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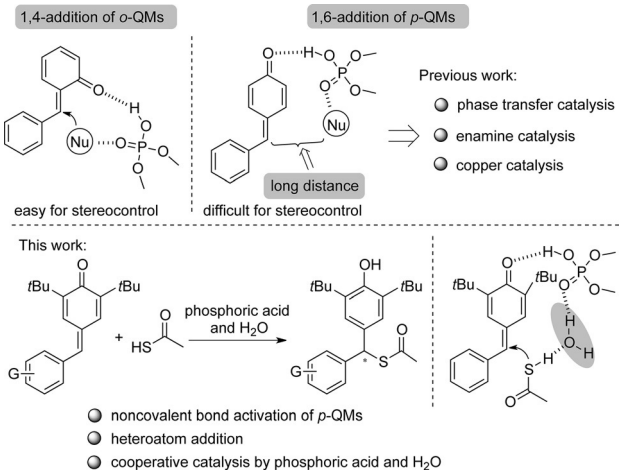
Phosphoric Acid Catalyzed Asymmetric 1,6-Conjugate Addition of Thioacetic Acid to *para*-Quinone Methides

Nan Dong, Zhi-Pei Zhang, Xiao-Song Xue, Xin Li, and Jin-Pei Cheng*

Abstract: *An asymmetric 1,6-conjugate addition of thioacetic acid with para-quinone methides has been developed by using chiral phosphoric acid catalysis in the presence of water. A series of sulfur-containing compounds were thus obtained in high yields with good to excellent enantioselectivities. Theoretical studies indicated that the water-bridged proton transfer is a potentially favorable reaction pathway. An unprecedented O−H···π interaction between water and the aromatic nucleus of chiral phosphoric acid was discovered to contribute significantly to the stereocontrol in the catalysis.*

Enantiomerically pure sulfur-containing compounds constitute an important class of chiral ligands, auxiliaries, and synthetic intermediates in organic chemistry.[1] Moreover, many chiral sulfur-containing molecules also exhibit pharmaceutical activities.[2] Several asymmetric sulfenylations at the α-position of carbonyl compounds with different electrophilic sulfur reagents have been successfully accomplished.[3] In contrast, asymmetric conjugate addition reactions with thiols or thioacetic acids as donors is a valuable method for the preparation of chiral sulfur-containing compounds.[4] However, unlike the well-developed 1,4-addition, examples of asymmetric 1,6-conjugate addition for sulfur-type nucleophiles are rare.[5]

Recently, *ortho*-quinone methides (*o*-QMs) have been extensively studied in catalytic enantioselective processes.[6,7] To our surprise, *para*-quinone methides (*p*-QMs), which are structural isomers of *o*-QMs and have been employed in the synthesis of natural products and bioactive molecules,[8] have been scarcely investigated in catalytic asymmetric transformations. It may be due to the fact that the distance and space position between the carbonyl and carbon–carbon double bond of *p*-QMs are not favorable for stereocontrol (Scheme 1). To date, only very limited examples of enantioselective additions of *p*-QMs have been documented.[9,10] In 2013, Fan and co-workers realized a catalytic asymmetric 1,6-conjugate addition of *p*-QMs with malonates under phase-transfer catalysis.[9a] Shortly afterwards, Jørgensen described a new organocatalytic concept for asymmetric α-alkylation of aldehydes by 1,6-conjugate addition of enamines to *p*-QMs.[9b]



Scheme 1. Strategies for 1,6-conjugate addition of *p*-QMs.

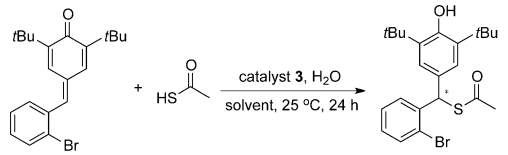
Very recently, Liao and co-workers reported an enantioselective copper-catalyzed 1,6-conjugate addition of bis(pinacolato)diboron to *p*-QMs.[9c] It is noteworthy that 1) the three aforementioned cases all involve covalent bond activation and 2) the activation of *p*-QMs is not involved in the catalysis. During the preparation of our manuscript, Sun and co-workers developed a catalytic asymmetric 1,6-conjugate addition of *p*-QMs through chiral Brønsted acid catalysis.[9d] Their process used in situ generated *p*-QMs as electrophiles, and expanded the scope to general *p*-QMs with various substitutions. Herein, we report a chiral phosphoric acid catalyzed asymmetric 1,6-conjugate addition of thioacetic acid to *p*-QMs (Scheme 1). The challenging remote stereocontrol was successfully solved by the synergistic combination of phosphoric acid and water. As a result, a number of chiral sulfur-containing diphenylmethane-type compounds, which are the core frameworks of bioactive molecules, were synthesized with high enantioselectivities.[11]

