Organic LETTERS

Letter

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Chiral Phosphoric Acid Catalyzed Asymmetric Oxidative Dearomatization of Naphthols with Quinones

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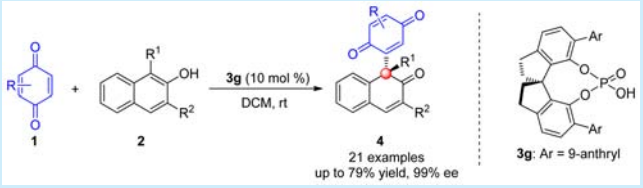
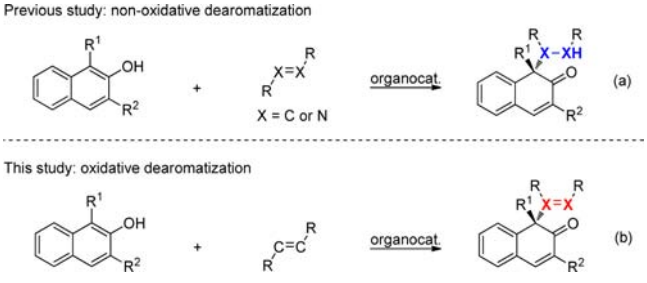
Supporting Information

ABSTRACT: A highly enantioselective oxidative dearomatization of naphthols with quinones catalyzed by a chiral spirocyclic phosphoric acid is described. The strategy provides concise access to enantioenriched cyclohexadienones with a quinone moiety. Remarkably, the obtained products could be easily transformed to a potentially useful dihydronaphtho[2,1-*b*]benzofuran scaffold.



The enantioselective dearomatization of phenols has received much attention because the product cyclohexadienones could be used for further transformations to provide various complex molecules and natural products.[1] In this regard, great progress has been made in the metal-[2] or hypervalent iodine[3]-mediated dearomatization reactions. However, there are limited reports on direct asymmetric organocatalytic dearomatization, all of which focus on the nonoxidative dearomatization.[4−6] Toste[4a] and You[4b] developed the phosphoric acid catalyzed fluorinative and chlorinative dearomatization. Recently, You and co-workers realized the organocatalytic enantioselective dearomatizations of 2-naphthols with nitroethylene or azodicarboxylates in the presence of a chiral thiourea or phosphoric acid catalyst (Scheme 1a).[5]

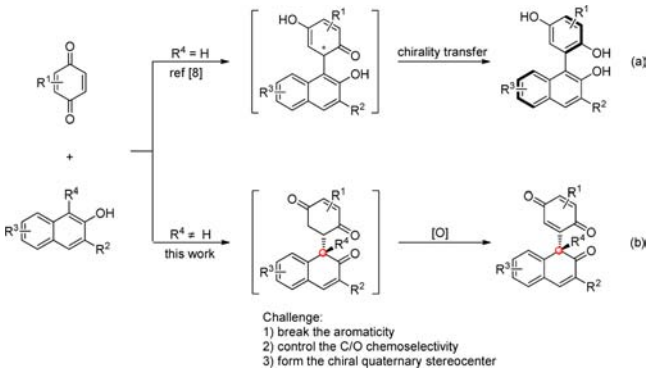
Scheme 1. Organocatalytic Dearomatization of 2-Naphthols



Despite these important contributions, the organocatalytic oxidative dearomatization has never been reported (Scheme 1b). Thus, the development of novel organocatalytic dearomatization, especially in oxidative conditions, would represent a major breakthrough in the field of dearomatization.

In recent years, the application of quinones or iminoquinones has attracted increasing attention in asymmetric organocatalysis as an expedient means to a range of chiral frameworks.[7] Inspired by this progress, and as a continuation of our efforts in catalytic asymmetric dearomatization of phenols,[1b,2o,p] we envisioned that the dearomatization of 2-naphthols with quinones might proceed to afford the cyclohexadienones with an all-carbon quaternary stereogenic center. Notably, during the preparation of this manuscript, Tan, Kürti and Bella's groups reported the arylation of 2-naphthols with quinones or iminoquinones, which led to the formation of biaryldiols (Scheme 2a).[8] In contrast, the envisioned

Scheme 2. Arylation of 2-Naphthols with Quinones and Derivatives



dearomatization of 2-naphthols with quinones remained a formidable pursuit, probably due to the high energy barrier for breaking the aromaticity of naphthyl rings. Other challenges are the formation of an all-carbon quaternary stereocenter and the choice of reasonable catalytic system to efficiently control the C/O chemoselectivity and induce stereoselectivity. Herein we described the chiral phosphoric acid[9] catalyzed enantioselective

