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CuH-Catalyzed Asymmetric 1,6-Conjugate Reduction of *p*-Quinone Methides: Enantioselective Synthesis of Triarylmethanes and 1,1,2-Triarylethanes

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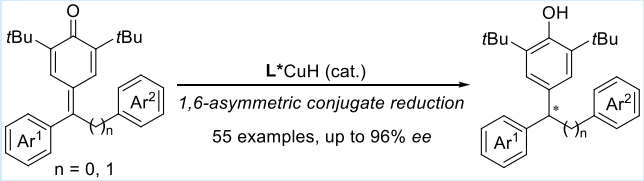
Supporting Information

ABSTRACT: The first copper hydride (CuH)-catalyzed asymmetric 1,6-conjugate reduction of *p*-quinone methides is reported. This protocol provides a new method to access a variety of triarylmethanes and 1,1,2-triarylethanes in good yields with excellent enantioselectivities and broad functional group tolerance.

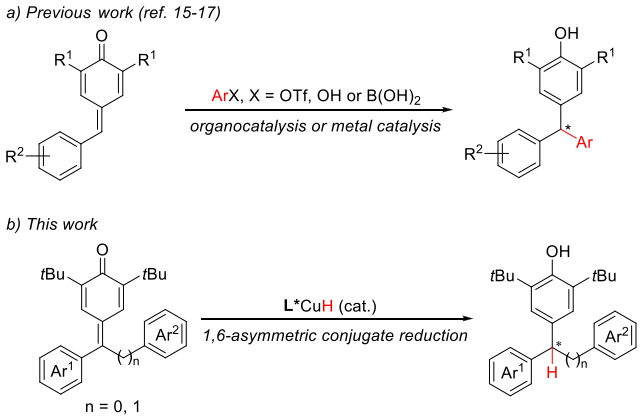


Because of the use of inexpensive metals, the mild reaction conditions and the operational simplicity, the application of nonracemically ligated CuH in asymmetric hydrosilylation reactions has drawn much attention during the last two decades.[1] In particular, CuH-catalyzed asymmetric reduction of ketones,[2] imines,[3] and enantioselective 1,4-reduction of α,β-unsaturated Michael acceptors[4] has been well-developed. However, CuH-catalyzed asymmetric 1,6-conjugate reduction, to the best of our knowledge, has not been reported yet.

Triarylmethanes are important molecules owing to their high utility in medicinal chemistry, materials science, and organic synthesis.[5] Although there are a number of methods available for the synthesis of racemic triarylmethanes,[6] the preparation of optically active derivatives remains a distinct challenge.[7] The classic approach for the synthesis of chiral triarylmethanes relies on stereospecific cross-coupling.[8] There are only a few approaches reported starting from racemic compounds, including Friedel−Crafts alkylation of electron-rich arenes,[9] transition-metal-catalyzed aryl addition,[10] desymmetrization of achiral triarylmethanes,[11] and enantioselective functionalization of C(sp^3)−H bonds.[12] These successful examples mostly focused on the C−C bond formation; however, there has been no report on the C−H bond formation.

Recently, as an important and readily available class of synthetic intermediates, *p*-quinone methides (*p*-QMs) have been extensively used to construct chiral diarylmethane compounds through 1,6-conjugate addition.[13] However, their applications in the synthesis of chiral triarylmethanes have been rarely investigated.[14] Liao, Sun, and Weng's groups independently reported organo or metal-catalyzed asymmetric 1,6-conjugate addition of aryl compounds to *p*-QMs for the preparation of chiral triarylmethanes directly or indirectly (Scheme 1a).[15−17] Although these are big advances, there are still limitations, for example, the requirement of multiple steps and limited scopes. We hypothesize that asymmetric reduction of unsymmetrical diaryl-substituted *p*-QMs can potentially serve as an attractive approach for the synthesis of enantioenriched triarylmethanes. However, by now, no relative experiment has reported. Because of the hardship in distinguishing two enantiotopic faces in prochiral substrates, this project is still an ultimate challenge. It occurred to us that placement of the coordinated chloro group, which can undergo further transformations such as cross-coupling reactions, at the

Scheme 1. Synthesis of Chiral Triarylmethanes through 1,6-Asymmetric Conjugate Addition of *p*-QMs



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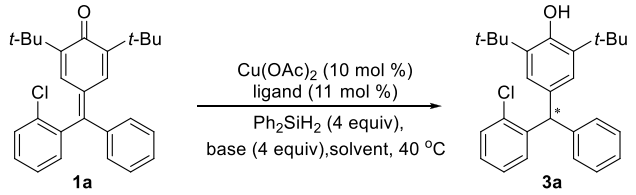
ortho-position of one arene might result in sufficient asymmetric bias in the transition state. Herein, we report the first CuH-catalyzed asymmetric 1,6-conjugate reduction of *p*-QMs as an approach to obtain enantiomerically enriched triarylmethanes and 1,1,2-triarylethanes (Scheme 1b).

