Organocatalytic Enantioselective Nucleophilic Addition of Indole Imine 5-Methides

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Abstract

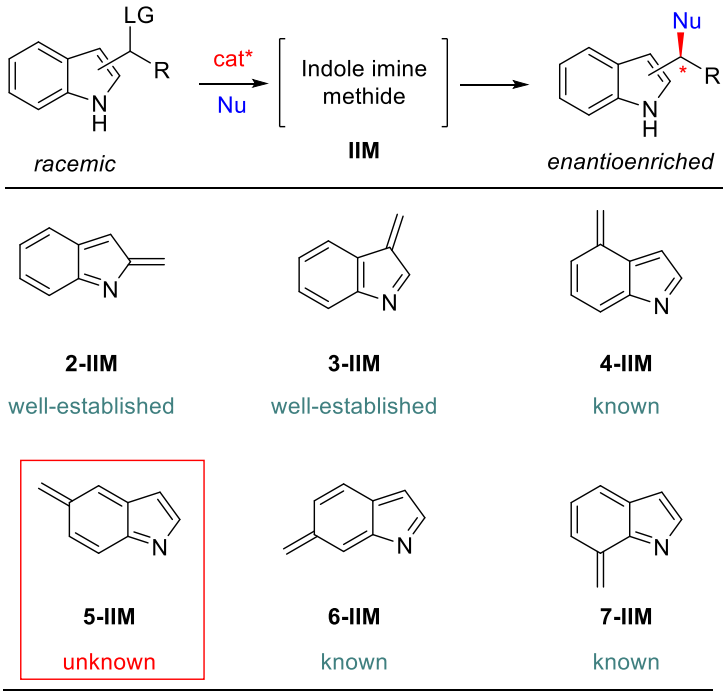
Despite the enormous developments in the asymmetric transformations of indole imine methides (IIMs), the remote asymmetric induction involving IIMs remains challenging due to the spatial interaction requirement between the substrate and catalyst. Herein we report the first catalytic asymmetric nucleophilic addition to indole imine 5-methide (5-IIM), the only topological isomer of IIMs whose asymmetric addition remains unknown. Considering the challenging remote stereocontrol, high efficiency and respectable enantioselectivity were achieved, providing access to a range of enantioenriched indole-containing triarylmethanes.

Indole is a privileged heterocycle with broad applications in both organic synthesis and medicinal chemistry.[1] Speficically, indole imine methides (IIMs) are highly versatile intermediates in the synthesis of diverse functionalized indole-containing molecules.[2,3] Similar to the reactivity of (aza-) quinone methides, IIMs are highly electrophilic and thus prone to nucleophilic addition at the methide position owing to their strong tendancy to rearomatization.[2,3] In particular, in the past decade, a wide range of catalytic asymmetric processes have been achieved by convenient *in situ* generation of IIMs followed by subsequent stereocontrolled nucleophilic addition or cycloaddition.[2] These processes, typically operated in a one-pot manner under mild conditions, have allowed facile access to diverse enantioenriched indole-containing molecules from simple racemic/achiral precursors.

Depending on the position of exocyclic methide unit, IIMs have multiple topological isomers, namely, indole imine 2-, 3-, 4-, 5-, 6-, 7-methides (Scheme 1).[2e,4-9] Amongh them, indole imine 2- and 3-methides (2- and 3-IIMs) are most studied isomers regarding their asymmetric transformations.[2,4,5] This is probably partly due to the short distance between the

