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Organocatalytic Asymmetric Formal [4 + 2] Cycloaddition of *in Situ* Oxidation-Generated *ortho*-Quinone Methides and Aldehydes

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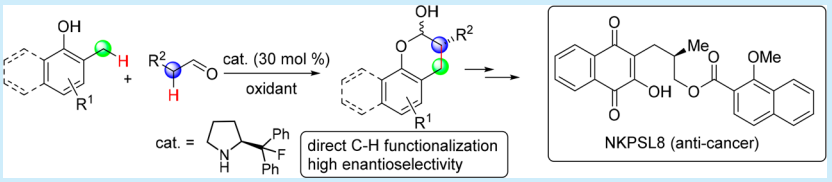
Supporting Information



ABSTRACT: An unprecedented chiral secondary amine-catalyzed formal [4 + 2] annulation of aldehydes and oxidation-generated β-unsubstituted *o*-QMs is reported. This asymmetric protocol allows direct functionalization of the benzylic C−H bonds and furnishes [4 + 2] cycloadducts, chromanols, with excellent enantioselectivity and in up to 92% yield. The usability of this approach was further demonstrated by the enantioselective synthesis of anticancer Rhinacanthins derivative NKPLS8.

Ortho-Quinone methides (*o*-QMs), a class of highly reactive molecules, have received considerable attention in the fields of organic chemistry and medicinal chemistry, as well as biology, since its first discovery over a hundred years ago.[1] The formation of *o*-QMs is mostly a dearomatization process and thus typically involves harsh conditions (e.g., high temperature, irradiation), which leads to incompatibility with a large number of organic reactions, especially in enantioselective transformations. As a result, early studies in asymmetric reactions have been mainly focused on the isolable *o*-QMs,[2] which are stabilized by multiple electron-rich substituents. The investigation of less stable *o*-QMs in enantioselective reactions was largely limited until recently.[3] Bach and co-workers reported in 2011 an unprecedented chiral phosphoric acid promoted asymmetric addition of indoles to *o*-QMs, which were *in situ* generated from substituted 2-(hydroxymethyl)phenol with the aid of a chiral phosphoric acid catalyst.[4] Since then, the strategy of *in situ* formation of *o*-QMs mediated by Brønsted acids has drawn extensive attention and tremendous progress has been made in the field of asymmetric chemistry within a few years.[5] Also, Brønsted base promoted *in situ* formation of *o*-QMs has also been developed in enantioselective reactions.[6] Furthermore, the fluoride-mediated generation of *o*-QMs has been explored by the Scheidt group in a number of NHC-catalyzed asymmetric reactions.[7] This *o*-QMs-formation approach was further exploited in the primary amine-catalyzed asymmetric reaction by Luo and co-workers.[8]

In the aforementioned reactions, a preinstalled leaving group, such as hydroxyl,[4,5] halide,[7,8] phenylsulfonyl,[6a] or tosyl,[6b,c] is requisite on the precursors to generate *o*-QMs *in situ*. The oxidative generation of *o*-QM from simple 2-alkylphenol,[1d] which enables direct functionalization of the less active benzylic C−H bond, would be a more atom-economic process.[9] However, current applications of this approach in asymmetric reactions have been mainly focused on the multiply substituted and stable *o*-QMs[10] while the use of less substituted *o*-QMs, particularly the β-unsubstituted *o*-QMs, remain elusive in the enantioselective chemical transformations. This is likely due to the high instability of these intermediates. Herein, following our interest in the chemistry of *o*-QMs,[11] we report our investigation on a secondary amine-catalyzed asymmetric [4 + 2] annulation of aldehydes and oxidation-generative β-unsubstituted *o*-QMs.

