Catalytic Asymmetric Inverse-Electron-Demand Oxa-Diels–Alder Reaction of In Situ Generated *ortho*-Quinone Methides with 3-Methyl-2-Vinylindoles**
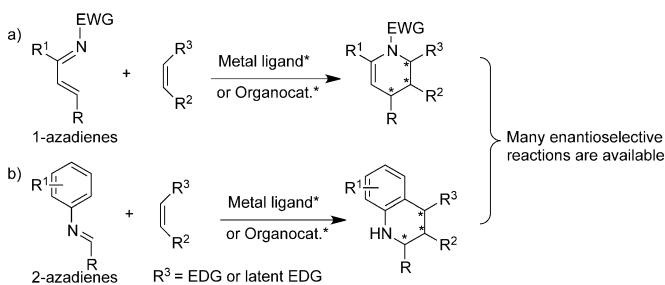
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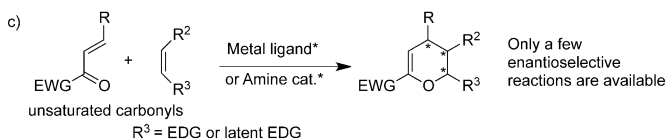
In memory of Professor Carlos F. Barbas III

Abstract: The first catalytic asymmetric inverse-electron-demand (IED) oxa-Diels–Alder reaction of ortho-quinone methides, generated in situ from ortho-hydroxybenzyl alcohols, has been established. By selecting 3-methyl-2-vinylindoles as a class of competent dienophiles, this approach provides an efficient strategy to construct an enantioenriched chroman framework with three adjacent stereogenic centers in high yields and excellent stereoselectivities (up to 99% yield, > 95:5 d.r., 99.5:0.5 e.r.). The utilization of ortho-hydroxybenzyl alcohols as precursors of dienes and 3-methyl-2-vinylindoles as dienophiles, as well as the hydrogen-bonding activation mode of the substrates met the challenges of a catalytic asymmetric IED oxa-Diels–Alder reaction.

Catalytic, enantioselective Diels–Alder (DA) reactions belong to the most fundamental and powerful tools in constructing enantioenriched six-membered ring systems.[1] Particularly, catalytic asymmetric inverse-electron-demand (IED) hetero-DA reactions have proven to be efficient and atom-economical methods for the synthesis of six-membered heterocycles with perfect regio- and stereoselectivities (Scheme 1).[2] As a result, elegant developments have been achieved in the research area of catalytic asymmetric IED aza-DA reactions,[1a,2a,b] which employed 1-azadienes (Scheme 1a)[3] or 2-azadienes (Scheme 1b)[2e–h,4] as electron-deficient dienes to react with electron-rich dienophiles in the presence of either chiral metal catalysts or organocatalysts. These well-developed approaches afforded nitrogenous heterocycles such as tetrahydropyridines and tetrahydroquinolines in excellent stereoselectivities. However, in sharp contrast, the catalytic asymmetric IED oxa-DA reactions are underdeveloped in spite of the fact that this class of transformation will efficiently build up oxygen-containing

Scheme 1. Profile of catalytic asymmetric hetero-Diels–Alder reactions. EDG = electron-donating group, EWG = electron-withdrawing group.

heterocyclic frameworks with multiple stereogenic centers.[2a,5] So far, only a few enantioselective IED oxa-DA reactions have been reported, and they predominantly utilize α,β-unsaturated carbonyl compounds as diene components to perform cycloadditions with electron-rich alkenes (Scheme 1c).[2a,6] Despite these creative works, great challenges still exist in the catalytic asymmetric IED oxa-DA reactions. The first one is the limited scope of dienes and dienophiles, which is mainly confined to α,β-unsaturated carbonyl compounds and vinyl ethers.[2a,6a–k] The second one is the limited catalyst system and activation mode, which is dominated by metal/chiral ligands,[2a,6a–i] and only a small number of transformations employed chiral amines as organocatalysts to activate aldehydes as dienophiles through enamine catalysis.[2a,6l–n] Therefore, the development of catalytic asymmetric IED oxa-DA reactions, especially those utilizing other types of dienes and dienophiles based on different catalytic activation modes, is of great significance.

