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Organocatalytic Asymmetric Nucleophilic Addition to *o*-Quinone Methides by Alcohols

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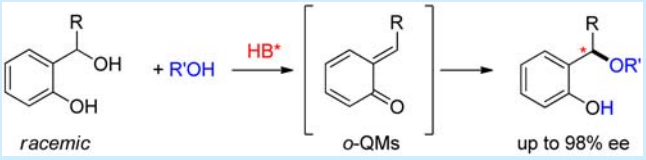
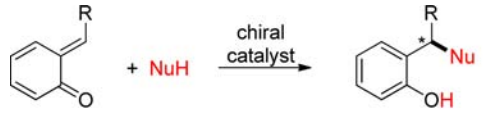
Supporting Information

ABSTRACT: The first catalytic asymmetric intermolecular alcohol conjugate addition to *o*-quinone methides (*o*-QMs) is disclosed. Due to reversible C−O bond formation and low nucleophilicity of alcohols, catalytic asymmetric oxa-Michael additions with simple alcohol nucleophiles to establish acyclic oxygenated carbon stereocenters remain scarce. The present reaction represents a rare example of this type. With a suitable chiral acid catalyst, the in situ formation of *o*-QMs and subsequent conjugate addition proceeded with high efficiency and enantioselectivity. The chiral ether products are versatile precursors to other chiral molecules.



Since their first introduction by Fries and Kann in 1907,[1] *o*-quinone methides (*o*-QMs) have been well-recognized as important intermediates in both organic synthesis and biological processes.[2] Their intriguing structural feature and versatile reactivity have led to the development of a variety of organic transformations of broad utility, such as Michael additions, 6π electrocyclizations, and [4 + 2] cycloadditions.[2] However, despite the long history of the studies on *o*-QMs, the exploitation of *o*-QMs in catalytic asymmetric synthesis has remained dormant until very recently.[2−5] In the past few years, a number of catalytic systems have been demonstrated to be effective for these asymmetric reactions (Scheme 1).[3−5] In particular, the formation of C−C bonds at the benzylic position with a carbon-centered nucleophile, in both conjugate addition and cycloaddition reactions, has been the focus of extensive investigations to date. In contrast, stereocontrolled carbon−heteroatom bond formation employing a heteroatom-centered nucleophile remains challenging and underdeveloped.[5]

Scheme 1. Introduction to Catalytic Asymmetric Addition to *o*-QMs



- NuH = carbon-based: well-established
- NuH = heteroatom-based: ***scarce***
- This work: NuH = alcohol (R'OH), excellent stereocontrol
- Challenges: weak nucleophilicity of alcohols, reversibility

In general, catalytic asymmetric conjugate addition reactions using nucleophiles based on heteroatoms, such as P, S, and N, have been well-established, but the use of alcohol nucleophiles for stereocontrolled C−O bond formation has been much less realized, particularly for intermolecular processes.[6] It is not only because of the relatively weak nucleophilicity of alcohols, but also related to the good leaving ability of alkoxide, which makes these reactions potentially reversible and thus difficult for stereocontrol.[6,7] As a result, currently known asymmetric oxa-Michael reactions with alcohol nucleophiles are mostly intramolecular or cascade processes to form cyclic products, which diminishes the complications by reversibility. Sigman and co-workers have systematically studied styrene alkoxylation reactions,[8] some of which involve diastereoselective conjugate addition of alcohols to *o*-QMs to establish the benzylic stereocenter.[8d−g] However, the stereoselectivity in the conjugate addition step proved to be controlled by the initially formed homobenzylic stereocenter but not directly by the chiral catalyst.[8d] Indeed, simple addition by alcohols in the absence of the homobenzylic stereocenter resulted in essentially racemic product formation, even with a chiral catalyst.[8a,b] Herein, we disclose the first direct catalyst-controlled intermolecular asymmetric conjugate addition of *o*-QMs by alcohols, which overcomes the reversibility issue to establish the acyclic benzylic stereocenter with high efficiency and enantioselectivity.[9]