Substituted chromanols can be found widely in natural products and biologically intriguing molecules, for instance, flavanol, tocopherols (vitamin E), and ubichromanol.[12] Some of the chromanols or their derivatives have proven to have antibacterial,[13] anticancer,[14] or antioxidant[15] properties. Accordingly, the efficient synthesis of these compounds, especially in an asymmetric manner, has received much attention in the field of synthetic chemistry over the years.[16] We envisaged that, as depicted in Scheme 1, the chiral 3-substituted chromanols can be efficiently prepared from a formal [4 + 2] annulation of *in situ* oxidation-generated β-unsubstituted *o*-QM **A** and enamine **B**, which forms *in situ* from aldehyde **2** and a chiral amine catalyst. However, these two intermediates are highly reactive and tend to react with other nucleophiles or electrophiles. Particularly, the highly unstable β-unsubstituted *o*-QM can undergo rapid nucleophilic attack by water, amine catalyst, or other nucleophiles, as well as dimerization or trimerization.[17] We determined that the key factor for this reaction is the rates of reaction: matching the

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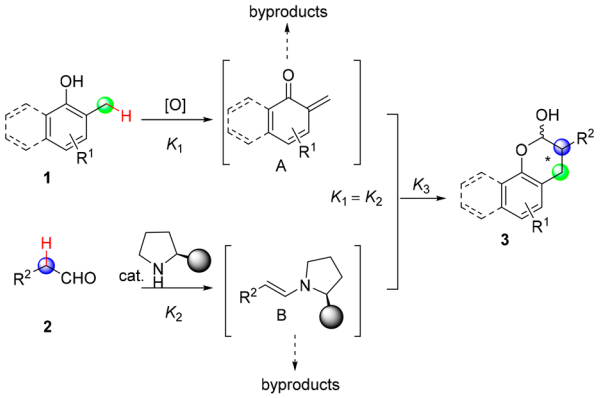
Scheme 1. Design of the Reaction

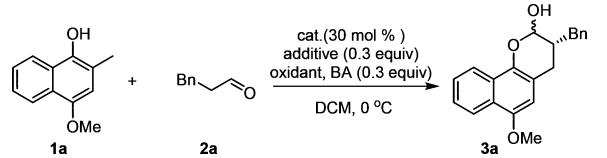


formation rates of intermediates **A** and **B** ($k_1 = k_2$) may help to reduce the formation of undesired byproducts.

Taking this into consideration, we commenced our investigation by employing readily available 4-methoxy-2-methyl-1-naphthol **1a** and 3-phenylpropanal **2a** as model substrates. Encouragingly, an initial experiment with L-proline (**I**) as catalyst and activated MnO_2 as oxidant afforded desired cycloadduct **3a** with moderate enantioselectivity though in only 20% yield (Table 1, entry 1). The use of chiral pyrrolidine (**II**) led to improved yield with comparable enantioselectivity whereas the reaction with bulkier catalyst **III** failed to furnish the expected product (entries 2, 3). Fortunately, fluorinated pyrrolindine (**IV**)[18] mediated this annulation process with significantly improved enantiocontrol (97% ee, entry 4).

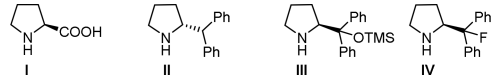
To further improve the yield, the oxidant used in this reaction was also investigated, but neither Ag_2O nor Ag_2CO_3 led to any improvement. We envisioned that the low yield of this reaction may be due to the slow formation rate of the enamine. Inspired by the report that a "buffer" system might be capable of accelerating enamine formation,[19] we used NaH_2PO_4 as the additive in this reaction, which indeed improved the yield from 60% to 78% (entry 8). Moreover, conducting this oxidation process in an inert atmosphere further boosted the yield to 90%, presumably as a result of slowing down *o*-QM formation rate in the absence of oxygen. Final solvent screening revealed chloroform as the optimal solvent for this process, delivering **3a** in 92% yield and with 96% ee (entry 11). It is worth mentioning that a lower catalyst loading, for instance, 10 mol %, resulted in a lower yield though with comparable enantioselectivity.