Received: August 31, 2016
Published: September 30, 2016

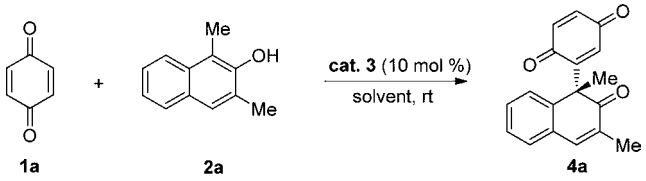
DOI: 10.1021/acs.orglett.6b02609
Org. Lett. 2016, 18, 5288−5291

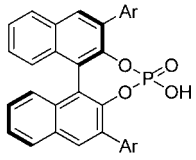
dearomatization of 2-naphthols with quinones, providing a new access to chiral cyclohexadienones with a quaternary stereocenter (Scheme 2b).

At the outset of our study, we evaluated the reaction of quinone **1a** and 1,3-dimethyl-2-naphthol **2a** in toluene at room temperature under the chiral phosphoric acid catalysis (Table 1). In the presence of typically used phosphoric acid **3a**, the reaction proceeded in moderate conversion and enantioselectivity (45% conv and 69% ee) without the observation of the competitive oxa-Michael side product (Table 1, entry 1). Encouraged by this promising result, we then screened several chiral phosphoric acids with different substituents and backbones to improve the efficiency and enantioselectivity (Table 1, entries 2–7). Among the examined catalysts, phosphoric acid **3g** afforded the best result in terms of both conversion and enantioselectivity (>95% conv and 91% ee, Table 1, entry 7). Of the solvents evaluated for the reaction catalyzed by **3g** (Table 1, entries 7–14), CH_2Cl_2 was found to be optimal, affording the product **4a** in 78% yield and 98% ee (Table 1, entry 8).[10] Lowering the amount of quinone **1a** to 1.0 equiv, the reaction gave a low yield of 28% and excellent ee of 95% (Table 1, entry 15, and more details in the Supporting Information).

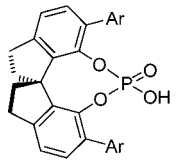
Having established the optimal reaction conditions, we next examined the substrate scope of this dearomatization reaction (Scheme 3). First, various 2-naphthol derivatives were surveyed. When the substituent at the C3-position was changed to other alkyl substituents, the reaction proceeded smoothly to afford the corresponding products in reasonable yields and excellent enantioselectivities (61–79% yield and 93–99% ee, **4a–i**). The use of a sterically hindered C3-phenyl-substituted naphthol could also afford the desired product in excellent stereocontrol, albeit with low yield (22% yield and 91% ee, **4j**). Unfortunately, only low yield and moderate enantioselectivity could be furnished when there was no substituent at the C3-position of naphthols (**4k**). For 1-methyl-3-bromo-2-naphthol, the reaction displayed no reactivity probably due to the reduced reactivity caused by the electron-withdrawing effect (**4l**). Moreover, alkyl substituents like ethyl, propyl, and allyl at the C1 position were all well tolerated, giving the desired products in good yields and excellent enantioselectivities (63–71% yield and 92–99% ee, **4m–o**).

Table 1. Optimization of the Reaction[a]





3a: Ar = 2,4,6-^{i}PrC$_6$H$_2$
3b: Ar = C$_6$H$_5$
3c: Ar = 2-naphthryl
3d: Ar = 9-anthryl
3e: Ar = 9-phenanthryl

