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Organocatalytic enantioselective conjugate addition of 2-naphthols to *ortho*-hydroxyphenyl substituted *para*-quinone methides: access to unsymmetrical triarylmethanes†

Yuyu Cheng,^a Zhiqiang Fang,^a Yanwen Jia,^a Zhongyue Lu,^a Wenjun Li^{id}*^b and Pengfei Li^{ib}*^aReceived 25th June 2019
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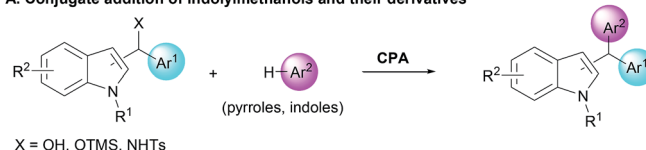
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The enantioselective conjugate addition of 2-naphthols to *ortho*-hydroxyphenyl substituted *para*-quinone methides has been achieved with the aid of a chiral phosphoric acid. Importantly, the reaction took place with excellent chemo- and regioselectivities. In addition, the protocol features a low catalyst loading, mild reaction conditions, and enables the formation of unsymmetrical triarylmethanes in good to high yields with generally high enantioselectivities.

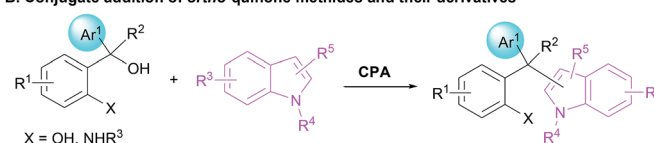
Unsymmetrical triarylmethanes, especially enantiomerically enriched triarylmethanes have been regarded as unique structural frameworks due to their remarkable significance in materials science, natural products, and medicinal chemistry.¹ Accordingly, much effort has been devoted to developing catalytic synthetic methodologies for accessing these motifs,² especially in an enantioselective fashion.³ However, besides limited examples of transition metal-mediated construction of chiral triarylmethanes,⁴ there are only a few organocatalytic enantioselective synthetic strategies,^{5–9} of which most processes focused on transformations of indolylmethanols (Scheme 1A),¹⁰ *in situ* generated *ortho*-quinone methides (*o*-QMs, Scheme 1B),¹¹ and *para*-quinone methides (*p*-QMs, Scheme 1C).¹² On the other hand, triarylmethanes containing the 2-naphthol moiety is a family of biologically active compounds,¹³ but reports on catalytic enantioselective construction of triarylmethanes bearing the 2-naphthol motif are very limited.¹⁴ In 2015, Schneider *et al.* realized the enantioselective construction of chiral triarylmethanes *via* a chiral phosphoric acid (CPA) catalyzed 1,4-addition of 2-naphthol to *o*-QMs generated from *ortho*-hydroxy benzhydrols (Scheme 2A).¹⁵ Similarly, in the presence of squaramide combined with excess base as acid scavenger, Xu *et al.* established an enantioselective 1,4-addition of 2-naphthols to *in situ*

generated *o*-QMs from 2-[phenyl(tosyl)methyl]phenols (Scheme 2B).¹⁶ Independently, Sun *et al.* developed a CPA catalyzed 1,6-addition between 2-naphthols and *p*-QMs *in situ* generated from *para*-hydroxy benzhydrols to construct the optically active triarylmethanes bearing 2-naphthol motif (Scheme 2C).¹⁷ In spite of these elegant approaches, the organocatalytic enantioselective construction of chiral

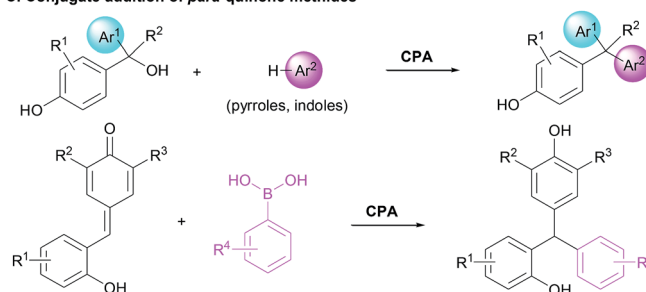
A. Conjugate addition of indolylmethanols and their derivatives



B. Conjugate addition of *ortho*-quinone methides and their derivatives



C. Conjugate addition of *para*-quinone methides

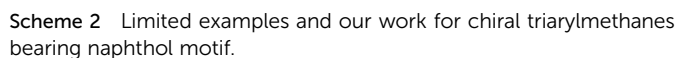


Scheme 1 Organocatalytic enantioselective construction of chiral triarylmethanes.