Table 1. Optimization of Asymmetric Reaction Conditions[a]



entry	cat.	oxidant	additive	yield (%)[b]	ee (%)[c]
1	**I**	MnO_2	–	20	74
2	**II**	MnO_2	–	53	−70
3	**III**	MnO_2	–	<5	–
4	**IV**	MnO_2	–	60	97
5[d]	**IV**	Ag_2O	–	51	97
6[d]	**IV**	Ag_2CO_3	–	24	96
7[e]	**IV**	MnO_2	–	58	95
8[f]	**IV**	MnO_2	NaH_2PO_4	78	96
9[f,g]	**IV**	MnO_2	NaH_2PO_4	89	96
10[f,g,h]	**IV**	MnO_2	NaH_2PO_4	90	96
11[f,g,h,i]	**IV**	MnO_2	NaH_2PO_4	92	96
12[f,g,h,j]	**IV**	MnO_2	NaH_2PO_4	74	96

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.15 mmol) and **2a** (0.45 mmol) in DCM (3.0 mL) in the presence of catalyst (0.045 mmol), oxidant (0.30 mmol), BA (0.045 mmol), and additive (0.15 mmol). [b]Isolated yields. [c]Ee was determined by chiral HPLC analysis of the corresponding diols resulted from reduction of **3a** with $NaBH_4$. [d]1.1 equiv of oxidant was used. [e]3 equiv of oxidant were used. [f]Conducted at rt. [g]The reaction was run under a N_2 atmosphere. [h]PNBA was used instead of BA. [i]$CHCl_3$ was used as solvent. [j]DCE was used as solvent. BA: benzoic acid; PNBA: *p*-nitrobenzoic acid.



To further improve the yield, the oxidant used in this reaction was also investigated, but neither Ag_2O nor Ag_2CO_3 led to any improvement. We envisioned that the low yield of this reaction may be due to the slow formation rate of the enamine. Inspired by the report that a "buffer" system might be capable of accelerating enamine formation,[19] we used NaH_2PO_4 as the additive in this reaction, which indeed improved the yield from 60% to 78% (entry 8). Moreover, conducting this oxidation process in an inert atmosphere further boosted the yield to 90%, presumably as a result of slowing down *o*-QM formation rate in the absence of oxygen. Final solvent screening revealed chloroform as the optimal solvent for this process, delivering **3a** in 92% yield and with 96% ee (entry 11). It is worth mentioning that a lower catalyst loading, for instance, 10 mol %, resulted in a lower yield though with comparable enantioselectivity.

With the optimal reaction conditions in hand, we then probed the scope of this asymmetric transformation. First, a vast range of aldehydes was investigated (Scheme 2). The electronic properties of the substituents on 3-phenylpropanal exhibited negligible effect on the reaction: all gave adducts (**3a**−**3e**) with 96% ee. Similarly, all aliphatic aldehydes, including propionaldehyde, are compatible with this protocol (**3h**−**3k**). In addition, the presence of an amino group on the aldehyde displayed no obvious impact on the reaction (**3m**, 90% ee). 2-Phenylacetaldehyde is also applicable in this process, though with slightly diminished enantioselectivity (**3f**, 85% ee). It is worth noting that, with less bulky catalyst **II** as a promoter, α-substituted aldehyde could also participate in the asymmetric reaction, leading to **3l** with all-carbon quaternary center in moderate yield and ee.

The scope of *o*-QM precursors was also studied. Besides 4-methoxy-1-naphthol, other 4-oxo-napthols proved to be compatible with this organocatalytic protocol (**3n**, **3o**, **3p**). Moreover, naphthols with a mild electron-rich substituent (R^1 = *p*-MeOPh, **3r**), as well as electron-deficient substituents (R^1 = Ph, **3q**; *p*-BrPh, **3s**), proceeded smoothly in this reaction, furnishing the corresponding adducts in good yields and with excellent enantioselectivities (up to 95% ee). However, we did not observe the formation of the desired product when 4-unsubstituted naphthol (R^1 = H) was used as the substrate, presumably due to the difficulty of *o*-QM formation.

We next turned our attention to more reactive and more challenging phenol-based *o*-QMs. As exhibited in Scheme 2, multiple substituted *o*-methylphenols took part in the reaction of 3-phenylpropanal (**2a**) smoothly, resulting in cycloadducts in moderate yields and with up to 95% ee (**3t**, **3u**, **3v**). As expected, less electron-rich phenols (R^1 = *t*-Bu, PMP) led to lower yields, but with comparable high enantioselectivities (**3w**, **3y**).