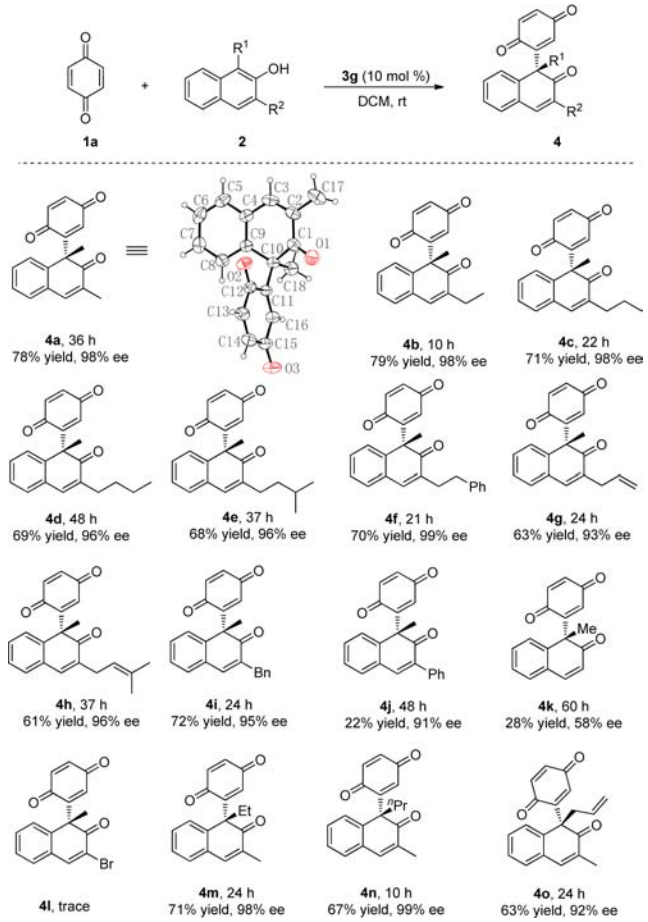


3f: Ar = 2,4,6-^{i}PrC$_6$H$_2$
3g: Ar = 9-anthryl

entry	cat.	solvent	time (h)	conv[b] (%)	ee[c] (%)
1	**3a**	toluene	48	45	69
2	**3b**	toluene	48	>95	42
3	**3c**	toluene	48	>95	35
4	**3d**	toluene	48	>95 (77)[d]	75
5	**3e**	toluene	48	>95	23
6	**3f**	toluene	48	30	24
7	**3g**	toluene	48	89	91
8	**3g**	CH_2Cl_2	36	>95 78)[d]	98
9	**3g**	DCE	36	>95	97
10	**3g**	xylene	48	>95	89
11	**3g**	mesitylene	48	>95	86
12	**3g**	PhF	48	>95	93
13	**3g**	THF	48	<5	
14	**3g**	Et_2O	48	<5	
15[e]	**3g**	CH_2Cl_2	36	45 (8)	95

[a]Unless otherwise stated, all reactions were carried out with 0.6 mmol (3.0 equiv) of **1a** and 0.2 mmol of **2a** in 2 mL of solvent under the catalysis of cat. **3** (0.02 mmol) at room temperature. [b]Determined by ^{1}H NMR of crude mixture. [c]Determined by chiral HPLC on a Chiralcel IC column. [d]Isolated yield was given in the parentheses. [e]1.0 equiv of **1a** was used.

Scheme 3. Scope of 2-Naphthols[a]



[a]All reactions were carried out with 0.6 mmol of **1** and 0.2 mmol of **2** in 2 mL of CH_2Cl_2 under the catalysis of cat. **3g** (0.02 mmol) at room temperature. The yields were reported as isolated yield after flash chromatography. The ees were determined by chiral HPLC on a Chiralcel column.

DOI: 10.1021/acs.orglett.6b02609
Org. Lett. 2016, 18, 5288–5291

Several quinones were next investigated (Table 2). The reaction was sluggish under the above optimal conditions. To

Table 2. Scope of Quinones[a]

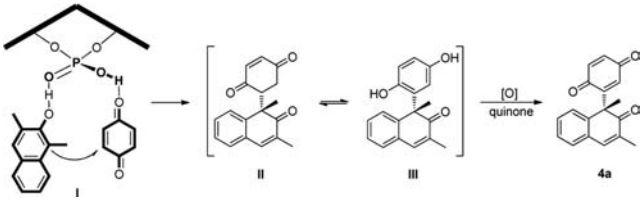
1		X = Me[b]	-	-	4p yield ee	35% 82%
2		X = Br	4q yield ee	21% 74%	4a 43% yield 46% ee	-
3		X = Cl[b]	4r yield ee	51% 89%	4a 12% yield	4s yield 10%
4		X = Cl[c]	-	-	4s yield ee	41% 18%
5		X = Br	4q' yield ee	55% -45%	-	-
6		X = Cl	4r' yield rac	64%	-	-

[a]All reactions were carried out with 0.6 mmol of **1** and 0.2 mmol of **2a** in 2 mL of DCM under the catalysis of cat. **3g** (0.02 mmol) at room temperature. The yields were reported as isolated yield after flash chromatography. The ees were determined by chiral HPLC on a Chiralcel column. [b]$CuCl_2 \cdot 2H_2O$ (10 mol %) added. [c]$Sc(OTf)_3$ (10 mmol %) added.

