

Cite this: *Chem. Sci.*, 2024, 15, 720

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 24th September 2023

Accepted 21st November 2023

DOI: 10.1039/d3sc05014a

rsc.li/chemical-science

# Primary activation of *para*-quinone methides by chiral phosphoric acid for enantioselective construction of tetraarylmethanes†

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Demonstrated here is an asymmetric nucleophilic addition *via* primary activation of *para*-quinone methides (*p*-QMs) based on a chiral phosphoric acid catalytic system. In sharp contrast to previous CPA-based bifunctional activation processes that all required the nucleophiles to have an effective hydrogen bond donor unit (e.g., OH, NH), here no such unit is required in the nucleophile. *N*-protected indole nucleophiles were successfully utilized for the synthesis of chiral tetraarylmethanes with high efficiency and enantioselectivity under mild conditions. Therefore, this protocol significantly expanded the scope of asymmetric transformations of *p*-QMs.

## Introduction

*Para*-Quinone methides (*p*-QMs) are versatile intermediates in organic synthesis and biological processes.<sup>1</sup> Recently, they have been demonstrated to be particularly powerful in asymmetric synthesis,<sup>2</sup> especially for the construction of quaternary stereogenic centers.<sup>3</sup> Their strong tendency for aromatization permits the catalytic asymmetric 1,6-conjugate nucleophilic addition to the remote methide position, enabling rapid construction of a range of a benzylic stereogenic centers.<sup>4,5</sup> While a range of catalytic asymmetric systems have been reported for these reactions, many of them required the presynthesis of those generally unstable QMs and thus limited the utility of such reactions.<sup>4</sup> In 2015, we reported the first example of using chiral phosphoric acids (CPAs) as catalysts for the asymmetric nucleophilic addition to *p*-QMs (Scheme 1a).<sup>5a</sup> Notably, this catalytic system does not require the presynthesis of *p*-QMs, as it allows the *in situ* generation of QMs from the corresponding

stable, racemic benzylic alcohols and subsequent asymmetric addition to take place in a one-pot fashion. Consequently, this protocol has been widely utilized since then.<sup>6</sup>

However, despite the broad utility of CPA catalysts<sup>7</sup> in *p*-QM chemistry,<sup>4-6</sup> it is worth noting that, due to the typically long distance between the carbonyl activation site and the nucleophilic addition site, so far all the CPA-catalyzed *p*-QM addition reactions took advantage of the bifunctional activation mode, *i.e.*, the CPA catalyst not only activates the QM carbonyl, but also has an effective hydrogen bonding interaction with the nucleophile partner (Scheme 1a).<sup>4h,5,6a-k</sup> This hydrogen bond interaction with the nucleophile not only helps achieve a tight enantiodetermining transition state, thereby facilitating enantiocontrol, but also increases the nucleophilicity of the nucleophile and reduces the reaction barrier. However, to the best of

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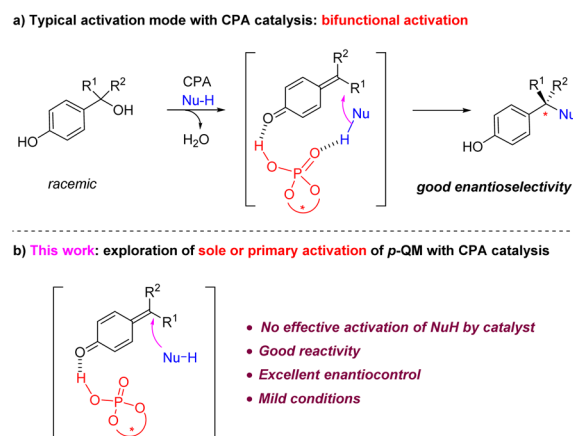
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† Electronic supplementary information (ESI) available: Experimental procedures and characterization for all new compounds. CCDC 2226390. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc05014a>



Scheme 1 Modes of activation in CPA-catalyzed asymmetric addition to *p*-QMs.

our knowledge, an efficient example of sole or primary activation of *p*-QM but without effective activation of the nucleophile by the CPA catalyst has not been demonstrated.<sup>8</sup> Herein we report a highly efficient example of this type (Scheme 1b).

