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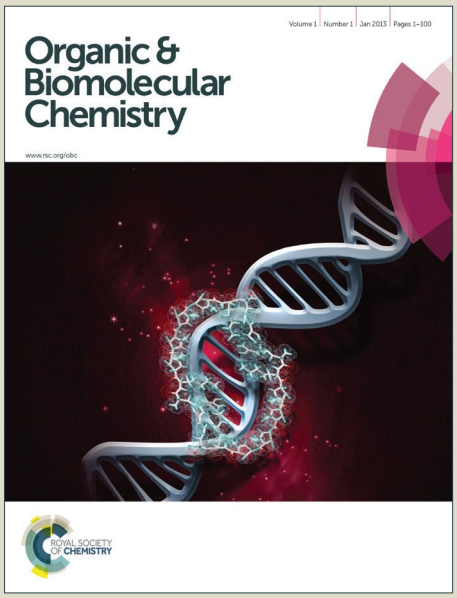

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ARTICLE

Chiral Phosphoric Acid Catalyzed Asymmetric Addition of Naphthols to *para*-Quinone Methides

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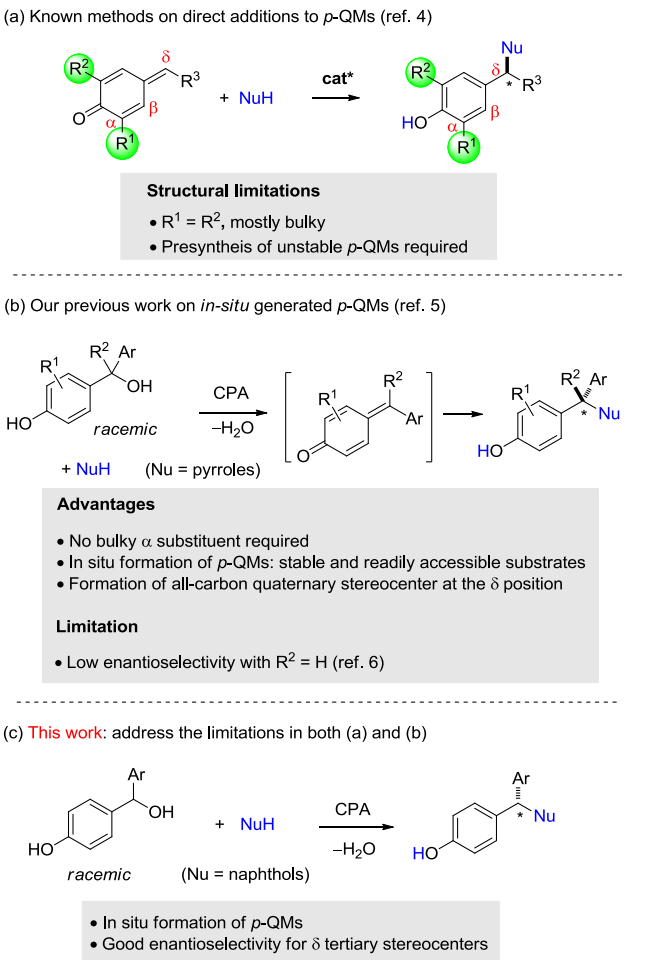
An asymmetric addition of naphthols to in-situ generated para-quinone methides catalyzed by a chiral phosphoric acid is described. A range of useful triarylmethanes can be generated from stable general para-hydroxybenzyl alcohols with good efficiency and enantioselectivity.