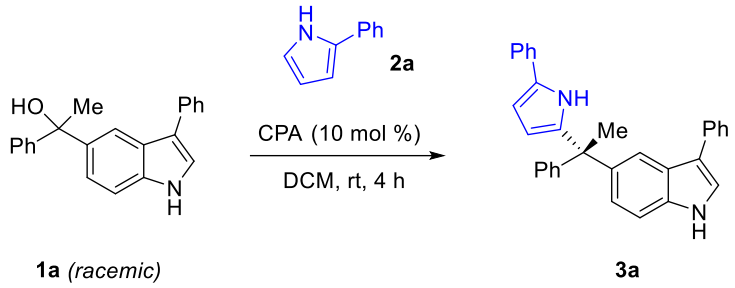
methide position and the imine motif, the typical catalytic activation site, which permits relatively easy stereocontrol. In contrast, other topological isomers, such as 4-, 6-, and 7-IIMs, have been mush less-explored for asymmetric synthesis, since catalytic remote stereocontrol is often required in these cases in order to achieve high enantioselectivity.[6-8] While sporadic examples are known for these isomers, however, 5-IIM is the only isomer whose asymmetric transformations remain unknown, to the best of our knowledge. Indeed, among all these topological isomers, 5-IIM has the longest distance between the methide and imine motifs, which exerts substantial challenge in effective stereocontrol by the catalyst. In this context, herein we fill this gap by introducing the the first catalytic asymmetric process of 5-IIMs, leading to efficient access to enantioenriched indole-containing triarylalkanes bearing a remote benzylic chirality.

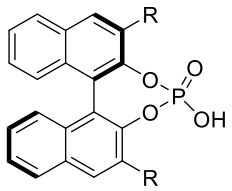
Scheme 1. Introduction to Topological Isomers and Current State of Catalytic Asymmetric Nucleophilic Addition of IIMs.



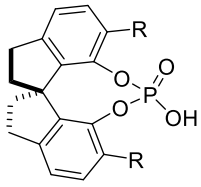
We employed the racemic indol-5-ylmethanol **1a** as the model precursor to 5-IIM and 2-phenyl-1*H*-pyrrole (**2a**) as the nucleophile for the initial study (Table 1). Chiral phosphoric acids (CPAs) were evaluated as potential catalysts for this reaction, condiering their general excellent performance in the asymmetric transformations of other IIMs and the related *para*-aza-quinone methides.[2,4-10] With the well-known TRIP catalyst (**A1**), the reaction in DCM at proceeded successfully at room temperature to form the desired product **3a** in 58% yield, albeit with only 76:24 enantiomeric ratio (er, entry 1). This results implied that the remote enantiocontrol was indeed challenging. Further considerable efforts were devoted to exhaustive screening of a wide range of other chiral phosphoric acids. Representative examples were shown (entires 2-6). Changing the 3,3'-substituents to 1-naphthyl and 1-anthryl led to improvement on both yield and enantioselectivity (entires 2-3). Further screening of SPINOL-derived CPAs identified that (*R*)-**B1** provided the highest enantioselectivity (entry 4). Further solvent screening indicated that coordinatings solvents, such as dietheyl ether and ethyl acetate, led to low yield and moderate enantioselectivity, likely due to competitive binding with the acid catalyst. (entries 7-8). In contrast, toluene slightly improved the enantioselective (91:9 er, entry 9).

Table 1. Evaluation of Conditions[a]





(*R*)-**A1**: R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
(*R*)-**A2**: R = 1-naphthyl
(*R*)-**A3**: R = 9-anthryl



(*R*)-**B1**: R = 1-naphthyl
(*R*)-**B2**: R = 9-anthryl
(*R*)-**B3**: R = 9-phenanthryl