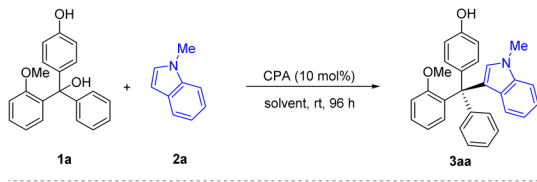
Nucleophiles currently widely used CPA-catalyzed asymmetric *p*-QM addition reactions include those with an N–H functionality (e.g., amines, indoles, pyrroles)<sup>5,6h–k</sup> or an O–H functionality (e.g., naphthols, carboxylic acids, 1,3-dicarbonyl compounds with enol tautomer).<sup>6a,b,d,e</sup> These functionalities are well-known hydrogen bond donors. In many of these reactions, control experiments by protecting these free N–H or O–H functionalities normally led to either dramatically low reactivity or low enantioselectivity, which confirmed the key role of their involvement in the secondary hydrogen bond interaction.

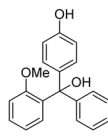
For example, in 2020, we reported the first catalytic asymmetric synthesis of chiral tetraarylmethanes *via* conjugate addition of pyrroles to *in situ* generated *p*-QMs bearing two aryl groups at the methide position.<sup>6h</sup> The unique three-dimensional structure together with their interesting biological activities promoted us to further develop new reactions for the synthesis of their analogues.<sup>6i,9</sup> In particular, indoles are extremely versatile pharmacophores in drugs.<sup>10</sup> However, indoles with a free N–H motif were not generally effective nucleophiles in this process. Therefore, we employed this reaction as an example to examine the possibility of sole or primary activation of *p*-QMs, which means the use of *N*-protected indoles to achieve high enantioselectivity in the absence of the secondary hydrogen bond interaction.

## Results and discussion

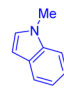
The initial study was carried out with racemic triarylmethanol **1a** as the model substrate and *N*-methylindole **2a** as the nucleophile. In the presence of 10 mol% of CPA (*R*)-**A1**, the desired tetraarylmethane **3aa** was smoothly obtained, with encouraging conversion and enantioselectivity (56% ee). It is worth noting that the reaction of **1a** with free indole (without substitution in the N–1 position) only resulted in 12% ee. It is also notable that this reaction was clean and the remaining substrate accounted for the remainder of mass balance. Encouraged by the initial results, we performed further optimization aiming to improve the enantiocontrol for this challenging situation. Various CPAs were evaluated (Table 1, entries 2–6). The steric hindrance of the 3,3'-substituents seemed to be crucial for enantiocontrol, as catalysts **A1** (ref. <sup>11</sup>) and **A2**,<sup>12</sup> bearing the bulky 2,4,6-triisopropylphenyl or 2,4,6-tricyclohexylphenyl groups, respectively, could give similar enantioselectivity, but the less hindered **A3** and **A4** could only give moderate enantiocontrol. Along these lines, we utilized a more hindered CPA **A5** bearing 2,6-diisopropyl-4-adamantylphenyl groups in the 3,3'-positions,<sup>13</sup> which proved superior and gave the best enantiocontrol (80% ee, Table 1, entry 5), though with moderate conversion. Extending the reaction time did not significantly enhance the reaction conversion. Then, our attention was turned to solvent screening (Table 1, entries 6–10). Toluene proved to be the optimal choice (97% conversion, 92% ee). After systematic optimization of reaction parameters, including concentration,