Introduction

For more than a century, *para*-quinone methides (*p*-QMs) have been a topic of extensive studies, not only because of their wide occurrence in natural products and biologically important molecules, but also due to their versatility as reactive intermediates in biologically processes and organic synthesis.[1-3] However, despite the long history of these studies, the exploitation of *p*-QMs for asymmetric synthesis has not been well-established. Indeed, highly efficient catalytic asymmetric reactions of *p*-QMs, typically nucleophilic 1,6-additions, have not been realized until very recently.[4-5]

In the past two years, a number of efficient catalytic systems, including metal catalysis and organocatalysis, have been developed for the addition of various nucleophiles to the δ position of *p*-QMs with excellent stereocontrol in the formation of C–C, C–B, and C–S bonds.[4] Notably, a common feature of these methods is the direct use of presynthesized *p*-QM substrates (Scheme 1a). Due to their relative instability, the *p*-QMs substrates employed in these reactions typically bear two bulky substituents (e.g., ^{t}Bu) at the two α positions, which represents a major limitation of these reactions, although the bulky ^{t}Bu substituent has been demonstrated to be removable afterwards.

Recently, we have reported a chiral phosphoric acid catalyzed efficient asymmetric 1,6-addition of pyrroles to a range of *p*-QMs generated in-situ from racemic tertiary *p*-hydroxybenzyl alcohols.[5] The reaction enjoys a broad substrate scope with various substitution patterns. Particular noteworthy is that no bulky substituents at the α positions are required owning to the compatible in-situ generation of *p*-QMs, thus obviating presynthesis of the unstable *p*-QMs. While all-carbon quaternary stereocenters from tertiary alcohols (via δ,δ-disubstituted *p*-QMs) can be generated with excellent efficiency and enantioselectivity, unfortunately this protocol cannot be directly extended to form tertiary stereocenter with high enantioselectivity, i.e., it is not applicable to secondary alcohols (via δ-monosubstituted *p*-QMs).[6] Thus, it represents a different



Scheme 1 Introduction to catalytic symmetric addition to *para*-quinone methides.

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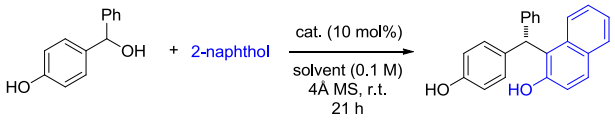
limitation. In continuation of our effort in this area, herein we report the formation of tertiary stereocenters from catalytic asymmetric 1,6-addition of δ-monosubstituted *p*-QMs in situ generated from secondary p-hydroxybenzyl alcohols with good to high enantioselectivity, thereby addressing both limitations in the previous methods (Scheme 1c).

Results and discussion

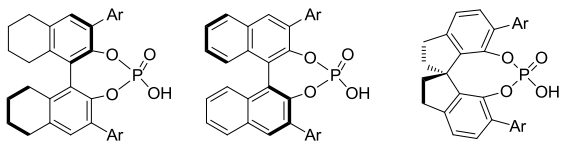
At the outset, we employed *p*-hydroxybenzyl alcohol **1a** as a representative substrate as well as precursor to the corresponding *p*-QM electrophile. With chiral phosphoric acid catalysis,[7-8] a brief survey of different nucleophiles indicated that 2-naphthols might be a family of promising nucleophiles with reasonable reactivity and tunable enantioselectivity.[9] The wide utility of naphthol-containing chiral molecules also prompted us to further optimize this reaction.[10] Careful evaluation of various chiral phosphoric acids indicated that the chiral backbone of the catalyst could affect both product yield and enantioselectivity (Table 1). Among these catalysts, the spirocyclic bis(indane)-derived chiral phosphoric acid **C3** catalyzed the reaction of **1a** and **2a** with the highest enantioselectivity, albeit in moderate yield (entry 8).[11]

Table 1 Reaction condition optimization



1a (*racemic*) **2a** **3a**

entry	cat.	solvent	yield (%)[b]	ee (%)[b]
1	(*R*)-**A1**	Et_2O	3	17
2	(*R*)-**A2**	Et_2O	55	64
3	(*S*)-**B1**	Et_2O	21	–2
4	(*S*)-**B2**	Et_2O	83	–38
5	(*S*)-**B3**	Et_2O	4	–22
6	(*S*)-**C1**	Et_2O	2	32
7	(*S*)-**C2**	Et_2O	23	18
8	(*S*)-**C3**	Et_2O	57	76
9	(*S*)-**C3**	CPME	37	82
10[c]	(*S*)-**C3**	CPME	63	86
11[c,d]	(*S*)-**C3**	CPME	11	68
12[c,e]	(*S*)-**C3**	CPME	93	90