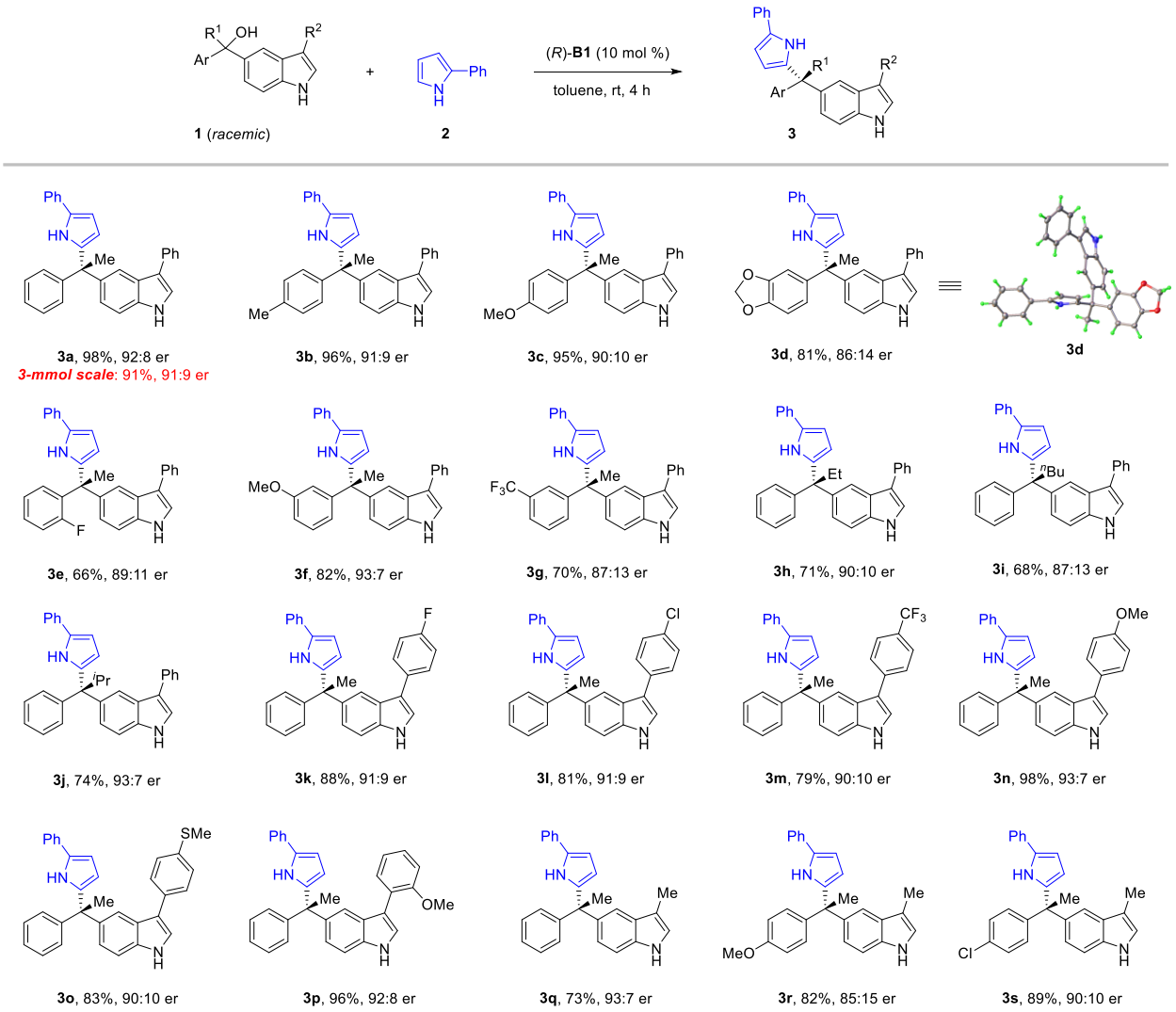
Entry	CPA	Solvent	Yield of 3a[b]	er of 3a[b]
1	(*R*)-**A1**	DCM	58%	76:24
2	(*R*)-**A2**	DCM	>95%	82:18
3	(*R*)-**A3**	DCM	>95%	87:13
4	(*R*)-**B1**	DCM	>95%	89:11
5	(*R*)-**B2**	DCM	74	86:14
6	(*R*)-**B3**	DCM	87	78:22
7	(*R*)-**B1**	EtOAc	22	-
8	(*R*)-**B1**	Et_2O	46	70:30
9	(*R*)-**B1**	toluene	>95%	91:9

[a] Reaction scale: **1a** (0.05 mmol), **2** (0.075 mmol, 1.5 equiv), catalyst (5 μmol, 10 mol %), solvent (0.5 mL), 4 h. [b] Yield was determined by ^{1}H NMR analysis of the crude mixture using

CH_2Br_2 as an internal standard. Er was determined by HPLC analysis on a chiral stationary phase.