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



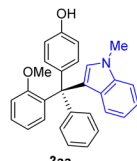


**1a**

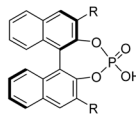


**2a**

CPA (10 mol%)  
solvent, rt, 96 h



**3aa**



**A1**, R = 2,4,6-Cy<sub>3</sub>C<sub>6</sub>H<sub>2</sub>

**A2**, R = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>

**A3**, R = 9-phenanthryl

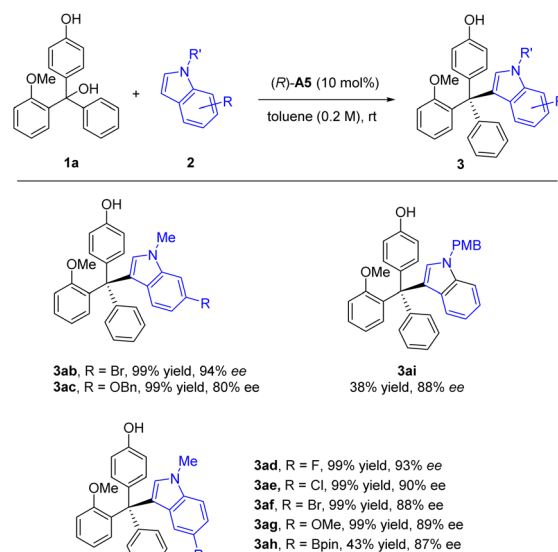
**A4**, R = 9-anthryl

**A5**, R = 2,6-Pr<sub>2</sub>-4-Ad-C<sub>6</sub>H<sub>2</sub>

| Entry           | CPA                     | Solvent            | Conv. <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|-----------------|-------------------------|--------------------|------------------------|---------------------|
| 1               | ( <i>R</i> )- <b>A1</b> | DCE                | 48                     | 56                  |
| 2               | ( <i>R</i> )- <b>A2</b> | DCE                | 41                     | 55                  |
| 3               | ( <i>R</i> )- <b>A3</b> | DCE                | 92                     | 16                  |
| 4               | ( <i>R</i> )- <b>A4</b> | DCE                | 55                     | 27                  |
| 5               | ( <i>R</i> )- <b>A5</b> | DCE                | 58                     | 80                  |
| 6               | ( <i>R</i> )- <b>A5</b> | DCM                | 41                     | 60                  |
| 7               | ( <i>R</i> )- <b>A5</b> | Toluene            | 97                     | 92                  |
| 8               | ( <i>R</i> )- <b>A5</b> | CHCl <sub>3</sub>  | 65                     | 91                  |
| 9               | ( <i>R</i> )- <b>A5</b> | 1,4-Dioxane        | NR                     | —                   |
| 10              | ( <i>R</i> )- <b>A5</b> | CH <sub>3</sub> CN | 90                     | 25                  |
| 11 <sup>d</sup> | ( <i>R</i> )- <b>A5</b> | Toluene            | 99                     | 92                  |

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), *N*-methylindole (0.2 mmol), CPA (10 mol%), solvent (1 mL), rt, 96 h. <sup>b</sup> Conversion was determined by <sup>1</sup>H NMR. <sup>c</sup> The ee value was determined by chiral HPLC. <sup>d</sup> *N*-methylindole (1.5 equiv.), toluene (0.5 mL), 72 h. NR = no reaction.

nucleophile equivalence, and temperature, we were able to achieve 99% conversion and 92% ee, which were determined to be the standard reaction conditions (Table 1, entry 11).