A1: Ar = 9-phenanthryl
A2: Ar = 9-anthryl

B1: Ar = TRIP
B2: Ar = 9-anthryl
B3: Ar = 9-phenanthryl

C1: Ar = TRIP
C2: Ar = 9-phenanthryl
C3: Ar = 9-anthryl

[a] Reaction scale: **1a** (0.1 mmol), **2a** (0.15 mmol), 4Å molecular sieves (20 mg), solvent (1 mL). [b] Yield was determined by ^1H NMR of the crude reaction mixture using CH_2Br_2 as internal standard. Ee value was determined by HPLC with a chiral column. [c] Run for 72 h. [d] Run without 4Å molecular sieves. [e] Run with 80 mg of molecular sieves.

Further solvent screening indicated that cyclopentyl methyl ether (CPME) is a superior solvent with respect to enantioselectivity (entry 9), but the yield was decreased (see the Supporting Information for more details). A longer reaction time (72 h) could slightly improve the yield and enantioselectivity (entry 10). It is worth noting that the use of 4Å molecular sieves is essential to these results. The reaction in the absence of molecular sieves proceeded with disappointingly low efficiency, even with an elongated reaction time (11% yield, entry 11). We reasoned that the molecular sieves might facilitate the generation of the *p*-QM intermediate by efficient removal of the water generated in this step, thereby promoting the subsequent C–C bond formation. With this in mind, we next increased the loading of molecular sieves, which to our delight resulted in both enhanced efficiency and excellent enantioselectivity (93% yield, 90% ee, entry 12).

With the optimized conditions, the substrate scope of the reaction was examined (Table 2). A range of secondary alcohols bearing different substituents, including electron-donating and electron-withdrawing groups, all smoothly participated in the intermolecular C–C formation process with good to excellent efficiency and enantioselectivity. A thiophene-incorporated product could also be formed without accident (**3i**). A range of 2-naphthols are all suitable nucleophiles for the desired products **3j-l**. The mild conditions are compatible with a variety of functional groups, including aryl halides, ethers, thioethers, and silyl-protected alcohols. Notably, in addition to 2-naphthols, the reaction with 1-naphthol as nucleophile also produced the corresponding 1,6-conjugate addition product **3m** in good yield, although the enantioselectivity is moderate. Unfortunately, the use 2-aminonaphthalene as the nucleophile resulted in no 1,6-conjugate addition product formation, presumably due to the high basicity of 2-aminonaphthalene that is enough to deactivate the acid catalyst. Phenol exhibited low reactivity as nucleophile, although C–C bond formation with its *para*-position could be observed. Phenols substituted at the para-position could react with the *ortho*-position, but with low enantioselectivity. Finally, it is worth noting that this process represents a new organocatalytic strategy for the synthesis of triarylmethanes, a family of useful molecules that often have applications as natural products and biologically important molecules as well as functional materials.[12]

As shown in Figure 1, a transition state was proposed to rationalize the role of the catalyst. We believe that the chiral phosphoric acid plays a bifunctional role to activate both the *para*-quinone methide electrophile and the naphthol nucleophile by hydrogen bonding. This tight transition state with the C–C bond-formation taking place in a pseudo-intramolecular mode is in agreement with the observed good reactivity and stereocontrol, particularly considering that the reactive center (the δ position) is relatively remote to the activation site (carbonyl oxygen) of the *p*-QM.