improve the reactivity, we ran the reaction by using additives in some cases.[11] Methyl-substituted quinone could be involved in the reaction in somewhat low yield (35%) and good enantioselectivity (82%) by adding $CuCl_2$ as an additive (entry 1). Unfortunately, the monohalogenated quinones **1c** and **1d** provided poor chemoselectivities in the reaction, affording the desired products **4q,r** in good enantioselectivities, together with the formation of halogen elimination products **4a**, probably due to the tautomerization process under oxidative conditions (entries 2 and 3). Furthermore, the use of symmetrical dihalogenated quinones only provided the halogen elimination products **4q−s** (entries 4−6). Interestingly, when **1f** and **1g** were used in the reaction, reversal of the absolute configuration of the products occurred, which might be due to the increased steric hindrance of the substrates. The lower stereocontrol might due to the fast, nonselective reaction induced by Lewis acid additives.

During the optimization of the reaction conditions, we found the yield could be significantly affected by the amount of quinone **1a**. In addition, if the reaction was performed under O_2 or Ar in 3.0 equiv of quinone, neither the yield nor ee was affected (see the Supporting Information for details). Hence, we surmised that the quinone might act not only as a reactant but also an oxidant. Based on the above experimental observations and previous studies,[7,8] a plausible transition state was proposed to interpret the results of the work (Scheme 4). First, the chiral phosphoric acid **3g** acted as a bifunctional

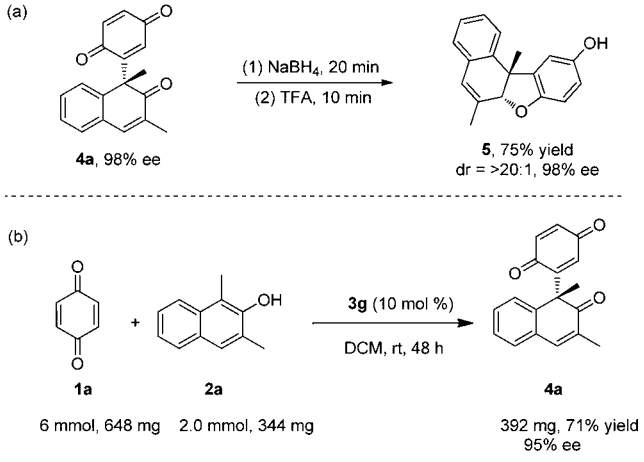
Scheme 4. Proposed Transition State



catalyst to activate both substrates via multiple hydrogen-bonding interactions (**I**) and promoted a Friedel−Crafts-type process rather than an oxa-Michael addition of naphthols and quinones to form intermediate **II**. The subsequent double enolization of intermediate **II** led to the formation of hydroquinone tautomer intermediate **III**, which could then be oxidized by quinone to the final product.

To further demonstrate the utility of this reaction, we then treated the reaction mixture with $NaBH_4$ to reduce the oxidized product followed by TFA to reprotonate the phenol sodium salts. Interestingly, a dihydronaphtho[2,1-*b*]benzofuran compound **5**, a useful building block in synthesis,[12] was obtained with a high diastereoselectivity of >20:1 and without any loss of enantioselectivity (Scheme 5a). Moreover, the reaction could be carried out on a more preparatively useful micromolar scale in comparably high yield with excellent enantioselectivity (Scheme 5b).

Scheme 5. Demonstration of Synthetic Utility of the Reaction



In summary, we have developed the first organocatalytic oxidative dearomatization of naphthols with quinones, leading to the formation of cyclohexadienones with an all-carbon quaternary stereocenter in good yields and excellent enantioselectivities. In addition, the obtained product could be easily transformed to a potentially useful dihydronaphtho-[2,1-*b*]benzofuran scaffold.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02609.

Crystallographic data of **4a** (CIF)

DOI: 10.1021/acs.orglett.6b02609
Org. Lett. 2016, 18, 5288−5291

Experimental procedures, experimental data, HPLC and NMR spectra of all compounds, and crystallographic data of **4a** (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for financial support from the NSFC (21432003, 21272102, 21572278, and 21502079) and the Program for Chang-Jiang Scholars and Innovative Research Team in University (IRT_15R27).

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(10) CCDC 1482904 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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