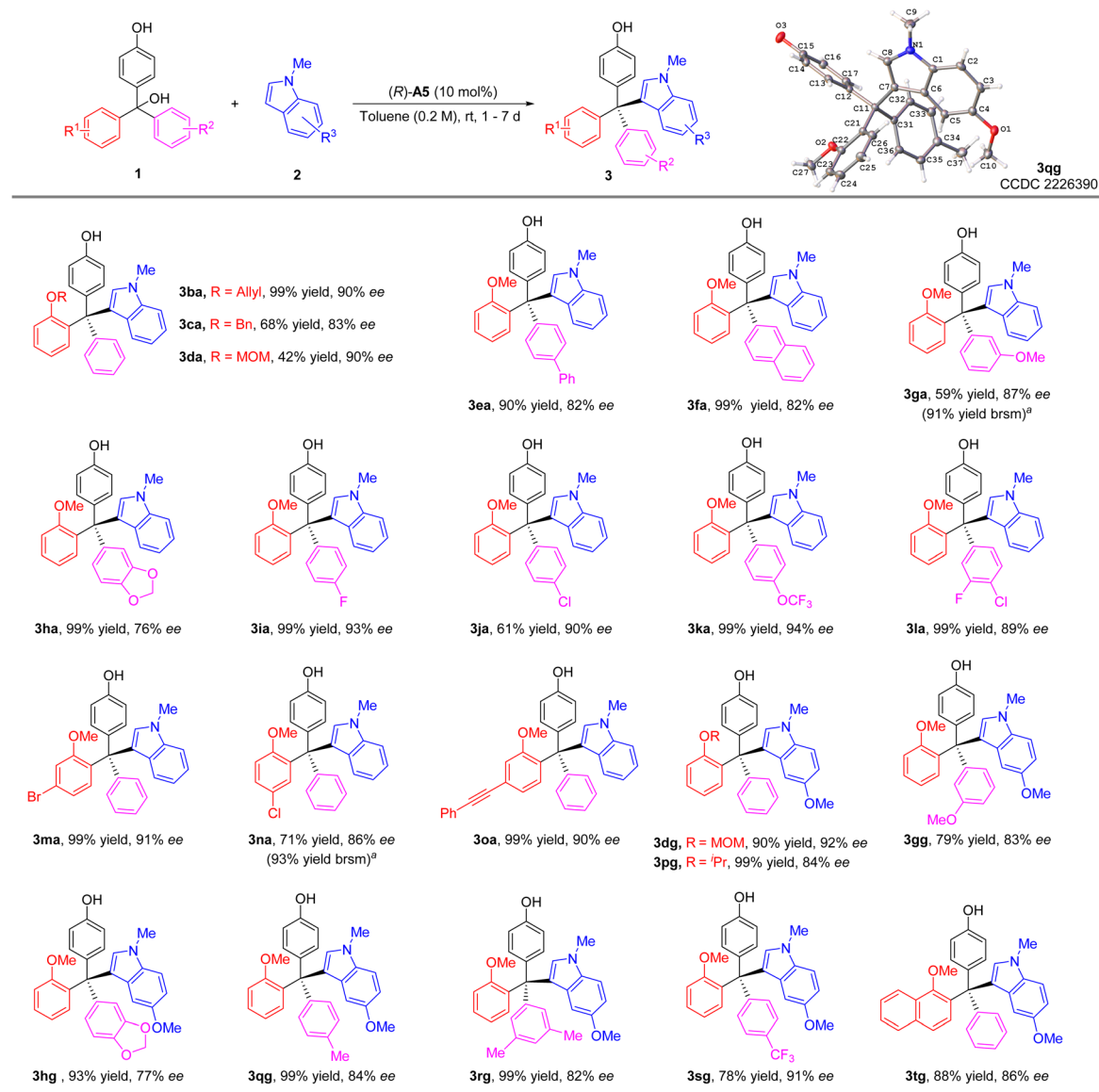
Scheme 2 Scope of *N*-protected indoles **2**. Standard conditions: **1a** (0.3 mmol), *N*-protected indole **2** (0.45 mmol), CPA (10 mol%), solvent (1.5 mL), rt, 1–7 days. Isolated yield. The ee value was determined by chiral HPLC.



Next, we proceeded to examine the nucleophile scope regarding *N*-protected indoles under the standard conditions (Scheme 2). Substitution with various electron-withdrawing or electron-donating substituents at the 5 or 6 position on the *N*-methyl indole skeleton successfully reacted to form the corresponding tetraarylmethane products in essentially quantitative yields and good to excellent enantioselectivities (80–94% ee, Scheme 2, **3ab** – **3ah**). In addition to the methyl group in the *N*-1 position, we also examined the PMB group, which maintained a high ee value, but at a reduced reaction rate.

We then investigated the reaction scope with various substituted triarylmethanols (Scheme 3). Different *ortho*-alkoxy groups, including the methoxymethoxyl (MOMO) group, in one of the aryl groups could serve as the hydrogen bond acceptor for the differentiation between the two aryl substituents on the

methide carbon of the *in situ* generated QM intermediates. The corresponding tetraarylmethane products were all obtained with high ee values (**3aa**–**3da**). Electron-donating substituents on the aryl group resulted in diminished enantioselectivity (**3ea**–**3ha**). However, electron-withdrawing groups were found to be beneficial to enantiocontrol (**3ia**–**3la**). The effect of substituents on the 2-methoxy-substituted phenyl ring was also explored. The corresponding products **3ma**–**3oa** could be synthesized smoothly with good enantioselectivities (86–91% ee). Moreover, 5-methoxy-1-methyl-1*H*-indole **2g** could also serve as a good nucleophile, leading to a range of substrates with diverse substituents in different positions (**3dg**–**3tg**). The low yields of **3ga** and **3na** were due to relatively slow conversion, but the reactions were clean themselves. Notably, in all these cases, the indole nucleophiles lack an obvious hydrogen bond



Scheme 3 Scope of triarylmethanols **1**. Standard conditions: **1a** (0.3 mmol), *N*-protected indole **2** (0.45 mmol), CPA (10 mol%), solvent (1.5 mL), rt, 1–7 days. Isolated yield. The ee value was determined by chiral HPLC. <sup>a</sup>Yield in parentheses was based on recovered starting material.



donor motif, which means the CPA catalyst primarily activates the *p*-QM for the reactivity.