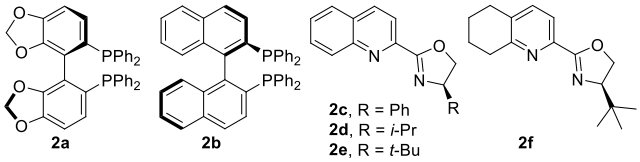
We embarked on this study with ligand screening by using *o*-Cl-substituted *p*-QM **1a** as the model substrate, Ph_2SiH_2 as the hydride source, K_2CO_3 as the base, and $Cu(OAc)_2$ as the catalyst (Table 1). Triarylmethane **3a** was formed with poor

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent	base	yield[b] (%)	ee[c] (%)
1	**2a**	*n*-hexane	K_2CO_3	16	−10
2	**2b**	*n*-hexane	K_2CO_3	13	−9
3	**2c**	*n*-hexane	K_2CO_3	42	51
4	**2d**	*n*-hexane	K_2CO_3	48	65
5	**2e**	*n*-hexane	K_2CO_3	95	79
6	**2f**	*n*-hexane	K_2CO_3	98	84
7	**2f**	cyclohexane	K_2CO_3	86	52
8	**2f**	*n*-pentane	K_2CO_3	88	83
9	**2f**	CH_2Cl_2	K_2CO_3	15	80
10	**2f**	EtOAc	K_2CO_3	84	42
11	**2f**	THF	K_2CO_3	trace	
12	**2f**	*n*-hexane	LiO*t*Bu	26	83
13	**2f**	*n*-hexane	Na_2CO_3	98	86
14[d]	**2f**	*n*-hexane	Na_2CO_3	95	90

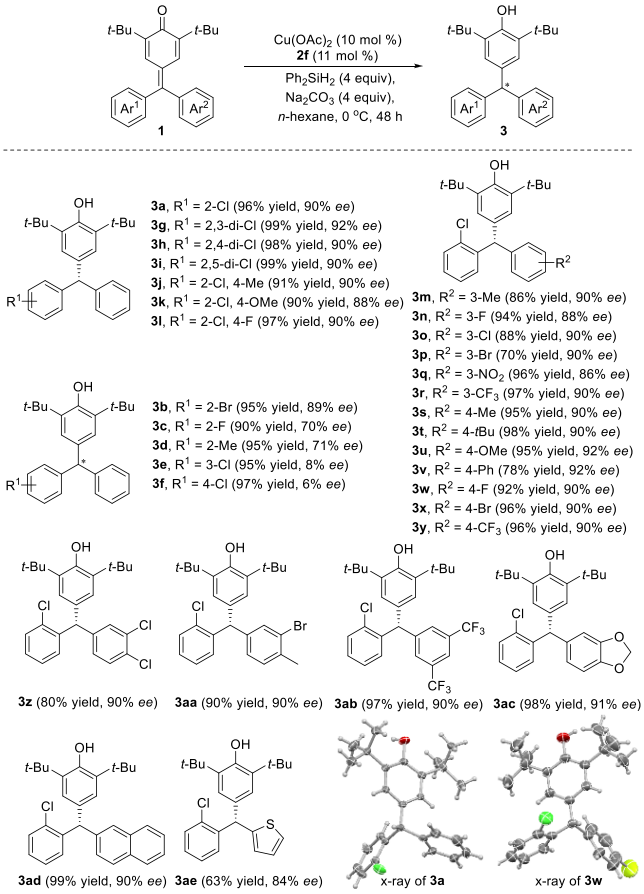
[a]Conditions: *p*-QM **1a** (0.1 mmol), copper(II) acetate (0.01 mmol), ligand (0.011 mmol), diphenylsilane (0.4 mmol), base (0.4 mmol) in solvent (4 mL). [b]Isolated yields. [c]Enantiomeric excess was determined by HPLC analysis on commercial chiral columns. [d]The reaction was carried out at 0 °C.



conversion and enantioselectivity with bisphosphine ligand **2a** or **2b** (entries 1 and 2). The oxazoline ligand **2c** resulted in moderate enantioselectivity (entry 3). We found that the use of ligands **2c−e**, which bear more bulky substituents on the oxazole ring, led to higher enantioselectivity (up to 79% ee and 95% yield, entries 3−5). When tetrahydroquinoline-based **2f** was used, 84% ee was obtained (entry 6). Next, solvent and base effects were examined. *n*-Hexane and Na_2CO_3 were identified as the best combination for this reaction (entries 6−13). To our delight, the enantioselectivity was increased to 90% while the temperature was lowered to 0 °C (entry 14).