Recently, *ortho*-hydroxybenzyl alcohols have emerged as active reaction partners in asymmetric catalysis for their characteristic of being readily converted into *ortho*-quinone methide (*o*-QM) intermediates[7] in the presence of a Brønsted acid (Scheme 2),[8] and should serve as a suitable diene for catalytic asymmetric IED oxa-DA reactions. However, previous reports on catalytic enantioselective transformations of *ortho*-hydroxybenzyl alcohols only included conjugate addi-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500215.
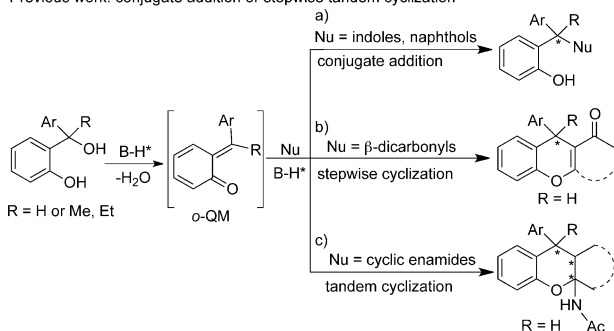
Scheme 2. Previous works on catalytic asymmetric reactions involving *ortho*-hydroxybenzyl alcohols.

tions (Scheme 2a)[8b–d] and stepwise cyclizations (Scheme 2 b).[8e,f] During the preparation and submission of this manuscript, Schneider and co-workers reported an elegant tandem cyclization using highly reactive cyclic enamides as nucleophiles (Scheme 2c).[8g,h] In spite of this progress, olefins of relatively low reactivity, that is, having no activating groups directly linking to the C=C bond, have not yet been employed in reactions with *ortho*-hydroxybenzyl alcohols.[9] The accomplishment of such a reaction would result in the enantioselective cycloaddition of this substrate class, thus achieving the catalytic asymmetric IED oxa-DA reaction. This transformation is highly desirable, but challenging because of the great demand in developing highly enantioselective procedures.
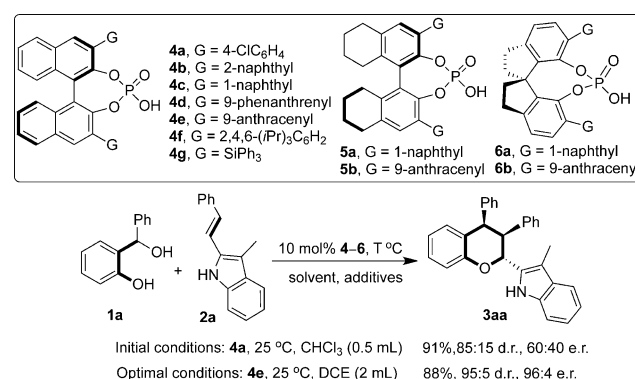
Inspired by the challenges in catalytic asymmetric IED oxa-DA reactions and in view of the biological importance of chiral chroman derivatives,[10] we design a chiral phosphoric acid[11] (CPA) catalyzed asymmetric IED oxa-DA reaction of *o*-QMs generated in situ from *ortho*-hydroxybenzyl alcohols (Scheme 3). Our previous work on indole-related enantiose-

Scheme 3. Design of a catalytic asymmetric IED oxa-DA reaction of in situ generated *o*-QMs and 3-methyl-2-vinylindoles.