To gain insight into the mechanism, we monitored the ee value of the substrate and product in the standard reaction of **1a** and **2a**. The ee value of **3aa** was essentially constant throughout the reaction. The remained starting material **1a** was kept racemic (Fig. 1). These results are consistent with the involvement of a *p*-QM intermediate and no kinetic resolution of the substrate.

To obtain more information about the key intermediate, we carried out several control experiments (Scheme 4). Firstly, upon protection of the free OH group in the substrate, the reaction of **4a** was completely shut down, suggesting that *p*-QM is likely the key intermediate. The importance of the hydrogen bond acceptor at the *ortho*-position was also investigated by employing substrates **4b** and **4c** bearing a methoxymethyl group and an ethyl group on the *ortho*-position, respectively. These substrates also didn't show reactivity, highlighting the role of the appropriate directing group in this catalytic system. We also evaluated the substrates **4d** and **4e**, in which the methoxy group was installed on the *meta* and *para* position, respectively. Although both transformations proceeded efficiently, the enantiocontrol was poor in both cases. Interestingly, the *ortho*-fluorine group could induce enantiocontrol effectively. The desired product **4fa** was obtained in 99% yield and 82% ee, demonstrating the same role of fluorine as that of the alkoxy group.

DFT studies were performed to gain more insights into the enantiodetermining transition states (Fig. 2). For the sake of computational cost, we employed (*R*)-**A2** (Table 1) as the model catalyst. Based on the computed transition state structures (**TS-S** and **TS-R**), the CPA activation on the *p*-QM intermediate is so strong that almost complete protonation of the carbonyl group can be observed. In contrast, there is no effective activation of the indole nucleophile by the CPA catalyst, which is consistent with our initial proposal. This is also in contrast to previous asymmetric nucleophilic additions to *p*-QMs by CPA catalysis, where strong nucleophile-CPA hydrogen bonding was typically observed. Moreover, during C-C bond formation, the hydrogen atom in the indole 3-position has interaction with the *ortho*-OMe directing group, and this interaction is more effective in **TS-S** than that in **TS-R**. Indeed, **TS-R** suffers great steric repulsion between the methoxy, phenyl group of **1a** and the CPA catalyst, but there is no such steric clash in **TS-S**. These factors

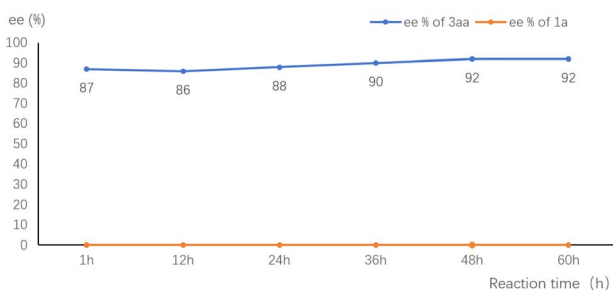
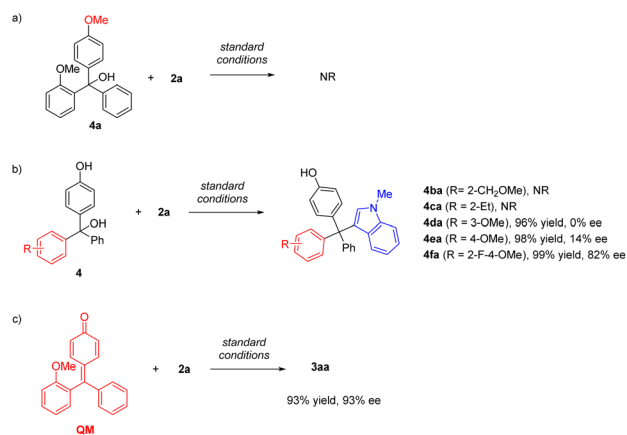


Fig. 1 ee value–time plot of **2a** and **3aa** in the model reaction.



Scheme 4 (a) Control experiment with a methyl-protected substrate. (b) Control experiments with different hydrogen bond acceptors.

are probably responsible for the higher computed energy of **TS-R** than **TS-S** (by 0.8 kcal mol<sup>-1</sup>), which is in qualitative agreement with the experimental outcome.