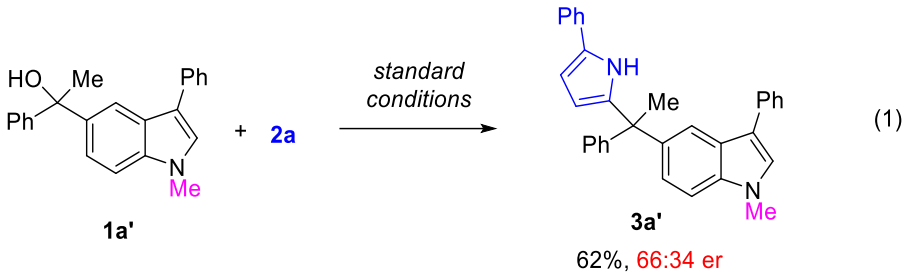
With the optimized conditions in hands, we next examined the reaction scope with various substituted indol-5-ylmethanols (Scheme 2). In general, this protocol provided efficient access to a wide range of indole-containing triarylalkanes **3a**-**3s** with high yield and good to high enantioselectivity. Electron-donating and electron-withdrawing substituents at different positions of the 5-benzylic aryl ring did not obviously affect the reaction efficeincy or enantioselectivity (**3b**-**3g**). Similarly, substrates with different aliphatic substituents at 5-benzylic position with different chain length (**3h-3i**) and steric hinderance (**3j**) all reacted without deterioration in enantioselectivity. Different functional groups, including aryl halide, trifluoromethyl, thioether, acetal, and ether, were compatible with the mild conditions. It is worth noting that the enantioselectivity was respectable, particularly considering that this process involves very remote sterocontrol. Finally, the robustness of this protocol was further demonstrated by a gram-scale synthesis of **3a**, resulting in comparable yield and enantioselectivity as the smalll-scale reaction. The structure and absolute configuration of the product 3d were confirmed unambiguously by X-ray crystallography (CCDC 2311114).

Scheme 2. Reaction Scope[a]



[a] Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), (*R*)-**B1** (0.03mmol), toluene (3.0 mL), 4 h.

To gain insight into the role of the hypothetical indole imine methide intermediate, we carried out a control experiment with *N*-methylated indole substrate **1a'**. Under the standard conditions, the reaction resulted in lower yield and significantly decreased enantioselectivity (eq 1), indicating the importance of the N-H functionality, which is crucial for the formation of the 5-IIM intermediate.



To further probe the reaciton mechanism, we investigated the time-dependence of the ee values of both the product **3a** and starting material **1a** throughout the reaction progress. The results showed that the ee value of **1a** increased over time, indicating kinetic resolution of the substrate (Figure 1a). However, the product ee remained constant during the reaction, which was consistent with the involvement of an achiral 5-IIM intermediate and thus enantioconvergent nature of this process. Taken together, these results may suggest that the direct S_N2 substituion pathway of indol-5-yl methanols is not operative in this process. In addition, the presence of kinetic resolution may suggest that the first step is irreversible. Thus, the second step, nucleophilic addition, is highly likely a fast step and thus the whole reaction might exhibit zeroth order in nucleophile. Indeed, subsequent kinetic studies indicated that this reaction rate had no dependence on nucleophile concentration (Figure 1b), which further confirmed that the first step is rate-determining and irreversible. The obeserved remote stereocontrol prompted us to gain more information about the possible enantiodetermining transition state. Interestingly, we observed positive non-linear effects (Figure 1c).[11] While there is no solid evidence for the formation of higher-order catalyst aggregates responsible for asymmetric induction, it could be possible that two or more chiral phosphoric acid molecules are involved in the

enantiodetermining transistion state to relay hydrogen bonding and enable better remote stereocontrol.

