of indole-based chiral heterocycles: strategies, reactions and outreach, *Acc. Chem. Res.*, 2020, **53**, 425–446; (*c*) F.-T. Shen, J.-Y. Wang, W. Tan, Y.-C. Zhang and F. Shi, Progresses in organocatalytic asymmetric dearomatization reactions of indole derivatives, *Org. Chem. Front.*, 2020, **7**, 3967–3998; (*d*) M. Y. Pang, H. H. Chang, Z. Feng and J. Zhang, Recent Advances in Transition-Metal-Catalyzed Tandem Dearomatization of Indoles, *Chin. J. Org. Chem.*, 2023, **43**, 1271–1291.

3 For reviews, see: (*a*) C. Zheng and S. L. You, Catalytic Asymmetric Dearomatization by Transition-Metal Catalysis: A Method for Transformations of Aromatic Compounds, *Chem-Us*, 2016, **1**, 830–857; (*b*) Z. L. Xia, Q. F. Xu-Xu, C. Zheng and S. L. You, Chiral phosphoric acid-catalyzed asymmetric dearomatization reactions, *Chem. Soc. Rev.*, 2020, **49**, 286–300; (*c*) C. Zheng and S. L. You, Advances in Catalytic Asymmetric Dearomatization, *ACS Cent. Sci.*, 2021, **7**, 432–444; (*d*) W. G. He, J. D. Hu, P. Y. Wang, L. Chen, K. Ji, S. Y. Yang, Y. Li, Z. L. Xie and W. Q. Xie, Highly Enantioselective Tandem Michael Addition of Tryptamine-Derived Oxindoles to Alkynones: Concise Synthesis of Strychnos Alkaloids, *Angew. Chem., Int. Ed.*, 2018, **57**, 3806–3809; (*e*) H. Tanaka, N. Ukegawa, M. Uyanik and K. Ishihara, Hypoiodite-Catalyzed Oxidative Umpolung of Indoles for Enantioselective Dearomatization, *J. Am. Chem. Soc.*, 2022, **144**, 5756–5761.

4 (*a*) S. E. Reisman, M. E. Kieffer and H. Wang, in *Asymmetric Dearomatization Reactions*, 2016; (*b*) G. H. Huang and B. L. Yin, Recent Developments in Transition Metal-Catalyzed Dearomative Cyclizations of Indoles as Dipolarophiles for the Construction of Indolines, *Adv. Synth. Catal.*, 2019, **361**, 405–425; (*c*) G. J. Mei, W. L. Koay, C. X. A. Tan and Y. X. Lu, Catalytic asymmetric preparation of pyrroloindolines: strategies and applications to total synthesis, *Chem. Soc. Rev.*, 2021, **50**, 5985–6012; (*d*) C. C. Lu, B. Y. Hao, Y. P. Han and Y. M. Liang, Recent Advances in the Synthesis of Indolines *via* Dearomative Annulation of *N*-acylindoles, *Asian J. Org. Chem.*, 2022, **11**, e202200312; (*e*) C. C. J. Loh and D. Enders, Exploiting the Electrophilic Properties of Indole Intermediates: New Options in Designing Asymmetric Reactions, *Angew. Chem., Int. Ed.*, 2012, **51**, 46–48.

5 For examples, see: (*a*) W. Shao, H. Li, C. Liu, C. J. Liu and S. L. You, Copper-Catalyzed Intermolecular Asymmetric Propargylic Dearomatization of Indoles, *Angew. Chem., Int. Ed.*, 2015, **54**, 7684–7687; (*b*) R. R. Liu, Y. G. Wang, Y. L. Li, B. B. Huang, R. X. Liang and Y. X. Jia, Enantioselective

Dearomative Difunctionalization of Indoles by Palladium-Catalyzed Heck/Sonogashira Sequence, *Angew. Chem., Int. Ed.*, 2017, **56**, 7475–7478; (*c*) Y. Miyazaki, B. Zhou, H. Tsuji and M. Kawatsura, Nickel-Catalyzed Asymmetric Friedel-Crafts Propargylation of 3-substituted Indoles with Propargylic Carbonates Bearing an Internal Alkyne Group, *Org. Lett.*, 2020, **22**, 2049–2053.