To further explore the versatility of our method, we selected the chiral product **3ka** as an example for derivatization. The phenolic hydroxyl group was readily transformed to a triflate group, which could be further modified into various functional groups. Under mild conditions, the triflate group of **3ka'** could be removed using Pd/C catalyzed reduction conditions, yielding a new tetraarylmethane **3ka'-1** in quantitative yield and 93% ee. Additionally, with nickel as catalyst, the triflate **3ka'** reacted with a Grignard reagent, PMPMgBr, resulting in the coupling product **3ka'-2** with a high retention of enantiomeric purity (Scheme 5).

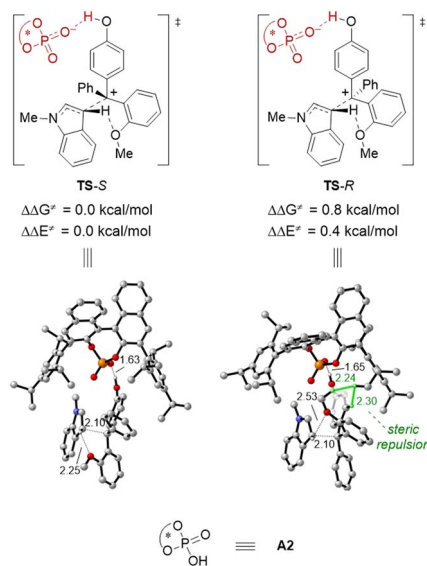
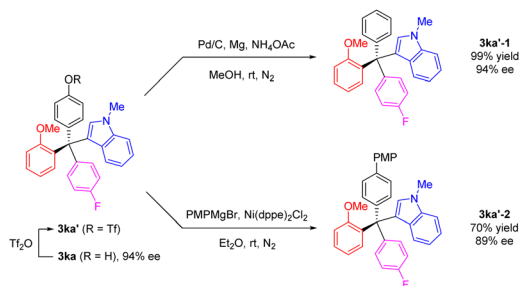


Fig. 2 DFT-optimized enantiodetermining transition states for the reaction of **1a** and **2a** using **A2** as a model catalyst.  $\Delta\Delta G^\ddagger$  and  $\Delta\Delta E^\ddagger$  are relative activation energies. The key values of the geometry structure are given in Å.



Scheme 5 Transformations of indole-based tetraarylmethane **3ka**.

## Conclusions

In conclusion, we have demonstrated an example of primary activation of *para*-quinone methides for their asymmetric nucleophilic addition with the CPA catalytic system. This is in sharp contrast to those previous CPA-based bifunctional activation processes that all required the nucleophiles to have an effective hydrogen bond donor unit (e.g., OH, NH). In the present reaction, *N*-protected indole nucleophiles were proved to be capable of such reactions. Thus, a range of previously inaccessible tetraarylmethanes were synthesized with high efficiency and enantioselectivity under mild conditions. Therefore, this protocol also expanded the power of CPA catalysis as well as the versatility of *p*-QMs in asymmetric synthesis. Further expansion of *p*-QM chemistry by means of sole/primary activation is underway in our laboratory.

## Data availability

Experimental procedures, spectral data and DFT data can be found in the ESI.†

## Author contributions

Jianwei Sun and Zhengyu Han supervised the project and wrote the manuscript. Jianwei Sun conceived the project. Biao Zhu and Yu Zang performed condition optimization, scope study and product derivatizations. Chaoshen Zhang performed DFT studies. Xiu-Qin Dong and Hai Huang conducted scientific discussions. All the authors proofread and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC, 22071210, 22101033, 22201023, and 22271242), the Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110), the Natural Science Foundation of Jiangsu Province (BK20210849), the Jiangsu Province Key Laboratory of Fine Petrochemical

Engineering (KF2102), the Innovation & Entrepreneurship Talents Plan of Jiangsu Province (JSSCRC2021536), and the Science, Technology and Innovation Committee of Shenzhen Municipality (JCYJ20200109141408054).