Our initial investigation was performed with the *p*-QM **1a**, thioacetic acid (**2a**), the phosphoric acid **3a** (1 mol%), and 10 mol% H_2O in toluene at 25 °C (Table 1). The choice of the phosphoric acid[12] could be assigned to the following facts: 1) Phosphoric acids have been verified as efficient catalysts for the 1,4-conjugate addition of *o*-QMs and 2) Recent work from the group of List demonstrated that thiocarboxylic acids could be activated by phosphoric acid.[13] To our delight, the desired product was obtained in excellent yield with a moderate e.r. value (entry 1). We then examined other chiral phosphoric acid catalysts. As a result, the catalyst **3e**, with a 3,3′-substituted anthryl scaffold, promoted the reaction at 25 °C, thus delivering the desired product in 92.5:7.5 e.r., and it was selected for further optimization

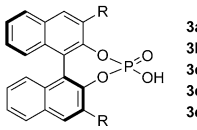
[*] N. Dong, Z.-P. Zhang, Dr. X.-S. Xue, Prof. X. Li, Prof. J.-P. Cheng
State key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Department of Chemistry (Tianjin), Nankai University
Tianjin 300071 (China)
E-mail: xin_li@nankai.edu.cn

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201509110.

Table 1: Optimization of the reaction conditions.[a]



catalyst:

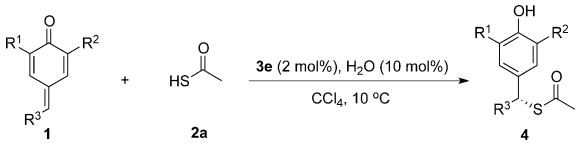


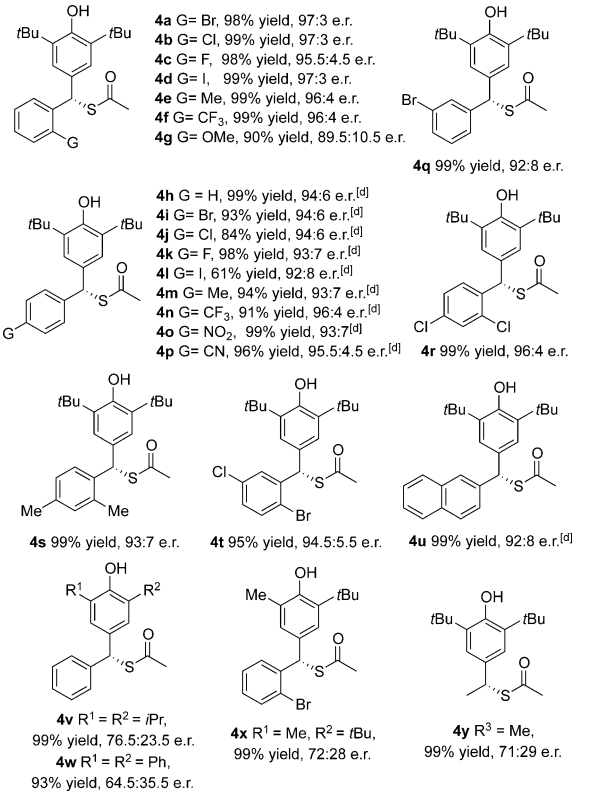
3a, R = 3,5-$(CF_3)_2C_6H_3$
3b, R = 2-naphthyl
3c, R = 2,4,6-$i Pr_3C_6H_2$
3d, R = 4-phenyl-C_6H_4
3e, R = 9-anthryl

Entry	Catalyst	H_2O	Solvent	Yield [%][b]	e.r.[c]
1	**3a**	10 mol %	toluene	98	61:39
2	**3b**	10 mol %	toluene	98	57:43
3	**3c**	10 mol %	toluene	44	64.5:35.5
4	**3d**	10 mol %	toluene	80	53:47
5	**3e**	10 mol %	toluene	94	92.5:7.5
6	**3e**	10 mol %	*p*-xylene	85	68:32
7	**3e**	10 mol %	mesitylene	85	91:9
8	**3e**	10 mol %	CCl_4	99	96.5:3.5
9	**3e**	10 mol %	DCM	94	91.5:8.5
10	**3e**	10 mol %	*n*-hexane	99	95.5:4.5
11	**3e**	–	CCl_4	99	69:31
12	**3e**	3Å M.S.	CCl_4	71	51:49
13	**3e**	2 mol %	CCl_4	94	96:4
14	**3e**	20 mol %	CCl_4	98	96:4
15[d]	**3e**	10 mol %	CCl_4	99	96.5:3.5
16[d,e]	**3e**	10 mol %	CCl_4	98	97:3

[a] The reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol), H_2O, and 1 mol% catalyst in 1 mL solvent at 25°C. [b] Yield of isolated products. [c] Determined by HPLC analysis. [d] 2 mol % catalyst was used. [e] The reaction was performed at 10°C and the reaction time was extended to 60 h. DCM = dichloromethane, M.S. = molecular sieves.