With the optimal reaction conditions in hand, we proceeded to study the reaction scope. A range of *ortho*-substituted *p*-QMs (**1a−d**) were transformed to the corresponding triarylmethanes in excellent yields with moderate to high ee values (Scheme 2). The introduction of a more electron-withdrawing *o*-chloro or *o*-bromo unit resulted in higher enantioselectivity (**3a**,**b** versus **3d**). However, as expected, *meta*- and *para*-

Scheme 2. Scope of Triarylmethanes[a]



[a]0.1 mmol scale. Yield of isolated product **3**. ee determined by HPLC analysis. See the SI for more details.

substituted *p*-QMs were reduced to the triarylmethanes **3e**,**f** with low enantioselectivities. In addition, disubstituted substrates **1g−l**, including 2,3-dichloro, 2,4-dichloro, 2,5-dichloro, 2-chloro-4-methyl, 2-chloro-4-methoxyl, and 2-chloro-4-fluoro units, were all readily converted at the present conditions. Next, the substituent effect on the second benzene core was examined. *p*-QMs that contained *meta*- or *para*-substituted electron-rich or electron-deficient aryl groups all underwent facile hydrosilylation, providing the corresponding triarylmethanes **3m−y** with similarly high levels of enantioselectivity. The absolute configurations of **3a** and **3w** were unambiguously established by X-ray crystallographic analysis. Substrates with disubstituted aryl groups were also good partners to generate **3z−ac** in 90−91% ee. Interestingly, 2-naphthyl and heterocyclic substituted *p*-QMs were also amenable to this protocol to give the corresponding products **3ad−ae** with 90% ee and 84% ee, respectively.

Furthermore, the hydrosilylation of benzyl-substituted *p*-QMs was investigated to provide chiral 1,1,2-triarylethanes, which are fundamental structural motifs present in numerous bioactive compounds and drugs (Figure 1).[18,19] In this case, SEGPHOS **2a** gave the best selectivities under similar conditions (Scheme 3).[20] A series of *p*-QMs **4a−l** bearing electron-rich, -deficient or -neutral aromatic substituents readily proceeded to afford the corresponding 1,1,2-triarylethanes **5a−l** in 90−96% ee and 80−98% yield. Substrates containing heterocycles (**4m**,**n**) and multisubstituted aryl (**4o**)

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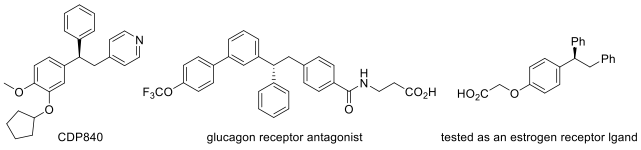
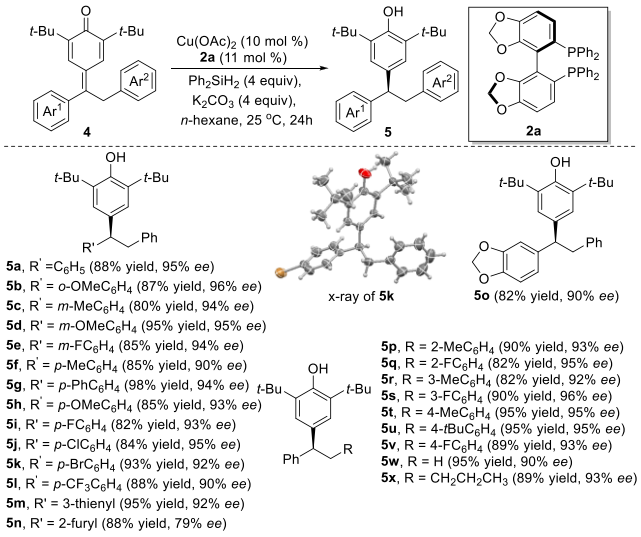


Figure 1. 1,1,2-Triarylethanes target molecules.