6 For selected examples, see: (*a*) B. M. Trost and J. Quancard, Palladium-catalyzed enantioselective C-3 allylation of 3-substituted-1*H*-indoles using trialkylboranes, *J. Am. Chem. Soc.*, 2006, **128**, 6314–6315; (*b*) Q. F. Wu, H. He, W. B. Liu and S. L. You, Enantioselective Construction of Spiroindolenines by Ir-Catalyzed Allylic Alkylation Reactions, *J. Am. Chem. Soc.*, 2010, **132**, 11418–11419; (*c*) B. M. Trost, W. J. Bai, C. Hohn, Y. Bai and J. J. Cregg, Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-substituted 1*H*-indoles and Tryptophan Derivatives with Vinylcyclopropanes, *J. Am. Chem. Soc.*, 2018, **140**, 6710–6717; (*d*) Y. Y. Hu, X. Q. Xu, W. C. Deng, R. X. Liang and Y. X. Jia, Nickel-Catalyzed Enantioselective Dearomative Heck-Reductive Allylic Defluorination Reaction of Indoles, *Org. Lett.*, 2023, **25**, 6122–6127.

7 For selected examples, see: (*a*) Q. Cai and S. L. You, Organocatalyzed Enantioselective Formal [4 + 2] CycloadditionCycloadclition of 2,3-disubstituted Indole and Methyl Vinyl Ketone, *Org. Lett.*, 2012, **14**, 3040–3043; (*b*) Z. H. Zhang and J. C. Antilla, Enantioselective Construction of Pyrroloindolines Catalyzed by Chiral Phosphoric Acids: Total Synthesis of (–)-Debromoflustramine B, *Angew. Chem., Int. Ed.*, 2012, **51**, 11778–11782; (*c*) Y. Zhou, Z. L. Xia, Q. Gu and S. L. You, Chiral Phosphoric Acid Catalyzed Intramolecular Dearomative Michael Addition of Indoles to Enones, *Org. Lett.*, 2017, **19**, 762–765.

8 For selected examples, see: (*a*) O. Lozano, G. Blessley, T. M. del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman and V. Gouverneur, Organocatalyzed Enantioselective Fluorocyclizations, *Angew. Chem., Int. Ed.*, 2011, **50**, 8105–8109; (*b*) W. Q. Xie, G. D. Jiang, H. Liu, J. D. Hu, X. X. Pan, H. Zhang, X. L. Wan, Y. S. Lai and D. W. Ma, Highly Enantioselective Bromocyclization of Tryptamines and Its Application in the Synthesis of (–)-Chimonanthine, *Angew. Chem., Int. Ed.*, 2013, **52**, 12924–12927; (*c*) X. W. Liang, C. Liu, W. Zhang and S. L. You, Asymmetric fluorinative dearomatization of tryptamine derivatives, *Chem. Commun.*, 2017, **53**, 5531–5534.

9 X. Y. Qu, Z. H. Li, J. Zhou, P. F. Lian, L. K. Dong, T. M. Ding, H. Y. Bai and S. Y. Zhang, Chiral Phosphoric Acid-Catalyzed Enantioselective Dearomative Electrophilic Hydrazination: Access to Chiral Aza-Quaternary Carbon Indolenines, *ACS Catal.*, 2022, **12**, 7511–7516.

10 For selected examples, see: (*a*) S. L. Zhu and D. W. C. MacMillan, Enantioselective Copper-Catalyzed Construction of Aryl Pyrroloindolines *via* an Arylation-Cyclization Cascade, *J. Am. Chem. Soc.*, 2012, **134**, 10815–10818; (*b*) C. Liu, J. C. Yi, X. W. Liang, R. Q. Xu, L. X. Dai and S. L. You, Copper(I)-Catalyzed Asymmetric Dearomatization of Indole Acetamides with 3-Indolylphenyliodonium Salts, *Chem.–Eur. J.*, 2016, **22**, 10813–10816.