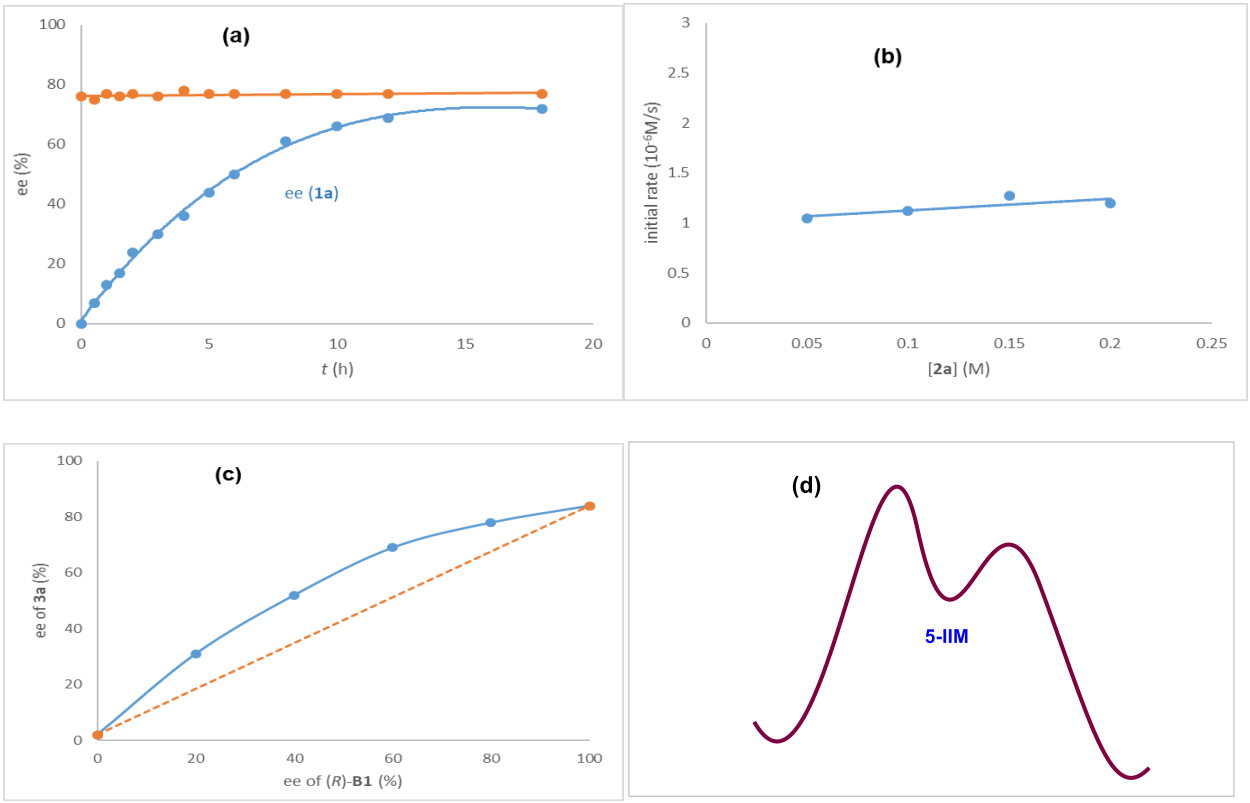
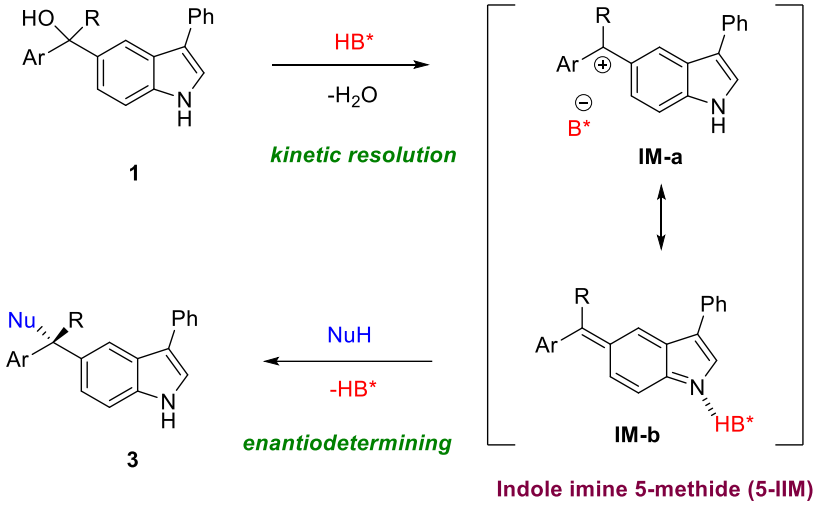


Figure 1. Mechanistic studies. (a) Time-dependence of substrate and product ee values. (b) Zeroth order in nucleophile. (c) Positive non-linear effects. (d) Proposed reaction coordinate diagram.