lective transformations[12] stimulated us to select 3-methyl-2-vinylindoles as dienophiles because the introduction of a methyl group at the C3-position of 2-vinylindoles could enable this class of substrates to act as dienophiles rather than dienes. In addition, the indole moiety will not only facilitate the formation of dual hydrogen bonds between the catalyst

and the two substrates, but also bring a biologically important indole moiety to the constructed chroman core.
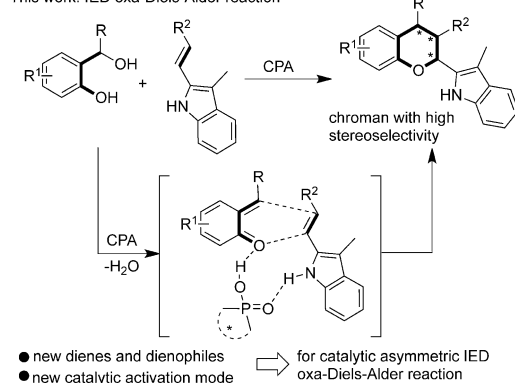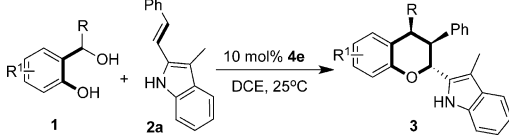
Herein, we report the first catalytic asymmetric IED oxa-DA reaction of in situ generated *o*-QMs and 3-methyl-2-vinylindoles, thus leading to highly diastereo- and enantioselective construction of the chroman scaffold with three adjacent stereogenic centers (up to > 95:5 d.r., 99.5:0.5 e.r.). This transformation utilized *ortho*-hydroxybenzyl alcohols as precursors of dienes and 3-methyl-2-vinylindoles as dienophiles, both of which are new substrates for catalytic asymmetric IED oxa-DA reactions. In addition, the hydrogen-bonding activation mode of the catalyst to the substrates has been little reported in catalytic asymmetric IED oxa-DA reactions.

Initially, the reaction of *ortho*-hydroxybenzyl alcohol (**1a**) and the 3-methyl-2-vinylindole **2a** in the presence of 10 mol % of the CPA **4a** in chloroform at 25 °C was utilized to test our hypothesis (Scheme 4). The IED oxa-DA reaction

Initial conditions: **4a**, 25 °C, CHCl₃ (0.5 mL)   91%,85:15 d.r., 60:40 e.r.
Optimal conditions: **4e**, 25 °C, DCE (2 mL)   88%, 95:5 d.r., 96:4 e.r.

Scheme 4. Catalysts and model reaction employed to optimize the reaction conditions. DCE = 1,2-dichloroethane.

proceeded smoothly to generate the chroman product **3aa** in good diastereoselectivity (85:15 d.r.) but with a low enantioselectivity (60:40 e.r.). To improve the enantioselectivity, this reaction was further subjected to catalyst screening and reaction conditions optimization by changing solvent, temperature, additives, and reagents ratio (see the Supporting Information for details). At last, the optimal reaction conditions were established by using the CPA **4e** as a catalyst in dichloroethane (DCE) at 25 °C, thus leading to **3aa** in an excellent stereoselectivity of 95:5 d.r. and 96:4 e.r.

With the optimal reaction conditions in hand, we then carried out the investigation on the substrate scope of *ortho*-hydroxybenzyl alcohols (**1**) by the catalytic asymmetric IED oxa-DA reactions with **2a**. As shown in Table 1, this protocol was applicable to a wide range of *ortho*-hydroxybenzyl alcohols (**1**) with different R/R¹ groups, and delivered the desired chroman derivatives **3** bearing multiple stereogenic centers in generally high yields and excellent stereoselectivities. Basically, both aromatic (entries 1–7) and aliphatic (entries 8–12) groups could be successfully employed as part of the substrates **1**, which smoothly participated in the reactions in good yields and high stereoselectivities. In detail, a variety of phenyl groups with electronically neutral