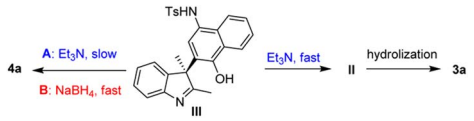
11 (*a*) L. H. Liao, C. Shu, M. M. Zhang, Y. J. Liao, X. Y. Hu, Y. H. Zhang, Z. J. Wu, W. C. Yuan and X. M. Zhang, Highly Enantioselective [3 + 2] Coupling of Indoles with Quinone Monoimines Promoted by a Chiral Phosphoric Acid, *Angew. Chem., Int. Ed.*, 2014, **53**, 10471–10475; (*b*) Q. L. Yu, Y. Fu, J. J. Huang, J. Y. Qin, H. H. Zuo, Y. H. Wu and F. R. Zhong, Enantioselective Oxidative Phenol-Indole [3 + 2] Coupling Enabled by Biomimetic Mn(III)/Bronsted Acid Relay Catalysis, *ACS Catal.*, 2019, **9**, 7285–7291; (*c*) Y. C. Zhang, J. J. Zhao, F. Jiang, S. B. Sun and F. Shi, Organocatalytic Asymmetric Arylative Dearomatization of 2,3-disubstituted Indoles Enabled by Tandem Reactions, *Angew. Chem., Int. Ed.*, 2014, **53**, 13912–13915; (*d*) Y. Wang, M. Sun, L. Yin and F. Shi, Catalytic Enantioselective Arylative Dearomatization of 3-methyl-2-vinylindoles Enabled by Reactivity Switch, *Adv. Synth. Catal.*, 2015, **357**, 4031–4040; (*e*) Q. J. Liu, J. Zhu, X. Y. Song, L. J. Wang, S. W. R. Wang and Y. Tang, Highly Enantioselective [3 + 2] Annulation of Indoles with Quinones to Access Structurally Diverse Benzofuroindolines, *Angew. Chem., Int. Ed.*, 2018, **57**, 3810–3814; (*f*) L. Y. Zhang, J. J. Hu, R. G. Xu, S. L. Pan, X. F. Zeng and G. F. Zhong, Catalytic Asymmetric Dearomative [3 + 2] Cyclisation of 1,4-quinone with 2,3-disubstituted Indoles, *Adv. Synth. Catal.*, 2019, **361**, 5449–5457.

12 For recent reviews, see: (*a*) W. Tan, J.-Y. Zhang, C.-H. Gao and F. Shi, Progress in organocatalytic asymmetric (4 + 3) cycloadditions for the enantioselective construction of seven-membered rings, *Sci. China: Chem.*, 2023, **66**, 966–992; (*b*) H.-H. Zhang and F. Shi, Organocatalytic Atroposelective Synthesis of Indole Derivatives Bearing Axial Chirality: Strategies and Applications, *Acc. Chem. Res.*, 2022, **55**, 2562–2580; (*c*) J. K. Cheng, S.-H. Xiao and B. Tan, Organocatalytic Enantioselective Synthesis of Axially Chiral Molecules: Development of Strategies and Skeletons, *Acc. Chem. Res.*, 2022, **55**, 2920–2937.

13 (*a*) B. Bi, Q. X. Lou, Y. Y. Ding, S. W. Chen, S. S. Zhang, W. H. Hu and J. L. Zhao, Chiral Phosphoric Acid Catalyzed Highly Enantioselective Friedel-Crafts Alkylation Reaction of C3-Substituted Indoles to β,γ-Unsaturated α-Ketimino Esters, *Org. Lett.*, 2015, **17**, 540–543; (*b*) M. J. Xiao, D. F. Xu, W. H. Liang, W. Y. Wu, A. S. C. Chan and J. L. Zhao, Organocatalytic Enantioselective Friedel-Crafts Alkylation/Lactonization Reaction of Hydroxyindoles with Methyleneoxindoles, *Adv. Synth. Catal.*, 2018, **360**, 917–924; (*c*) L. Cai, Y. L. Zhao, T. K. Huang, S. S. Meng, X. Jia, A. S. C. Chan and J. L. Zhao, Chiral Phosphoric-Acid-Catalyzed Regioselective and Enantioselective C7-Friedel-Crafts Alkylation of 4-Aminoindoles with Trifluoromethyl Ketones, *Org. Lett.*, 2019, **21**, 3538–3542; (*d*) S. Y. Yang, L. Li and J. L. Zhao, Chiral Phosphoric Acid-Catalyzed Chemo- and Enantioselective *N*-Alkylation of Indoles with Imines, *Adv. Synth. Catal.*, 2022, **364**, 4166–4172; (*e*)

Y. L. Zhao, R. Xiao, W. B. Fang and J. L. Zhao, Chiral phosphoric acid-catalyzed chemo and enantioselective 1,2-addition of isatin-derived β,γ-unsaturated α-ketoesters with 4-aminoindoles at the C7 position, *Org. Chem. Front.*, 2023, **10**, 718–723.

14 Intermediate **III** was quickly oxidized to **II** with the addition of Et_3N in air, and **II** underwent hydrolyzation to give **3a**, and no cyclizaiton product was obtained. However, the cyclization process was significantly accelerated with the addition of $NaBH_4$..



15 A. Arase, M. Hoshi, T. Yamaki and H. Nakanishi, Lithium borohydride-catalysed selective reduction of carbonyl group of conjugated and unconjugated alkenones with borane in tetrahydrofuran, *J. Chem. Soc., Chem. Commun.*, 1994, 855–856.

16 CCDC 2344473 contains the supplementary crystallographic data for this paper.