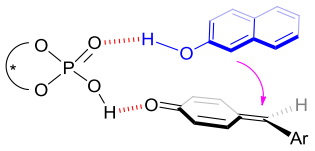
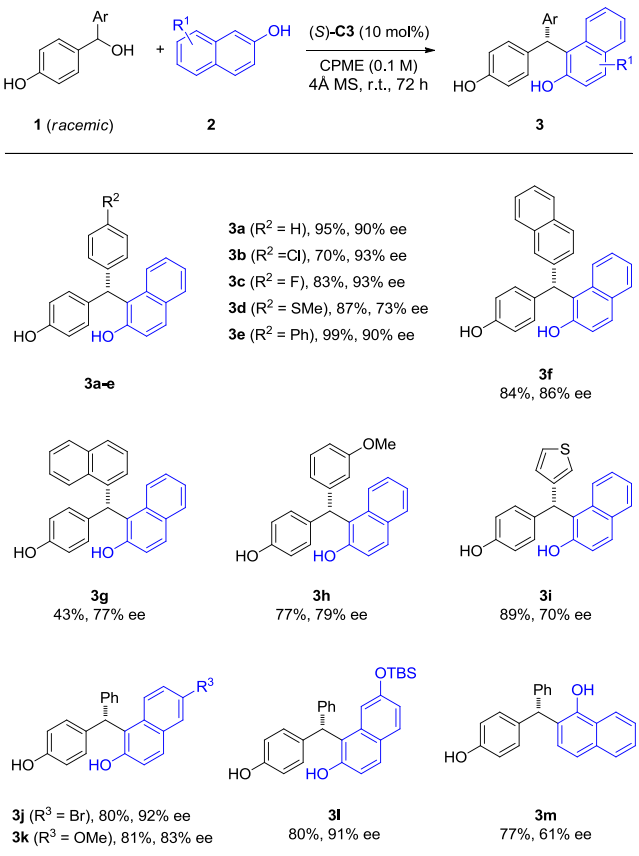


Figure 1 Possible transition state

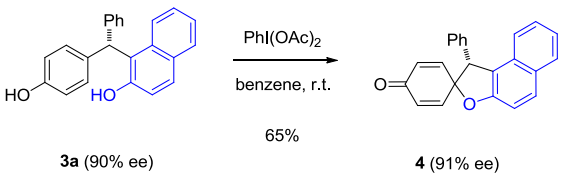
Furthermore, to demonstrate the potential utility of the enantioenriched naphthol-containing triaryl molecules, we carried out a derivatization reaction of the representative product **3a** (Scheme 2). In the presence of $PhI(OAc)_2$, **3a** underwent smooth oxidative cyclization to form the spirocyclic

Table 2 Reaction scope[a]



[a] The yield provided is isolated yield. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), 4Å MS (160 mg), (*S*)-**C3** (5.7 mg, 10 mol%), CPME (2 mL), r.t., 72 h.

cyclohexadienone **4**. Notably, no erosion in enantiomeric excess was observed in the cyclization. Further functionalizations of compound **4** can also be easily envisioned to synthesize other chiral polycyclic molecules.



Scheme 2 Product derivatization.

Conclusions

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In summary, we have developed an efficient organocatalytic enantioselective intermolecular addition of naphthols to in-situ generated *para*-quinone methides. The reaction addressed limitations of existing catalytic asymmetric reactions of *para*-quinone methides, the majority of which directly use the presynthesized unstable *para*-quinone substrates typically bearing bulky α-substituents. Our strategy features compatible acid-catalyzed in-situ generation of *para*-quinone methides, thereby obviating the use of bulky substituents and significantly expanding the substrate scope. The generation of tertiary chiral stereocenter in the useful triarylmethane products is also complementary to our previous method for all-carbon quaternary stereocenter formation with pyrrole addition. Overall, it is a new addition to the under-developed asymmetric reactions of general *para*-quinone methides. Extension of this catalytic systems to other useful nucleophiles are underway in our laboratory.

Acknowledgements

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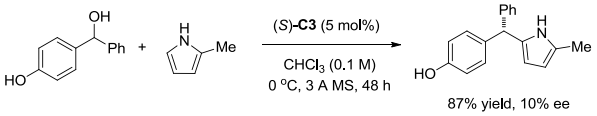

87% yield, 10% ee

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