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Table 1: Substrate scope of the *ortho*-hydroxybenzyl alcohols **1**.[a]
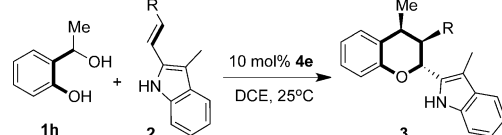
Entry	3	R/R¹ (1)	Yield [%][b]	d.r.[c]	e.r.[d]
1	3aa	Ph/H (1a)	88	95:5	96:4
2	3ba	p-FC$_6$H$_4$/H (1b)	60	>95:5	95:5
3	3ca	m-FC$_6$H$_4$/H (1c)	77	89:11	96:4
4	3da	p-ClC$_6$H$_4$/H (1d)	81	89:11	96:4
5	3ea	p-MeC$_6$H$_4$/H (1e)	99	86:14	92:8
6	3fa	m-MeC$_6$H$_4$/H (1f)	99	86:14	94:6
7	3ga	m-MeOC$_6$H$_4$/H (1g)	84	88:12	95:5
8	3ha	Me/H (1h)	97	>95:5	99:1
9	3ia	n-pentyl/H (1i)	82	>95:5	98:2
10	3ja	n-hexyl/H (1j)	83	>95:5	98:2
11	3ka	iBu/H (1k)	82	>95:5	96:4
12	3la	cyclopropyl/H (1l)	89	93:7	99:1
13	3ma	Ph/4-F (1m)	67	93:7	97:3
14	3na	Ph/4-Cl (1n)	75	93:7	94:6
15	3oa	Ph/4-Br (1o)	72	95:5	94:6
16	3pa	Ph/4-MeO (1p)	93	88:12	95:5
17	3qa	Me/4-Br (1q)	50	86:14	98:2

[a] Unless otherwise indicated, the reaction was carried out at the 0.05 mmol scale and catalyzed by 10 mol% **4e** in DCE (2 mL) at 25 °C for 12 h. The molar ratio of **1**/**2a** was 1:1. [b] Yield of isolated product. [c] The d.r. value was determined by ¹H NMR spectroscopy. [d] The e.r. value was determined by HPLC.

Table 2: Substrate scope of the 3-methyl-2-vinylindoles **2**.[a]

Entry	3	R (2)	Yield [%][b]	d.r.[c]	e.r.[d]
1	3hb	p-MeC$_6$H$_4$ (2b)	99	95:5	98:2
2	3hc	m-MeC$_6$H$_4$ (2c)	99	95:5	99.5:0.5
3	3hd	o-MeC$_6$H$_4$ (2d)	99	>95:5	99:1
4	3he	p-FC$_6$H$_4$ (2e)	99	>95:5	99:1
5	3hf	o-FC$_6$H$_4$ (2f)	99	>95:5	99:1
6	3hg	m-ClC$_6$H$_4$ (2g)	99	>95:5	99:1
7	3hh	p-BrC$_6$H$_4$ (2h)	80	>95:5	99:1
8	3hi	Me (2i)	71	>95:5	96:4
9	3hj	Et (2j)	68	>95:5	98:2

[a] Unless otherwise indicated, the reaction was carried out at the 0.05 mmol scale and catalyzed by 10 mol% **4e** in DCE (2 mL) at 25 °C for 12 h. The molar ratio of **1h**/**2** was 1:1. [b] Yield of isolated product. [c] The d.r. value was determined by ¹H NMR spectroscopy. [d] The e.r. value was determined by HPLC.

(entry 1), poor (entries 2–4), and rich (entries 5–7) substituents could be utilized in the reaction without significant difference in enantioselectivity (94:6 to 96:4 e.r.) except for the substrate **1e** (92:8 e.r.). More importantly, a series of alkyl groups including linear (entries 8–10), branched (entry 11), and cyclic (entry 12) ones proved to be competent R substituents, and gave the products **3ha**–**la** in overall excellent yields and perfect stereoselectivities. It should be noted that in previous catalytic enantioselective transformations, the R groups of *ortho*-hydroxybenzyl alcohols were almost aromatic,[8c–g] and aliphatic R groups have scarcely been utilized. In our case, both aromatic and aliphatic R groups work well, and the latter was superior to the former with regard to stereoselectivity (entries 8–12 versus 1–7). The applicability of various R groups provides a good opportunity for synthesizing optically pure chromans with structural diversity. Besides, the R¹ group linked to the phenyl ring could be varied from electron-withdrawing to electron-donating substituents (entries 13–17), thus providing the products **3** in good yields and good to excellent stereoselectivities.