^aDepartment of Chemistry and Shenzhen Key Laboratory of Marine Archaea Geo-Omics, Southern University of Science and Technology, Shenzhen, Guangdong, 518055, China. E-mail: lipf@sustech.edu.cn; flyli1980@gmail.com

^bDepartment of Medicinal Chemistry, School of Pharmacy, Qingdao University, Qingdao, Shandong, 266021, China. E-mail: liwj@qdu.edu.cn

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Initial investigations were carried out using a series of **CPAs** for the model reaction of 4-(2-hydroxybenzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dienone **1a** with 2-naphthol **2a** in dichloromethane at room temperature for 24 h. As shown in Table 1, with a catalyst loading of 10 mol%, **CPA-1** mediated reaction proceeded smoothly to afford the triarylmethane **3aa** in 81% yield with 5% ee (entry 1). An essential enhancement was achieved when the reaction was catalyzed by **CPA-3**, furnishing **3aa** in 90% yield with 91% ee (entry 3). To our delight, further modification of catalyst structure led to the formation of **3aa** in 95% yield with 94% ee (entry 5). With **CPA-5** as the suitable catalyst, reaction media was screened (entries 7–11). Solvent was found to have a great influence on the reaction efficiency and stereoselectivity, and dichloromethane was identified as the best reaction media. Notably, decreasing the catalyst loading from 10 mol% to 1 mol%, the desired triarylmethane **3aa** was still obtained in 95% yield with 94% ee when the reaction was carried out in CH₂Cl₂ of 1.0 mL at room temperature for 24 h (entry 12). Shorting reaction time

Having optimized the catalyst structure and reaction conditions, we then explored the substrate scope of this organocatalytic enantioselective transformation. Firstly, the generality of 2-naphthols component was evaluated (Table 2). Pleasingly, a wide range of 2-naphthols **2a-h** reacted smoothly with *p*-QM **1a** to afford the corresponding enantioenriched triarylmethanes **3aa-ah** in high yields (70–95%) with excellent enantioselectivities (93–96%). Various different substituents, including electron-withdrawing (Br, CN, CO₂Me, CO₂Et) and electron-donating groups (MeO, EtO) at different positions of the aromatic ring of the 2-naphthols component were tolerated with only slight effects on the reaction efficiency and asymmetric induction. No significant electronic effects were observed for the substituents on the aromatic moiety. Confirmed by the impressive results, the organocatalytic enantioselective conjugate addition of *p*-QMs has been successfully extended to a variety of 2-naphthols and provided an efficient and facile access to optically active triarylmethanes.

Reaction scheme showing the synthesis of CPA-5 and CPA-6. The reaction involves compound 1a (4,4'-di-tert-butyl-2,2'-biphenyl-5,5'-diol) reacting with compound 2a (2-naphthol) in the presence of CPA (10 mol%) in CH₂Cl₂ at room temperature for 24 hours to yield product 3aa. The product 3aa is a dimeric structure where two units of 1a are linked via a central biphenyl unit derived from 2a. The reaction is shown for the synthesis of CPA-5 and CPA-6, which are derivatives of 3aa with different substituents R₁ and R₂.

CPA-1 R¹ = SiPh₃, R² = OH
 CPA-2 R¹ = 3,5-(CF₃)₂C₆H₃, R² = OH
 CPA-3 R¹ = 2,4,6-i-Pr₃C₆H₂, R² = OH
 CPA-4 R¹ = 2,4,6-i-Pr₃C₆H₂, R² = NHTf

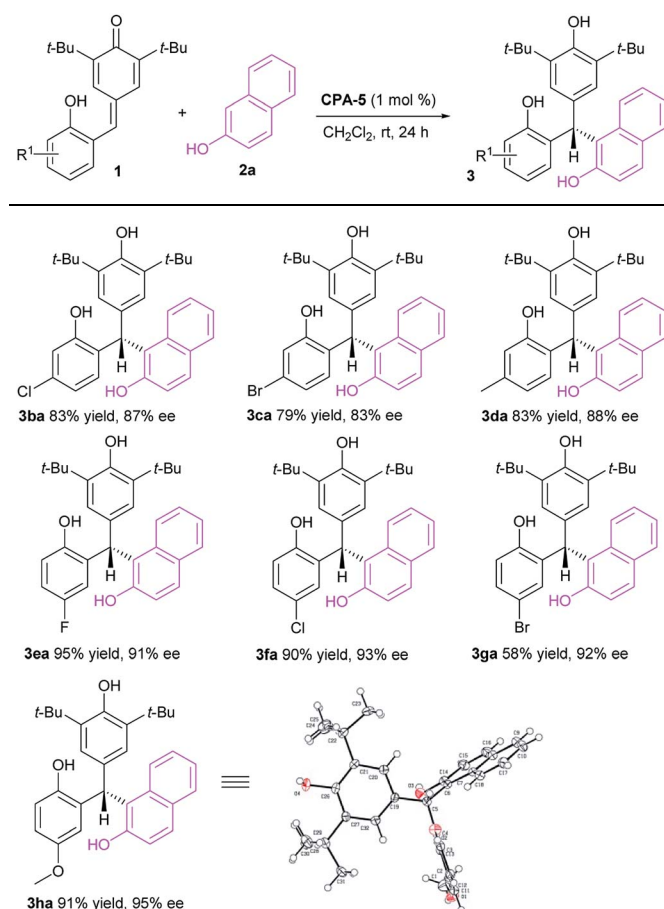
^a Unless noted, **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst (10 mol%) in the solvent (2.0 mL) at room temperature for 24 h. ^b Isolated yield. ^c Determined by HPLC analysis using a chiral stationary phase. ^d **CPA-5** (1 mol%), CH₂Cl₂ (1.0 mL). ^e **CPA-5** (1 mol%), CH₂Cl₂ (1.0 mL), 12 h.