Based on the above results and analysis, a reaction diagram and a possible reaction mechanism is proposed (Figure 1d and Scheme 3). The chiral phosphoric acid catalyst initially activates the tertiary alcohol moiety, leading to the elimination of a water molecule from substrate **1** to form the ion pair **IM-a**, consisting of an indo-5-yl carbocation and a chiral phosphate anion. This intermediate is stabilized by the resonance form **IM-b**, which can be

viewed as a CPA-activated indole imine 5-methide (5-IIM). Subsequent asymmetric nucleophilic addition takes place at the 5-methide position to form the desired products **3** with enantiocontrol. While the exact structure of the enantiodetermining transition state is unknown, it can also be hypothesized that the pyrrole nucleophile may also have hydrogen bond interaction with the basic phosphoryl (P=O) motif of the catalyst in a bifunctional activation mode.

Scheme 3. Proposed Mechanism



In summary, we have developd the first catalytic asymmetric reactions of indole imine 5-methides. With this process, all the topological isomers of indole imine methides have been successfully demonstrated for asymmetric synthesis. The ultra long distance between the imine and methide motifs in this case posed substrantial challenges in remote enantiocontrol. By careful catalyst screening and condition optimization, excellent efficiency and good enantioselectivity were achieved for the intermolecular C–C bond formation with a range of indol-5-ylmethanols, which provided efficent access to diverse enantioenriched indole-containing triarylmethanes bearing a remote stereogenic center. Control experiments and kinetic studies

were consistent with the involvement of an IIM intermediate and further suggested that the initial dehydration step is rate-determining and irreversible.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Additional experimental and computational details, and spectroscopic data of all compounds (PDF).

X-ray crystallography data (CIF)

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Notes

The authors declare no competing financial interest.

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References

1. (a) Sundberg, R. J.; *Indoles*; Academic Press: London, 1996. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110*, 4489.
2. Selected reviews on indole imine methides: (a)Wang, L.; Chen, Y.; Xiao, J. Alkylideneindoleninium Ions and Alkylideneindolenines: Key Intermediates for the Asymmetric Synthesis of 3-Indolyl Derivatives. *Asian J. Org. Chem.* **2014**, *3*, 1036. (b)Mei, G.-J.; Shi, F. Indolylmethanols as Reactants in Catalytic Asymmetric Reactions. *J. Org. Chem.* **2017**, *82*, 7695. (c) Zhang, Y.-C.; Jiang, F.; Shi, F. Organocatalytic Asymmetric Synthesis of Indole-Based Chiral Heterocycles: Strategies, Reactions, and Outreach. *Acc. Chem. Res.* **2020**, *53*, 425. (d) Kikuchi, J.; Terada, M. Enantioconvergent Substitution Reactions of Racemic Electrophiles by Organocatalysis. *Chem.–Eur. J.* **2021**, *27*, 10215. (e) Li, X.; Li, Z.; Sun, J. Quinone Methides and Indole Imine Methides as Intermediates in Enantioselective Catalysis. *Nat. Synth.* **2022**, *1*, 426.
3. Reviews on asymmetric reactions of QMs: (a) Pathak, T. P.; Sigman, M. S. Applications of *ortho*-Quinone Methide Intermediates in Catalysis and Asymmetric Synthesis. *J. Org. Chem.*