Then, the use of various 3-methyl-2-vinylindoles (**2**) was examined by the catalytic asymmetric IED oxa-DA reactions with the *ortho*-hydroxybenzyl alcohol **1h**. As shown in Table 2, a series of 3-methyl-2-vinylindoles with various terminal substituents including aromatic and aliphatic ones served as suitable substrates in the reaction, thus offering the indole-substituted chromans **3** in high yields and perfect stereoselectivities. For terminal phenyl groups, both electron-rich and electron-poor substituents at different positions of the phenyl ring uniformly delivered excellent stereoselectiv-

ities (entries 1–7). Notably, this approach could be applied to the 2-vinylindoles **2i,j** bearing terminal alkyl groups such as methyl or ethyl, thus affording products **3hi,hj** in good yields and excellent stereoselectivities (entries 8 and 9). This scope offers more chances for obtaining structurally diverse chromans with high optical purity.

The absolute configuration of **3pa** (99.5:0.5 e.r. after recrystallization) was unambiguously determined to be (2*R*,3*S*,4*R*) by single-crystal X-ray diffraction analysis (in Scheme 5).[13] The absolute configuration of the other prod-
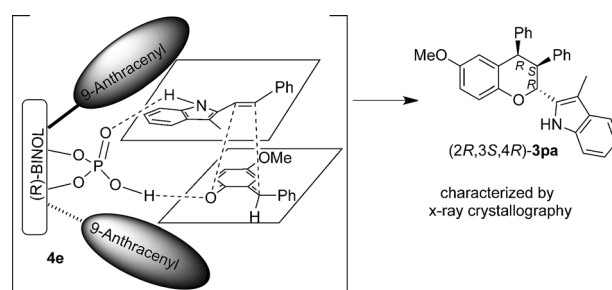

Scheme 5. Suggested transition state.

ucts **3** were assigned by analogy. On the basis of the experimental results, we suggested a possible transition state to explain the stereochemistry of this catalytic asymmetric IED oxa-DA reaction. As exemplified by the formation of product **3pa** (Scheme 5), the CPA **4e** simultaneously forms two hydrogen bonds with 3-methyl-2-vinylindole and the *o*-QM, which was generated in situ from *ortho*-hydroxybenzyl alcohol, thus facilitating the stereoselective IED oxa-DA reaction to give the experimentally observed (2*R*,3*S*,4*R*)-**3pa**. The excellent stereoselectivity is attributed to the dual hydrogen-bonding activation mode and the chiral environment created by **4e**. In all of the experiments (Tables 1 and 2), only two diastereomers of **3** with unchanged *trans*-geometry

of the original C=C bond were detected with high d.r. values. Besides, TLC revealed that the reaction was very clean, and no other intermediate product or byproduct was generated. Moreover, the intercepting reaction[4b] using indole as a nucleophilic trapping reagent disclosed that no desired interrupted product was generated (see the Supporting Information for details). These results indicated that there is a high possibility that the reaction undergoes a concerted pathway.[14]