Table 2: Substrate scope with respect to the *p*-QMs.[a–c]



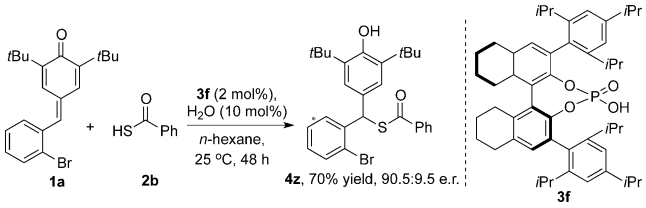


[a] The reactions were carried out with **1** (0.1 mmol), **2a** (0.2 mmol), H_2O (0.01 mmol), and 2 mol% **3e** in 1 mL CCl_4 at 10°C for 10 min–60 h. [b] Yield of the isolated product. [c] The e.r. values were determined by HPLC analysis. The absolute configuration of the product was determined by X-ray analysis of **4a**.[14] [d] 5 mol% **3e** and 20 mol% H_2O were used at −20°C for 1–120 h.[15]

(entry 5). Screening of the solvent revealed that the reaction was favored by CCl_4 (entry 8). Several control experiments were carried out to investigate the role of water. Moderate enantioselectivity was obtained without the water additive, while almost racemic **4a** was obtained when water was replaced by molecular sieves (entries 11 and 12). These results indicated that water is essential for the stereocontrol. After further screening of other reaction parameters, the optimal reaction conditions were finally selected to be 2 mol% **3e** and 10 mol% H_2O in CCl_4 at 10°C, which gave **4a** in 98% yield with 97:3 e.r. (entry 16).

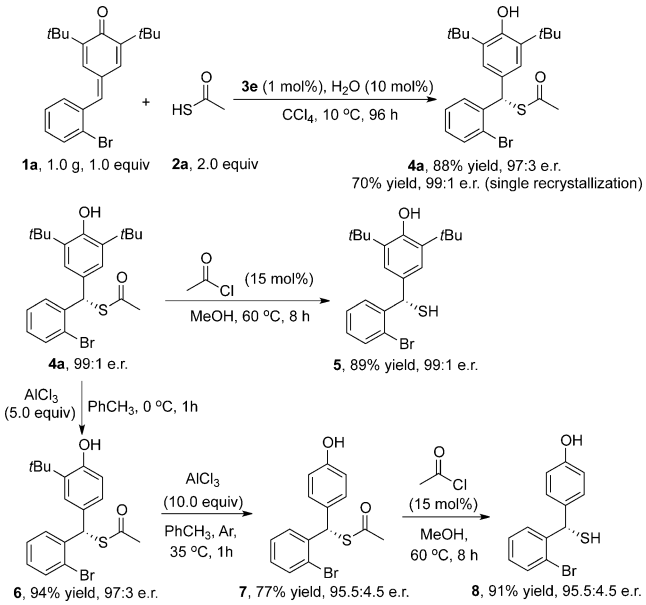
We next examined the scope of the various chemically stable *p*-QMs under the optimized reaction conditions. For 4-substituted *p*-QMs, the optimal reaction conditions are slightly different, in which the reaction was conducted with 5 mol% catalyst and 20 mol% H_2O at −20°C.[15] As shown in Table 2, the 1,6-conjugate addition products **4a–u** were obtained in high yields with good to excellent enantioselectivities. Better stereocontrol was observed for 2-substituted *p*-QMs (**4a–g**) over 3- or 4-substituted substrates (**4h–q**). Further examination of the data revealed that the electronic nature of the substituents on the aromatic ring of the *p*-QMs dramatically influences the enantioselectivities. As for 2-substituted *p*-QMs, the e.r. values of the products containing electron-neutral and electron-deficient aryls all showed excellent e.r. values (**4a–f**). In contrast, the enantioselectivity of the 2-MeO-substituted product **4g** was relatively low. Some doubly-substituted and naphthyl-substituted *p*-QMs also showed very good reactivities and enantioselectivities (**4r–u**). Furthermore, the substrates with the less bulky substituents at C2 and C6 of **1** also worked with this 1,6-conjugate addition strategy, and moderate e.r. values were obtained for the desired products (**4v** and **4w**). When the substrate was a nonsymmetric *p*-QM, moderate enantioselectivity was obtained (**4x**).[16] In addition, the substrate with a methyl substituent (R^3) was also attempted, and the 1,6-conjugate addition product **4y** was obtained in 99% yield with 71:29 e.r.