Inspired by the recent success of using *o*-hydroxybenzyl alcohols for in situ generation of *o*-QMs and their subsequent asymmetric bond formation with chiral phosphoric acid catalysis,[3,4,10] we employed alcohol **1a** as the model substrate and *n*-butanol as the nucleophile (Table 1). Initial evaluation of some representative chiral phosphoric acids for the reaction in DCM solvent at room temperature indicated that most of these catalysts could catalyze the reaction to form the desired product, albeit with moderate enantioselectivity (entries 1−6). The spiroindane-based catalyst **B1** did not show any catalytic activity, probably due to the combination of low acidity and

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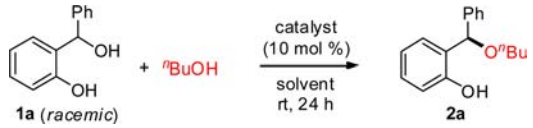
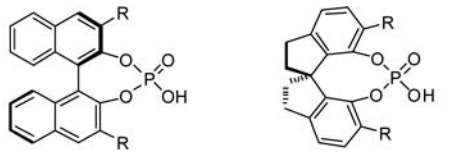
Table 1. Reaction Optimization[a]



1a (*racemic*) 2a

entry	catalyst	solvent	yield[b] (%)	er[c] (%)
1	**A1**	DCM	30	40:60
2	**A2**	DCM	92	40:60
3	**A3**	DCM	93	37:63
4	**B1**	DCM	<10	
5	**B2**	DCM	93	80:20
6	**B3**	DCM	92	87:13
7	**B3**	toluene	50	82:18
8	**B3**	THF	<10	
9	**B3**	$CHCl_3$	80	72:25
10[d]	**B3**	DCM	93	91:9
11[d,e]	**B3**	DCM	91	95:5
12[d,e,f]	B3	**DCM**	**90**	**95:5**



(*R*)-**A1**: R = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
(*R*)-**A2**: R = 9-anthryl
(*R*)-**A3**: R = 9-phenanthryl

(*R*)-**B1**: R = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
(*R*)-**B2**: R = 9-anthryl
(*R*)-**B3**: R = 9-phenanthryl

[a]**1a** (0.05 mmol), *n*-butanol (0.06 mmol), catalyst (10 mol %), solvent (1.0 mL). [b]Estimated by ^{1}H NMR of the crude product with trichloroethylene as internal standard. [c]Determined by HPLC. [d]Run with 3 Å molecular sieves (10 mg) as an additive. [e]Run at 0.025 M concentration for 48 h. [f]Run with 5 mol % of **B3**.

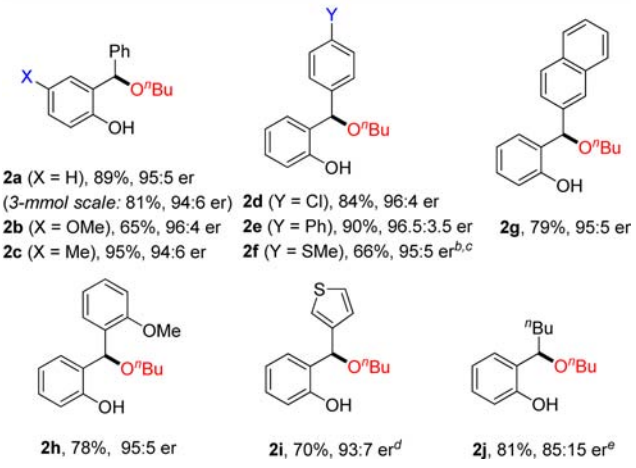
bulky 3,3′-subsituents. Among them, catalyst **B3** exhibited the best performance (entry 6). Other solvents proved inferior. In particular, the reaction in THF did not proceed, presumably due to its competing binding to the acid catalyst (entry 8). Further optimization indicated that the use of 3 Å molecular sieves and a lower concentration could give both good efficiency and enantioselectivity (entry 11).[11] A lower catalyst loading (5 mol %) did not affect the efficiency or enantioselectivity (entry 12).

A range of *o*-hydroxybenzyl alcohols can smoothly participate in the efficient intermolecular C−O bond formation processes with good to excellent enantioselectivity (Scheme 2). The reaction exhibits good compatibility with various substituents at different positions. Heterocycles can also be incorporated into the product. Furthermore, a wide range of alcohols, including methanol and primary and secondary alcohols, are also excellent nucleophiles for the asymmetric conjugate additions (Table 2). The mild conditions can tolerate a wide range of functional groups, such as halides, silyl-protected alcohols, (thio)ethers, esters, phthalimides, alkenes, alkynes, etc. It is worth noting that secondary alcohols are generally less reactive and thus require longer reaction time than primary ones. In addition, alcohols with additional Lewis basic site may have competing binding with the catalyst and thus also require longer reaction time. Nevertheless, they all reacted with good to excellent yield and enantioselectivity.