2011, *76*, 9210. (b) Caruana, L.; Fochi, M.; Bernardi, L. J. M. The emergence of quinone methides in asymmetric organocatalysis. *Molecules* **2015**, *20*, 11733. (c) Wang, Z.; Sun, J. Recent Advances in Catalytic Asymmetric Reactions of *o*-Quinone Methides. *Synthesis* **2015**, *47*, 3629. (d) Jaworski, A. A.; Scheidt, K. A. Emerging Roles of in Situ Generated Quinone Methides in Metal-Free Catalysis. *J. Org. Chem.* **2016**, *81*, 10145. (e) Li, W.; Xu, X.; Zhang, P.; Li, P., Recent Advances in the Catalytic Enantioselective Reactions of *para*-Quinone Methides. *Chem. Asian J.* **2018**, *13*, 2350. (f) Lima, C. G. S.; Pauli, F. P.; Costa, D. C. S.; de Souza, A. S.; Forezi, L. S. M.; Ferreira, V. F.; de Carvalho da Silva, F. *para*-Quinone Methides as Acceptors in 1,6-Nucleophilic Conjugate Addition Reactions for the Synthesis of Structurally Diverse Molecules. *Eur. J. Org. Chem.* **2020**, *2020*, 2650. (g) Dorsch, C.; Schneider, C. Asymmetric Brønsted Acid Catalyzed Cycloadditions of *ortho*-Quinone Methides and Related Compounds. *Synthesis* **2022**, *54*, 3125.

4. Selected examples on asymmetric reactions of 2-indole imine methides: (a) Qi, S.; Liu, C.-Y.; Ding, J.-Y.; Han, F.-S. Chiral Phosphoramide-catalyzed Enantioselective Synthesis of 2,3'-Diindolylarylmethanes from Indol-2-yl Carbinols and Indoles. *Chem. Commun.* **2014**, *50*, 8605. (b) Sun, X.-X.; Zhang, H.-H.; Li, G.-H.; He, Y.-Y.; Shi, F. Catalytic Enantioselective and Regioselective [3+3] Cycloadditions Using 2-Indolylmethanols as 3 C Building Blocks. *Chem.–Eur. J.* **2016**, *22*, 17526. (c) Zhang, H.-H.; Wang, C.-S.; Li, C.; Mei, G.-J.; Li, Y.; Shi, F. Design and Enantioselective Construction of Axially Chiral Naphthyl-Indole Skeletons. *Angew. Chem. Int. Ed.* **2017**, *56*, 116. (d) Sun, M.; Ma, C.; Zhou, S.-J.; Lou, S.-F.; Xiao, J.; Jiao, Y.; Shi, F. Catalytic Asymmetric (4+3) Cyclizations of In Situ Generated ortho-Quinone Methides with 2-Indolylmethanols. *Angew. Chem. Int. Ed.* **2019**, *58*, 8703. (e) Goricke, F.; Schneider, C. Palladium-Catalyzed, Enantioselective (3+2)-Cycloannulation of β-Keto Esters with Alkylidene 2H-Indoles toward Complex Indole-Based Heterocycles. *Org.*

Lett. **2020**, *22*, 6101. (f) Li, T.-Z.; Liu, S.-J.; Sun, Y.-W.; Deng, S.; Tan, W.; Jiao, Y.; Zhang, Y.-C.; Shi, F. Regio- and Enantioselective (3+3) Cycloaddition of Nitrones with 2-Indolylmethanols Enabled by Cooperative Organocatalysis. *Angew. Chem. Int. Ed.* **2021**, *60*, 2355.