Table 2 Scope of 2-naphthols^a

^a Unless noted, **1a** (0.20 mmol), **2** (0.24 mmol), **CPA-5** (1 mol%) in CH_2Cl_2 (1.0 mL) at room temperature for 24 h. Products **3aa–ah** were obtained in isolated yield and ee values were determined by chiral HPLC analysis.

With these encouraging data in hand, we then investigated the substrate scope of *p*-QMs **1** in the **CPA-5** catalyzed conjugate addition of 2-naphthol **2a** (Table 3). It was found that this strategy was applicable to various *p*-QMs **1b–h** bearing different types of substituents to furnish the corresponding optically active triarylmethanes **3ba–ha** in generally high yields with enantioselectivities. Both electron-withdrawing (F, Cl, Br) and electron-donating groups (Me, MeO) could be introduced into different positions of the aromatic ring of *p*-QMs with a little effect on the reaction efficiency and stereoselectivity. The absolute configuration of **3ha** was unambiguously confirmed by X-ray crystallography.²¹ In all, a broad scope of *p*-QMs has been successfully involved in the organocatalytic conjugate addition of 2-naphthols for the chemo-, regio- and enantioselective construction of chiral triarylmethanes.

To demonstrate the robustness and utility of this synthetic strategy, the scale up of the reaction were carried out (Scheme 3A). The **CPA-5** mediated conjugate reaction of *p*-QM **1a** at 1.0 mmol proceeded well under the standard conditions to generate **3aa** in 82% yield with 93% ee. When

Table 3 Scope of *para*-quinone methides.^a

^a Unless noted, **1** (0.20 mmol), **2a** (0.24 mmol), **CPA-5** (1 mol%) in CH_2Cl_2 (1.0 mL) at room temperature for 24 h. Products **3ba–ha** were obtained in isolated yield and ee values were determined by chiral HPLC analysis.

the reaction was scaled up to 4.5 mmol, the product **3aa** was obtained in 84% yield with 95% ee, which indicated this protocol has the potential for a large-scale production. The reaction of 1-naphthol furnished racemic products in 76% yield under standard conditions (Scheme 3B). The transformation of **3aa** was also investigated. Treated with $\text{PhI}(\text{OAc})_2$, product **4aa** was isolated in 31% yield with 96% ee (Scheme 3C). Then employing **3aa** as ligand in catalytic asymmetric aldol reaction was surveyed. The initial result indicated that the $\text{Ti}(\text{Oi-Pr})_4/\mathbf{3aa}$ system mediated the asymmetric aldol reaction of ZnEt_2 to 2-naphthaldehyde effectively to generate adduct in 59% yield, although the enantioselectivity was low (Scheme 3D).

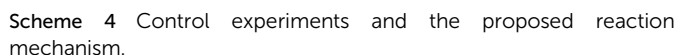
To light some insight into the reaction mechanism, control experiments were carried out (Scheme 4A). When the hydroxyl group of *p*-QM **1a** was shielded by *t*-butyldimethylsilyl (TBS) group (*p*-QM **5a**), the reaction was found to proceed quite slowly and the corresponding product **6aa** was





In conclusion, we have established the enantioselective construction of optically active triarylmethanes bearing naphthol motif *via* a chiral phosphoric acid mediated conjugate addition of 2-naphthols to 2-hydroxyphenyl *p*-QMs. A series of enantioenriched (83–96%) triarylmethanes were obtained in 58–95% yields. Moreover, transformation

A. Control experiments



and application of triarylmethanes were investigated. Further modification of substrates to generate practical chiral triarylmethanes are undergoing in our lab.

Conflicts of interest

There are no conflicts to declare.

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