Enantioselective Synthesis

International Edition: DOI: 10.1002/anie.201607039
German Edition: DOI: 10.1002/ange.201607039

Organocatalytic, Enantioselective Synthesis of Cyclohexadienone Containing Hindered Spirocyclic Ethers through an Oxidative Dearomatization/Oxa-Michael Addition Sequence

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Abstract: *An unprecedented enantioselective oxa-Michael reaction of α-tertiary alcohols using cinchona-alkaloid-based chiral bifunctional squaramide catalysts is reported. An oxidative dearomatization of phenol followed by an enantioselective oxa-Michael addition sequence provided a broad array of chiral sterically hindered tetrahydrofurans and tetrahydropyrans attached to a cyclohexadienone moiety in spiro fashion. In general, good yields and excellent enantioselectivities (up to 99 %) were observed. The chiral oxo-cycles obtained have easily been transformed into chromans without disturbing the enantioselectivity.*

Enantioselective synthesis of sterically hindered ethers such as tetrahydrofurans/-pyrans is a long-standing challenge in organic chemistry.[1] Nevertheless, such moieties are ubiquitous in natural products and pharmaceuticals. Although, enantioselective intramolecular oxa-Michael addition is one of the most straightforward routes to chiral oxa-cycles,[2,3] the enantioselective synthesis of sterically hindered tetrahydrofurans/-pyrans through the oxa-Michael addition of α-tertiary alcohols constitutes a daunting, yet unsolved, challenge owing to their α-crowding and thereby reduced nucleophilicity.[4]

Cyclohexadienone connected to a tetrahydrofuran moiety in a spiro-fashion (CHD-spiro-THF) is a fascinating skeleton found in natural products aculeatins A–D and an aculeatin analogue A, which are active antimalarial agents against the *P. falciparum* 3D7 strain (Figure 1 a).[5] There have been many attempts to synthesize such a CHD-spiro-THF moiety; most are achiral[6a–g] or from chiral substrates.[6h–j] To the best of our knowledge, a catalytic enantioselective synthesis of such a moiety is elusive. Therefore, the development of catalytic enantioselective methods to construct such moieties should be significantly rewarding.

Oxidative dearomatization (OD) of phenols[7] to provide cyclohexadienone, followed by an enantioselective desymmetrization of a cyclohexadienone (DC)[8] moiety remained a powerful strategy for the synthesis of architecturally complex molecules. To the best of our knowledge, only Gaunt et al. have reported performing both steps in sequence.[9] Recently, the enantioselective desymmetrization of cyclohexadienone **I** through the oxa-Michael addition of

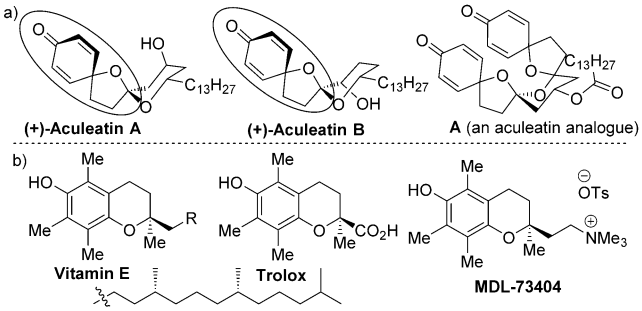
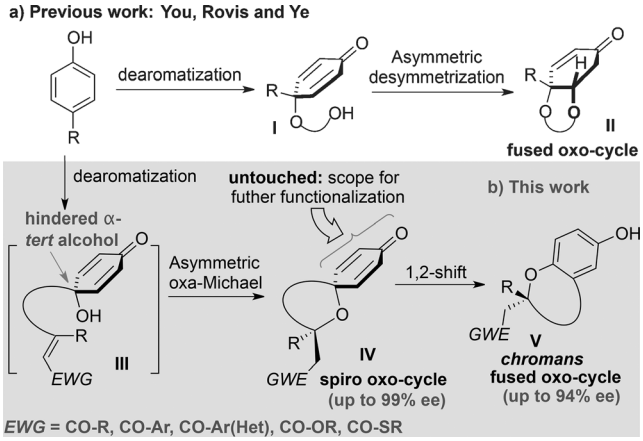


Figure 1. a) Natural products that have a cyclohexadienone-containing spiro-THF moiety. b) Natural products that have a chroman moiety.

a tethered alcohol attached to a cyclohexadienone moiety for the synthesis of fused oxa-cycle **II** was described (Scheme 1 a).[10] We presumed a direct use of α-tertiary alcohols, attached to a cyclohexadienone moiety and with a tethered enone (shown in **III**, Scheme 1 b), to participate in asymmetric oxa-Michael reactions to the tethered enone for the synthesis of sterically hindered tetrahydrofuran/tetrahydropyran **IV**. Furthermore, the spiro-cyclohexadienone moiety in the product would remain untouched, which would potentially allow further functionalization induced by the chiral C–O center.

Development of a sequential organocatalysis remains an active area of research.[11] In recent years, asymmetric oxa-Michael reactions using bifunctional organocatalysts bearing an H-bond donor moiety and a tertiary amino group on a chiral scaffold,[12] has gained considerable momentum in



Scheme 1. a) Dearomatization/enantioselective oxa-Michael reaction on cyclohexadienone. b) Dearomatization/enantioselective oxa-Michael reaction on tethered enone.