To further understand the reaction mechanism, we carried out a series of control experiments. First, in the presence of a substoichiometric amount of *n*-butanol (0.6 equiv), the

Scheme 2. Reaction Scope[a]

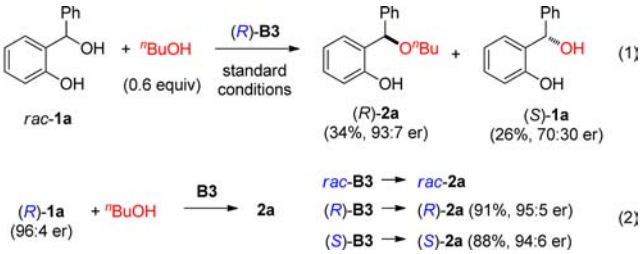
1 2



2a (X = H), 89%, 95:5 er
(*3-mmol scale:* 81%, 94:6 er)
2b (X = OMe), 65%, 96:4 er
2c (X = Me), 95%, 94:6 er
2d (Y = Cl), 84%, 96:4 er
2e (Y = Ph), 90%, 96.5:3.5 er
2f (Y = SMe), 66%, 95:5 er[b,c]
2g, 79%, 95:5 er
2h, 78%, 95:5 er
2i, 70%, 93:7 er[d]
2j, 81%, 85:15 er[e]

[a]**1** (0.3 mmol), *n*-butanol (0.36 mmol), **B3** (5 mol %), 3 Å MS (60 mg), DCM (12 mL); isolated yield. [b]Run at −20 °C. [c]Run for 96 h. [d]Run for 72 h. [e]Run with 10 mol % of **B3**.

remaining substrate **1a** was found to be enantioenriched (eq 1). Moreover, during the reaction progress, the ee values of the



product and substrate were also carefully monitored over time, which indicated that substrate kinetic resolution exists. Next, the enantioenriched (*R*)-**1a** was separately synthesized and subjected to the reaction with *n*-butanol (eq 2) in the presence of catalyst **B3** in different enantiomeric forms. The results indicated that it is the absolute configuration of the catalyst, rather than the substrate, that determines the product stereochemistry. The observation is also consistent with the intermediacy of achiral *o*-QM intermediates. It is worth noting that the reaction catalyzed by (*S*)-**B3** is much slower than that by (*R*)-**B3**, indicating the former is a mismatched case, which is in agreement with the kinetic resolution results obtained in eq 1.

We also examined the reversibility of this process. The enantioenriched product (*R*)-**2m** was treated with a catalytic amount of (*S*)-**B3** and racemic **A4**, respectively (eq 3). Erosion in enantiopurity of **2m** was observed, with the latter being more significant. The results indicated that, as alluded earlier, the second step (conjugate addition to *o*-QM) is reversible. The reversibility was further confirmed by the reaction between (*R*)-**2a** and benzyl alcohol under the standard conditions (eq 4). The formal substitution product (*R*)-**2m** was obtained. The *R* configuration of the product further suggested that the process proceeds via the reversely generated *o*-QM intermediate but

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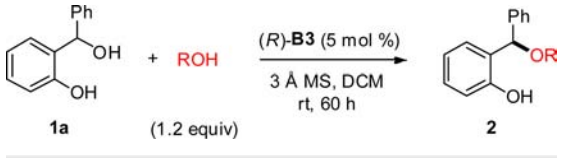
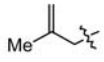
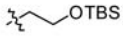
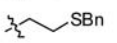
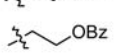
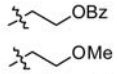
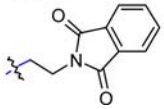
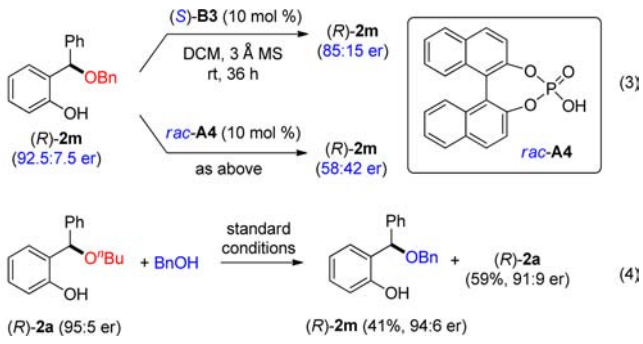
Table 2. Alcohol Scope[a]