## Notes and references

- (a) S. E. Rokita, *Quinone Methides*, John Wiley & Sons, Inc., New York, 2009, p. 456; (b) N. J. Willis and C. D. Bray, *Chem.-Eur. J.*, 2012, **18**, 9160–9173; (c) S. Gnaim and D. Shabat, *Acc. Chem. Res.*, 2014, **47**, 2970–2984; (d) Q. Li, T. Dong, X. Liu, X. Zhang, X. Yang and X. Lei, *Curr. Org. Chem.*, 2014, **18**, 86–92; (e) M. S. Singh, A. Nagaraju, N. Anand and S. Chowdhury, *RSC Adv.*, 2014, **4**, 55924–55959.
- For selected reviews, see:(a) L. Caruana, M. Fochi and L. Bernardi, *Molecules*, 2015, **20**, 11733–11764; (b) A. Parra and M. Tortosa, *ChemCatChem*, 2015, **7**, 1524–1526; (c) W. Li, X. Xu, P. Zhang and P. Li, *Chem.-Asian J.*, 2018, **13**, 2350–2359; (d) C. G. S. Lima, F. P. Pauli, D. C. S. Costa, A. S. de Souza, L. S. M. Forezi, V. F. Ferreira and F. de Carvalho da Silva, *Eur. J. Org. Chem.*, 2020, 2650–2692; (e) X. Li, Z. Li and J. Sun, *Nat. Synth.*, 2020, **1**, 426–438.
- For selected reviews and examples to construct quaternary stereogenic centers, see:(a) B. Wang and Y.-Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207–1222; (b) K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191; (c) M. Buschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal and L. E. Overman, *Angew. Chem., Int. Ed.*, 2016, **55**, 4156–4186; (d) X. P. Zeng, Z. Y. Cao, Y. H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330–7396; (e) P. Chen, M. J. Lv, J. K. Cheng, S. H. Xiang, X. Z. Ren, J. Zhang and B. Tan, *Chem. Sci.*, 2023, **14**, 2330–2335.
- For examples with pre-synthesized *p*-QMs, see:(a) W. D. Chu, L. F. Zhang, X. Bao, X. H. Zhao, C. Zeng, J. Y. Du, G. B. Zhang, F. X. Wang, X. Y. Ma and C. A. Fan, *Angew. Chem., Int. Ed.*, 2013, **52**, 9229–9233; (b) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2014, **136**, 15929–15932; (c) Y. Lou, P. Cao, T. Jia, Y. Zhang, M. Wang and J. Liao, *Angew. Chem., Int. Ed.*, 2015, **54**, 12134–12138; (d) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104–12108; (e) K. Zhao, Y. Zhi, A. Wang and D. Enders, *ACS Catal.*, 2016, **6**, 657–660; (f) Y. H. Deng, X. Z. Zhang, K. Y. Yu, X. Yan, J. Y. Du, H. Huang and C. A. Fan, *Chem. Commun.*, 2016, **52**, 4183–4186; (g) C. Ma, Y. Huang and Y. Zhao, *ACS Catal.*, 2016, **6**, 6408–6412; (h) N. Dong, Z. P. Zhang, X. S. Xue, X. Li and J. P. Cheng, *Angew. Chem., Int. Ed.*, 2016, **55**, 1460–1464; (i) S. Li, Y. Liu, B. Huang, T. Zhou, H. Tao, Y. Xiao, L. Liu and J. Zhang, *ACS Catal.*, 2017, **7**, 2805–2809; (j) S. Santra, A. Porey, B. Jana and J. Guin, *Chem. Sci.*, 2018, **9**, 6446–6450; (k) Y. Lu, N. He, X. Miao and D. Wang, *Org. Chem. Front.*, 2022, **9**, 4840–4845; (l) H. H. Li, Y. N. Meng, C. M. Chen, Y. Q. Wang, Z. X. Zhang, Z. Xu, B. Zhou and L. W. Ye, *Sci. China: Chem.*, 2023, **66**, 1467–1473.
- (a) Z. Wang, Y. F. Wong and J. Sun, *Angew. Chem., Int. Ed.*, 2015, **54**, 13711–13714; (b) Z. Wang, F. Ai, Z. Wang,