Furthermore, gram-scale synthesis was also conducted with this protocol, affording chromanol **3q** with identical enantioselectivity and in 72% yield (Scheme 3). This enantioenriched compound was readily transformed to a number of biologically interesting molecules without significant erosion of optical purity, such as coumarin **4** and chromane **5**.

The absolute configuration of the cycloadduct **3p** was determined by single crystal X-ray diffraction of its corresponding reduction product **3p-1** (CCDC 1583972). The configurations of other adducts were assigned analogously

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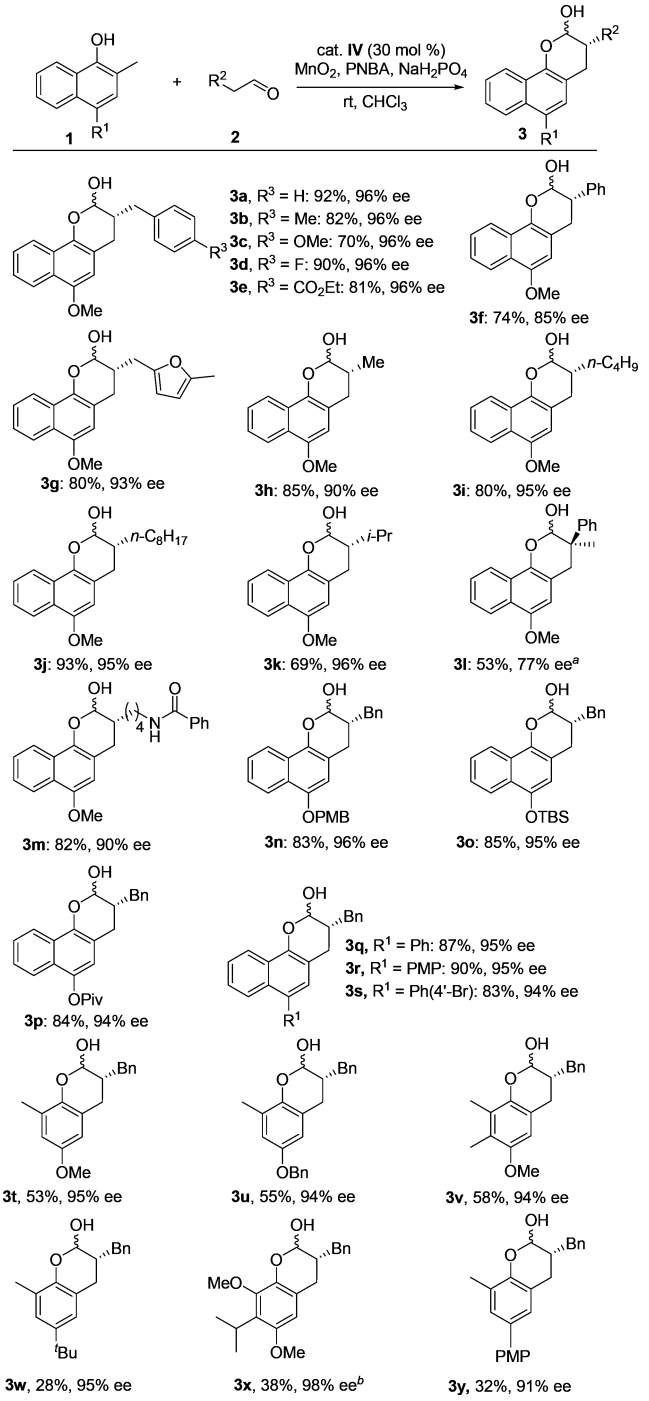
Scheme 2. Scope of the Reaction[a]