entry	R	2	yield (%)[b]	er (%)[c]
1	Me	2k	92	86:14
2	Et	2l	89	93:7
3	Bn	2m	84	92.5:7.5
4	^{t}BuCH$_2$	2n (X-ray)	65	92.5:7.5
5	allyl	2o	77	94:6
6		2p	90	94.5:5.5
7		2q	76	96:4
8[d]	^{i}Pr	2r	72	94.5:5.5
9[d]	cyclobutyl	2s	91	93:7
10[d]	cyclopentyl	2t	74	93:7
11[d]		2u	89	94:6
12[d]		2v	71	97:3
13[d]		2w	74	96.5:3.5
14[d]		2x	71	95.5:4.5
15[e]		2y	65	95:5
14[d]		2z	70	99:1

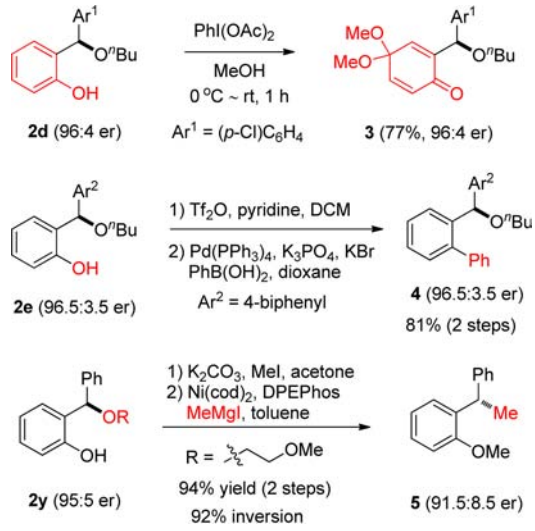
[a]**1a** (0.3 mmol), alcohol (0.36 mmol), (*R*)-**B3** (5 mol %), 3 Å MS (60 mg), DCM (12 mL). [b]Isolated yield. [c]Determined by HPLC analysis. [d]Run for 72 h. [e]Run for 96 h.



not an S_N2 pathway.[12] Therefore, in view of the reversible C−O bond formation involved, the observed excellent stereocontrol in our standard protocol is remarkable.

The enantioenriched ethers obtained from our reaction can be easily transformed to other useful chiral molecules (Scheme 3). For example, phenol **2d** can be oxidized to cyclohexadienone **3**, which is poised for further functionalizations. Phenol **2e** can also be easily triflated for subsequent efficient cross-coupling to form biaryl **4**, with the benzylic stereocenter remaining intact. Notably, no erosion in enantiopurity was observed in these transformations. Furthermore, after simple protection of the phenol group, the newly established chiral ether **2y** can be utilized as electrophile in an efficient cross-coupling reaction to furnish the enantioenriched 1,1-diarylalkane **5** with high enantiospecificity.[13,14]

Scheme 3. Product Derivatizations



In summary, we have developed the first catalytic asymmetric intermolecular alcohol addition to *o*-QMs. It is not only a rare example of asymmetric heteroconjugate additions of *o*-QMs but also a new example of the surprisingly small family of asymmetric oxa-Michael additions with simple alcohol nucleophiles to establish acyclic oxygenated carbon stereocenters. The efficient intermolecular C−O bond-forming process, overcoming the unfavorable complications due to reversibility and low alcohol nucleophilicity, proceeds with generally high efficiency and enantioselectivity. The mild conditions exhibit broad functional group compatibility. Control experiments provided important insights into the reaction mechanism. Substrate kinetic resolution is involved in the process. The reversible C−O bond formation has been confirmed, highlighting the observed remarkable stereocontrol. The chiral ether products have also been demonstrated to be versatile precursors to other useful chiral molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03072.

Experimental procedures and compound characterization data (PDF)

X-ray data for **2n** (CIF)

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Notes

The authors declare no competing financial interest.

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