5. Selected examples on asymmetric reactions of 3-indole imine methides: (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. Asymmetric Brønsted Acid Catalysis: Enantioselective Nucleophilic Substitutions and 1,4-Additions. *Angew. Chem. Int. Ed.* **2008**, *47*, 593. (b) Sun, F.-L.; Zeng, M.; Gu, Q.; You, S.-L. Enantioselective Synthesis of Fluorene Derivatives by Chiral Phosphoric Acid Catalyzed Tandem Double Friedel–Crafts Reaction. *Chem. Eur. J.* **2009**, *15*, 8709. (c) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. Highly Enantioselective Alkylation Reaction of Enamides by Brønsted-Acid Catalysis. *Org. Lett.* **2009**, *11*, 4620. (d) Song, L.; Guo, Q.-X.; Li, X.-C.; Tian, J.; Peng, Y.-G. The Direct Asymmetric α-Alkylation of Ketones by Brønsted Acid Catalysis. *Angew. Chem. Int. Ed.* **2012**, *51*, 1899. (e) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. Proline-Catalyzed Asymmetric Formal α-Alkylation of Aldehydes via Vinylogous Iminium Ion Intermediates Generated from Arylsulfonyl Indoles. *Angew. Chem. Int. Ed.* **2008**, *47*, 8707. (f) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Wu, D.; Xiang, H.; Zhou, X. Highly Enantioselective Michael Addition of Malononitrile to Vinylogous Imine Intermediates Generated in situ from Arylsulfonyl Indoles. *Chem. Eur. J.* **2010**, *16*, 10955. (g) Wang, C.-S.; Li, T.-Z.; Liu, S.-J.; Zhang, Y.-C.; Deng, S.; Jiao, Y.; Shi, F. Axially Chiral Aryl-Alkene-Indole Framework: A Nascent Member of the Atropisomeric Family and its Catalytic Asymmetric Construction. *Chin. J. Chem.* **2020**, *38*, 543.

6. Chen, Z.; Wang, L.; Qian, Y.; Lin, X. Chiral Phosphoric Acid Catalyzed Enantioselective [4+3]-Cyclization Reaction of Indol-4-ylmethanols and Quinone Esters. *Synlett* **2020**, *32*, 1231.
7. Yue, C.; Fang, X.; Cao, Y.; Antilla, J. C. Chiral Phosphoric Acid Catalyzed Asymmetric Synthesis of Hetero-triarylmethanes from Racemic Indolyl Alcohols. *Angew. Chem. Int. Ed.* **2018**, *57*, 11004.
8. Wang, H.-Q.; Xu, M.-M.; Wan, Y.; Mao, Y.-J.; Mei, G.-J.; Shi, F. Application of 7-Indolylmethanols in Catalytic Asymmetric Arylations with Tryptamines: Enantioselective Synthesis of 7-Indolylmethanes. *Adv. Synth. Catal.* **2018**, *360*, 1850.
9. For recent reviews and leading studies on chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Nakashima, D.; Yamamoto, H. Design of Chiral N-Triflyl Phosphoramide as a Strong Chiral Brønsted Acid and Its Application to Asymmetric Diels−Alder Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047. (e) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277. (f) James, T.; Gemmeren M. van; List, B. Development and Applications of Disulfonimides in Enantioselective Organocatalysis. *Chem. Rev.* **2015**, *115*, 9388.
10. For the related asymmetric reactions of *para*-aza-quinone methide: (a) Chen, M.; Sun, J. Catalytic Asymmetric N-Alkylation of Indoles and Carbazoles via 1,6-Conjugate Addition of

Aza-*para*-Quinone Methides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4583. (b) Chen, M.; Qian, D.; Sun, J. Organocatalytic Enantioconvergent Synthesis of Tetrasubstituted Allenes via Asymmetric 1,8-Addition to aza-para-Quinone Methides. *Org. Lett.* **2019**, *21*, 8127. (b) Zhang, L.; Han, Y.; Huang, A.; Zhang, P.; Li, P.; Li, W. Organocatalytic Remote Stereocontrolled 1,8-Additions of Thiazolones to Propargylic Aza-*p*-quinone Methides. *Org. Lett*. **2019**, *21*, 7415.

11. For selected examples of non-linear effects observed with chiral phosphoric acid catalysis: (a) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. Asymmetric Organocatalytic Three-Component 1,3-Dipolar Cycloaddition: Control of Stereochemistry via a Chiral Brønsted Acid Activated Dipole. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (b) Momiyama, N.; Konno, T.; Furiya, Y.; Iwamoto, T.; Terada, M. Design of Chiral Bis-phosphoric Acid Catalyst Derived from (R)-3,3'-Di(2-hydroxy-3-arylphenyl)binaphthol: Catalytic Enantioselective Diels-Alder Reaction of α,β-Unsaturated Aldehydes with Amidodienes. *J. Am. Chem. Soc.* **2011**, *133*, 19294.