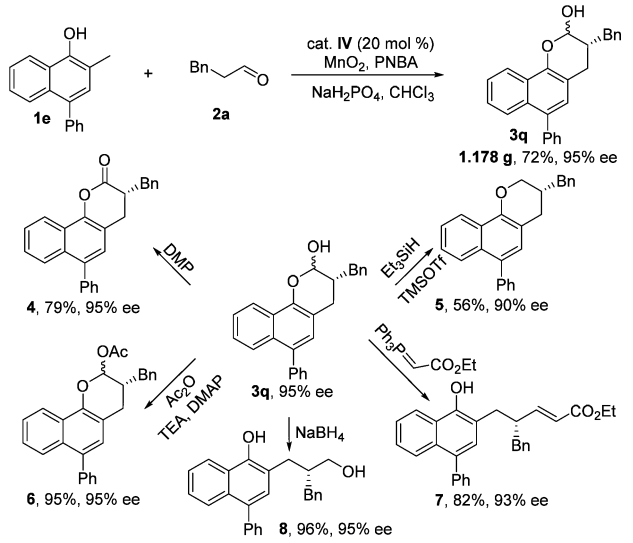


[a]Catalyst **II** was used. [b]Conducted in benzene with Ag_2O (1.2 equiv) as oxidant.

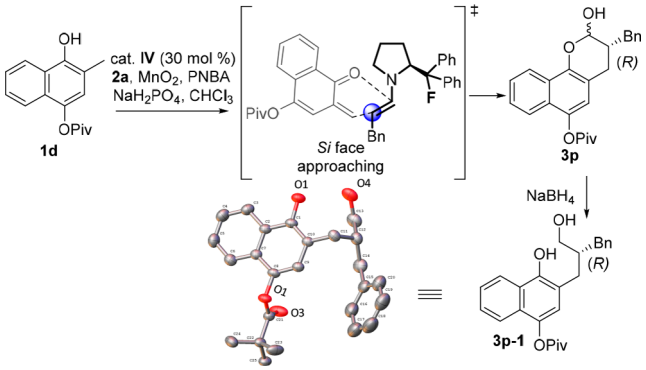
(Scheme 4). To understand the stereochemical outcome of this chiral amine-mediated process, a transition state of this reaction is also proposed.[20]

Rhinacanthins, isolated from the roots of medicinal plant *Rhinacanthius nasutus* (Acanthaceae),[21] are a class of naphthoquinone ester derivatives exhibiting intriguing biological activities.[22] Particularly, a racemic form of Rhinacanthins derivative NKPLS8 showed promising anticancer activities (e.g., IC_{50} for HeLa: 0.38 μM).[22a] Nevertheless, the synthesis of optically active NKPLS8 has not been documented

Scheme 3. Chemical Transformations of 3ea

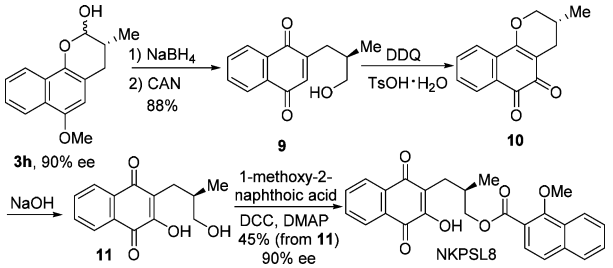


Scheme 4. Proposed Transition State



and thus the biological activities of this compound have not been thoroughly investigated. As depicted in Scheme 5, starting from enantioenriched **3h**, optically active NKPLS8 was readily synthesized in five steps with 90% ee.

Scheme 5. Enantioselective Synthesis of Optically Active Rhinacanthins Derivative NKPLS8



In summary, we have developed an asymmetric formal [4 + 2] annulation of aldehydes and β-unsubstituted *o*-QMs with a chiral secondary amine as the catalyst. The effective application of highly unstable β-unsubstituted *o*-QMs, which are *in situ* generated from the oxidation of *o*-methylphenols, in this enantioselective process enables direct functionalization of the benzylic C−H bonds. This protocol allows facile access to biologically important chromanols in moderate to excellent yields and with up to 98% ee. The usability of this method was

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further demonstrated by the efficient asymmetric synthesis of the anticancer Rhinacanthins derivative NKPLS8.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03539.

Experimental procedures, characterizations, and crystal data for **3p-1** (PDF)

Accession Codes

CCDC 1583972 contains 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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