To verify the suggested activation mode, a control experiment using the N-methyl-protected 3-methyl-2-vinylindole **2k** as a substrate was performed under the standard reaction conditions [Eq. (1)]. As expected, no reaction occurred, and
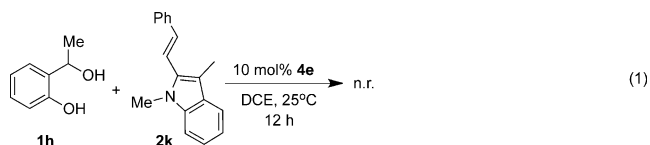

thus demonstrated that the N−H group of 2-vinylindoles played a crucial role in the reactivity of the reaction. Moreover, we investigated the effect of *Z/E* configuration of the substrates **2** on the reaction by utilizing (*Z*)-**2a** as a reaction component [Eq. (2)]. Very interestingly, this
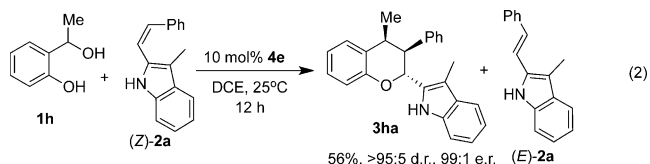
reaction generated the product **3ha** in a moderate yield and excellent stereoselectivity, and it had the same relative and absolute configuration as the product produced from (*E*)-**2a** (Table 1, entry 8). At the same time, a small amount of (*E*)-**2a** was observed, by TLC, in the reaction mixture along with some remaining (*Z*)-**2a**. This phenomenon indicated that (*Z*)-**2a** could be transformed into (*E*)-**2a** during the reaction process, and ultimately took part in the reaction to afford **3ha** with the observed configuration. Furthermore, this result implied that utilizing the *Z/E* mixture of **2** would not affect the stereoselectivity of the reaction, thus avoiding the arduous isolation of the *Z/E* isomers of **2**. Indeed, when (*Z/E*)-**2a** was employed in the reaction under the standard reaction conditions, the desired product **3ha** was obtained in a high yield (92 %) and with a perfect stereoselectivity of greater than 95:5 d.r. and 99:1 e.r. [Eq. (3)].
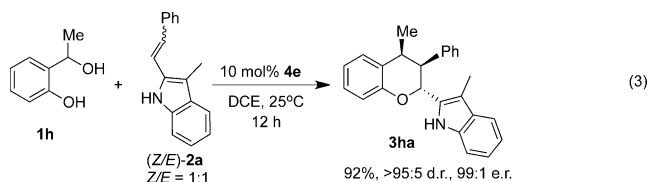
To investigate the role of the C3-methyl group in **2**, we tried the reaction using the 2-vinylindole **2l** as a substrate [Eq. (4)]. However, no cycloaddition product was observed and only the conjugate addition product **3al** was generated. This result demonstrated that the C3-methyl group of **2** is important for the designed IED oxa-DA reaction.
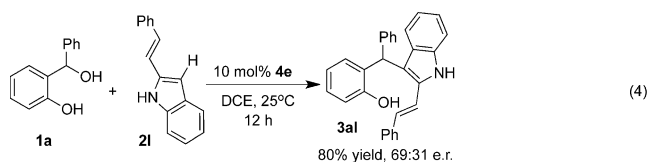
In summary, we have established the first catalytic asymmetric IED oxa-DA reaction of *o*-QMs generated in situ from *ortho*-hydroxybenzyl alcohols. By selecting 3-methyl-2-vinylindoles as a class of competent dienophiles, this approach provides an efficient strategy to construct the enantioenriched chroman framework with three adjacent stereogenic centers in high yields and excellent stereoselectivities. The utilization of *ortho*-hydroxybenzyl alcohols as precursors of dienes and 3-methyl-2-vinylindoles as dienophiles, as well as the hydrogen-bonding activation mode of the catalyst to the substrates met the challenges of the catalytic asymmetric IED oxa-DA reaction. In addition, this reaction also represents the first highly enantioselective construction of a chroman scaffold involving an indole moiety, which can be applicable to a variety of substrates, thus offering a good opportunity for the synthesis of biologically important chiral chroman derivatives with structural diversity.

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[13] CCDC 1042547 (**3pa**) 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, see the Supporting Information for details.

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