Scheme 3. Scope of 1,1,2-Triarylethanes[a]



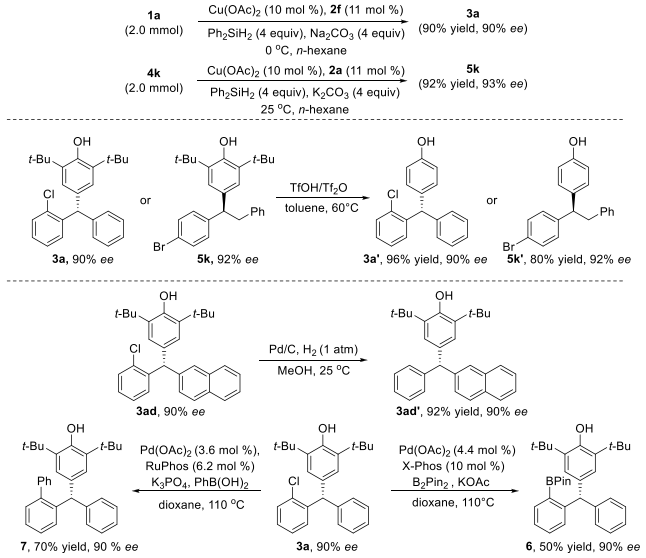
[a]0.1 mmol scale. Yield of isolated product **5**. ee determined by HPLC analysis. See the SI for more details.

were all smoothly reacted with CuH under the current conditions. The absolute configuration of (*S*)-**5k** was unambiguously established by X-ray crystallographic analysis. In addition, the influence of substituents on the phenyl rings of benzyls was investigated. The reactions with *p*-QMs **4p-v** bearing a variety of substituents on the aromatic rings all readily converted to give the desired 1,1,2-triarylethanes **5p−v** in 92−96% ee. Finally, the reaction could also be extended to methyl and butyl substituents, and the corresponding products could be obtained in 90% ee (**5w**) and 93% ee (**5x**), respectively.

The synthetic potential of this strategy could be established by performing scale-up experiments and postfunctionalization reactions (Scheme 4). When starting from **1a** or **4k** (2.0 mmol), the gram-scale preparation of **3a** or **5k** could be performed without a major impact on either reaction yield or enantioselectivity. By treating **3a** or **5k** with a mixture of Tf_2O and TfOH in toluene, the de-*tert*-butylation products **3a′** and **5k′** were obtained in excellent yields without a loss of stereoselectivity. Additionally, when undergoing further palladium-catalyzed reactions, the chloro group could transform to the desired dechlorinated, phenylated, and boronated products in moderate to excellent yields.

A plausible stereocontrol model is shown in Figure 2. Two transition structures **I** and **II**, in which the π-stacking interactions between the tetrahydroquinoline moiety and phenyl group might be involved, are respectively shown to result in the triarylmethane with (*S*) and (*R*) configurations. Structure **I** is energetically more favored than **II** owing to the steric repulsion existed in **II** between the tertiary butyl group of the oxazoline ligand **2f** and the *o*-Cl phenyl group of the *p*-QM

Scheme 4. Scale-up Experiments and Post-Functionalization Reactions



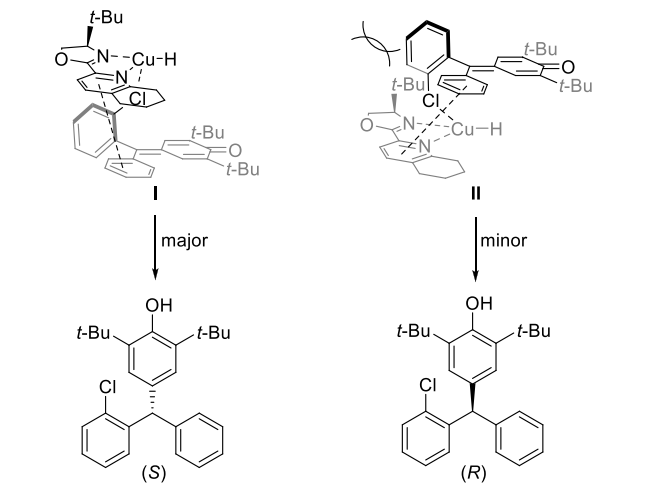


Figure 2. Rationale for enantioselection.

1a. Thus, (*S*)-configured triarylmethane was afforded in a large excess.

In conclusion, we have developed the first CuH-catalyzed asymmetric 1,6-conjugate reduction of *p*-QMs. It provided chiral triarylmethanes and 1,1,2-triarylethanes in good yields (up to 99%) with excellent enantioselectivities (up to 96% ee). A unique *o*-chloride effect was viewed in the synthesis of triarylmethanes, which led to high enantioselectivity. This approach afforded a potential alternative to prepare a variety of chiral triarylmethanes due to its easy removal and further transformations of the chloro group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02308.

Detailed experimental procedures, spectral data, and analytical data (PDF)

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CCDC 1915124, 1915126, and 1943869 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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