To further enlarge the substrate scope, thiobenzoic acid (**2b**) was examined as nucleophile.[17] As shown in Scheme 2, under the catalysis by **3f**, the 1,6-conjugate addition strategy worked with **2b**, thus giving the desired product **4z** in 70% yield with 90.5:9.5 e.r.



Scheme 2. 1,6-Conjugate addition of thiobenzoic acid (**2b**) and *p*-QM.

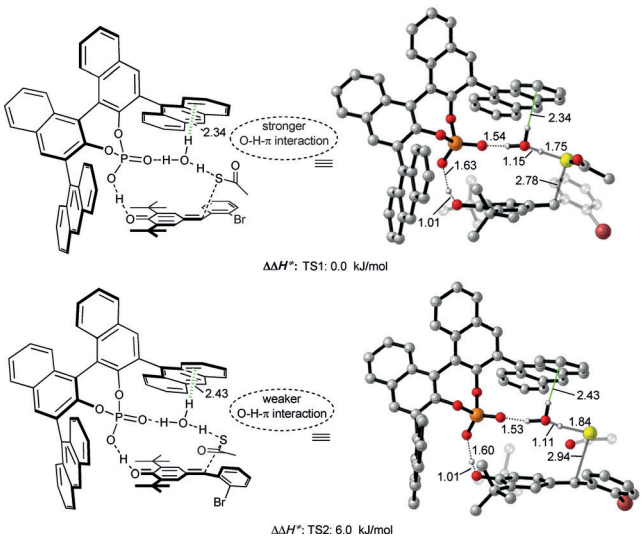
To probe the efficiency of current asymmetric 1,6-conjugate addition strategy in preparative synthesis, a gram-scale reaction of **1a** and **2a** were investigated with only 1 mol% **3e** under the optimal reaction conditions



Scheme 3. Gram-scale reaction and transformation of the product.

(Scheme 3). To our delight, the desired product **4a** was obtained without any loss of enantioselectivity (97:3 e.r.). The e.r. value further increased to 99:1 after a single recrystallization. Deacetylation of **4a** by treatment with acetyl chloride generated the chiral thiol **5** in 89% yield and the 99:1 e.r. value was maintained. Notably, most of substrates studied were 2,6-di-*tert*-butyl *p*-QMs because of their facile synthesis and inherent stability,[18] and thus weakened the synthetic value of the 1,6-conjugate addition strategy. To overcome this shortcoming, a stepwise $AlCl_3$-mediated de-*tert*-butylation of **4a** was attempted and afforded **7** in 72% yield over two steps with a slight loss of enantioselectivity (Scheme 3). The compound **7** can also be deacetylated by treatment with acetyl chloride. As a result, the chiral **8** was obtained and the 95.5:4.5 e.r. was maintained.

Based on previous studies on the reaction mechanism of water participation,[19] we suspected that water may be involved in the transition state (TS) as the hydrogen bond bridging molecule in the current 1,6-addition system. Indeed,



Scheme 4. Computed relative energies in enthalpy and geometries for the enantiocontrolling TS. Most hydrogen atoms have been removed for clarity.

the DFT calculated enantiocontrolling TS structures do support our hypothetical mechanism (Scheme 4).[20] Interestingly, it was found that the water molecule not only acts as a shuttle to transfer a proton from thioacetic acid to phosphoric acid during the 1,6-conjugate addition, but also hydrogen interacts with the aromatic nucleus of the phosphoric acid catalyst through a O-H···π interaction to stabilize the TSs.[19d,21] Closer scrutiny of the TS structures reveals that the O-H···π interaction in TS1 should be stronger than that in TS2, and should be the key factor inducing the enantioselectivity. Notably, the calculated enantioselectivity based on the water-bridged 1,6-conjugate addition was 92:8 e.r. in favor of the *S*-configured product, and is in good agreement with the experimental result.

In summary, we have developed a highly enantioselective 1,6-conjugate addition of thioacetic acid and *p*-QMs by using chiral phosphoric acid catalysis. A number of chiral sulfur-containing diphenylmethane-type compounds were synthesized in high yields and enantioselectivities. The addition of water has proven to be critical to the stereoselectivity. Further calculations indicated a potentially favorable pathway through the water-bridged proton transfer. Moreover, an unprecedented O-H···π interaction between H_2O and the aromatic nucleus of the catalyst was discovered to have a significant contribution to the stereocontrol.

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Keywords: asymmetric catalysis · conjugation · organocatalysis · quinones · sulfur

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[15] For the conditions of screening 4-substituted *p*-QM substrates, see Table S2 in the Supporting Information.

[16] The nonsymmetric *p*-QM used to prepare **4x** was a mixture of stereoisomers with 5:1 d.r.

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