- W. Zhao, G. Zhu, Z. Lin and J. Sun, *J. Am. Chem. Soc.*, 2015, **137**, 383–389.
- 6 For selected examples of CPA-catalyzed *in situ* generated *p*-QMs, see: (a) Y. F. Wong, Z. Wang and J. Sun, *Org. Biomol. Chem.*, 2016, **14**, 5751–5754; (b) D. Qian, L. Wu, Z. Lin and J. Sun, *Nat. Commun.*, 2017, **8**, 567; (c) M. Chen and J. Sun, *Angew. Chem., Int. Ed.*, 2017, **56**, 11966–11970; (d) W. Li, X. Xu, Y. Liu, H. Gao, Y. Cheng and P. Li, *Org. Lett.*, 2018, **20**, 1142–1145; (e) J. Yan, M. Chen, H. H. Y. Sung, I. D. Williams and J. Sun, *Chem.-Asian J.*, 2018, **13**, 2440–2444; (f) D. Ma, C. B. Miao and J. Sun, *J. Am. Chem. Soc.*, 2019, **141**, 13783–13787; (g) H. Wu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2019, **141**, 11372–11377; (h) X. Li, M. Duan, Z. Deng, Q. Shao, M. Chen, G. Zhu, K. N. Houk and J. Sun, *Nat. Catal.*, 2020, **3**, 1010–1019; (i) Z. Wang, Y. Zhu, X. Pan, G. Wang and L. Liu, *Angew. Chem., Int. Ed.*, 2020, **59**, 3053–3057; (j) Z. Li, Y. Li, X. Li, M. Wu, M. L. He and J. Sun, *Chem. Sci.*, 2021, **12**, 11793–11798; (k) Z. Han, Y. Zang, C. Liu, W. Guo, H. Huang and J. Sun, *Chem. Commun.*, 2022, **58**, 7128–7131; For an example of PTC-catalyzed *in situ* generated *p*-QMs, see: (l) Y. J. Fan, L. Zhou and S. Li, *Org. Chem. Front.*, 2018, **5**, 1820–1824.
- 7 (a) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566–1568; (b) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357; (c) G. Adair, S. Mukherjee and B. List, *Aldrichimica Acta*, 2008, **41**, 31–39; (d) S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190–2201; (e) D. Kampen, C. M. Reisinger and B. List, *Top. Curr. Chem.*, 2010, **291**, 395–456; (f) M. Terada, *Synthesis*, 2010, 1929–1982; (g) J. Yu, F. Shi and L. Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156–1171; (h) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539–4549; (i) M. Terada, *Curr. Org. Chem.*, 2011, **15**, 2227–2256; (j) I. Ćorić, S. Vellalath, S. Müller, X. Cheng and B. List, *Top. Organomet. Chem.*, 2013, **44**, 165–194; (k) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047–9153; (l) C. Zhu, K. Saito, M. Yamanaka and T. Akiyama, *Acc. Chem. Res.*, 2015, **48**, 388–398; (m) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277–9306; (n) T. James, M. van Gemmeren and B. List, *Chem. Rev.*, 2015, **115**, 9388–9409.
- 8 For examples of sole activation of other types of electrophiles by CPA, see: (a) T. Akiyama, Y. Honma, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2008, **350**, 399–402; (b) Y. Xie and B. List, *Angew. Chem., Int. Ed.*, 2017, **56**, 4936–4940; (c) Z. Wang and J. Sun, *Org. Lett.*, 2017, **19**, 2334–2337, For examples of CPA activation of both nucleophile and electrophile, see Ref. 7.
- 9 (a) X. Tan, Z. Deng, Q. Wang, S. Chen, G. Zhu and J. Sun, *Nat. Synth.*, 2023, **2**, 275–285, For another recent work by others on chiral tetraarylmethane synthesis, see: (b) M. Liu, B. Shen, C. Liu, P. Yu and P. Li, *J. Am. Chem. Soc.*, 2023, **145**, 14562–14569.
- 10 (a) S. Schierle, C. Flauaus, P. Heitel, S. Willems, J. Schmidt, A. Kaiser, L. Weizel, T. Goebel, A. S. Kahnt, G. Geisslinger, D. Steinhilber, M. Wurglics, G. E. Rovati, A. Schmidtko, E. Proschak and D. Merk, *J. Med. Chem.*, 2018, **61**, 5758–5764; (b) V. Praveen Kumar, J. Renjitha, C. T. Fathimath Salfeena, K. T. Ashitha, R. S. Keri, S. Varughese and S. B. Somappa, *Chem. Biol. Drug Des.*, 2017, **90**, 703–708; (c) C. Zhang, Y. Qu and B. Niu, *Bioorg. Med. Chem.*, 2016, **24**, 5781–5786; (d) T. V. Sravanthi and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10.
- 11 S. Hoffmann, A. M. Seayad and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 7424–7427.
- 12 W. Yang, Z. Wang and J. Sun, *Angew. Chem., Int. Ed.*, 2016, **55**, 6954–6958.
- 13 X. Cheng, S. Vellalath, R. Goddard and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 15786–15787.