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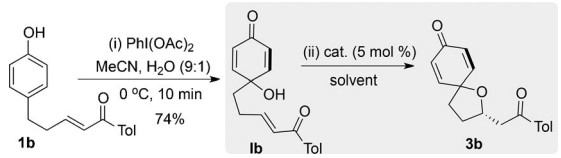
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607039.

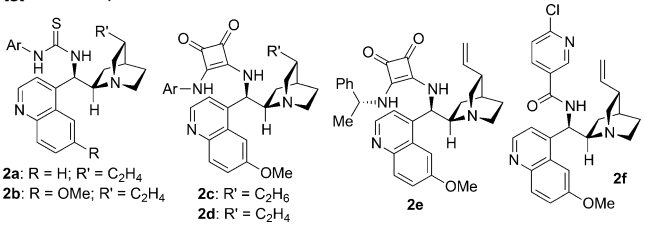
catalytic endeavors.[2,3] As a part of our effort to extend the power of these transformations,[3] we decided to utilize a similar mode of action for the present reaction. First, an OD of substituted phenol **1b** was performed using $PhI(OAc)_2$ as an oxidant to prepare the desired 4-hydroxy cyclohexadienone **Ib**, which was used for the asymmetric oxa-Michael addition in the presence of various organocatalysts as shown in Table 1 (for details, see the Supporting Information). The

Table 1: Optimization of the reaction conditions.[a]



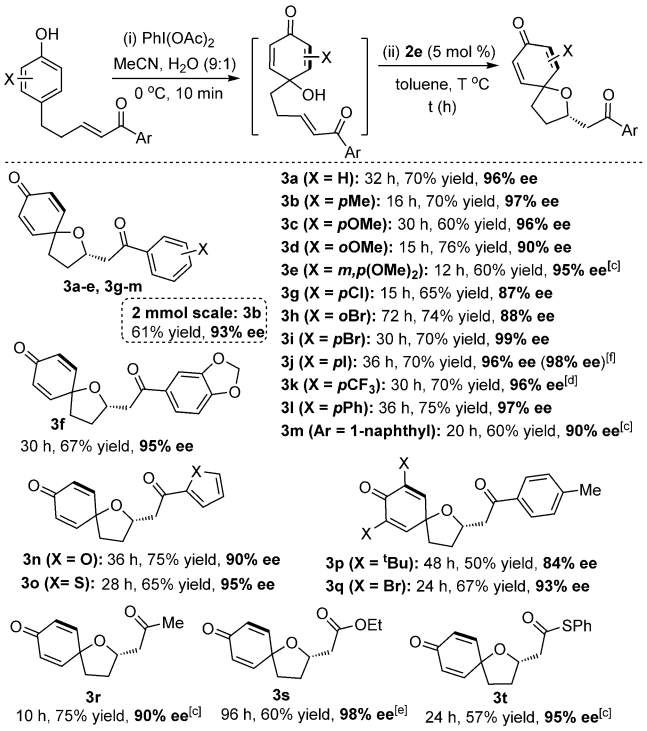
Entry	2	Solvent	Yield [%][b]	*ee* [%][c]
1	**2a**	Toluene	44	59
2	**2b**	Toluene	86	93
3	**2c**	Toluene	66	91
4	**2d**	Toluene	53	94
5	**2e**	Toluene	85 (70)[g]	95 (97)[d]
6	**2f**	Toluene	77	55
7	**2e**	Other solvents[f]	< 92	< 94
8	**2e**	Toluene	82	96[e]

[a] Reaction conditions: (i) **1b** (0.6 mmol, 1 equiv), $PhI(OAc)_2$ (0.6 mmol, 1 equiv), $MeCN:H_2O$ (9:1), 0 °C for 10 min. (ii) **Ib** (0.02 mmol, 1 equiv), catalyst (5 mol %) in solvent (0.3 mL, 0.1 M) at rt, 9 h. [b] The conversion/yield was calculated based on ^1H NMR spectroscopy of the crude reaction mixture using diphenylacetonitrile as an internal standard. [c] The *ee*'s were determined by chiral HPLC analysis. [d] Sequential synthesis. [e] at 0 °C. [f] See the Supporting Information. [g] Isolated yield.



optimal catalyst **2e** provided a yield of 85% and 95% *ee* (entry 5). The screening of the solvents (see the Supporting Information) revealed that toluene was the optimal solvent (entry 5). When the reaction temperature was lowered to 0 °C, the selectivity was enhanced to 96% *ee* (entry 8). Once the optimized reaction conditions were established, a sequential reaction was carried out, which yielded an even better selectivity (97% *ee*, entry 5).

Various phenol derivatives were tested using the optimized sequential reaction conditions to examine the generality of the reaction. The results are summarized in Scheme 2. Electron-rich substituents such as *p*-Me (**3b**), *p*-OMe (**3c**), *o*-OMe (**3d**), *m*,*p*-diOMe (**3e**), and *m*,*p*-OCH_2O (**3f**) worked smoothly, resulting high stereo-controlled products with excellent selectivity (90–97% *ee*). Electron-deficient substituents such as *p*-Cl (**3g**), *o*-Br (**3h**), *p*-Br (**3i**), *p*-I (**3j**), and *p*-F_3C (**3k**) showed a similar effect on selectivity (87–99% *ee*).



Scheme 2. Substrate scope for CHD-spiro-THF.[a,b,g] [a] Reaction conditions: (i) **1** (0.1 mmol, 1 equiv), $PhI(OAc)_2$ (0.1 mmol, 1 equiv), in $MeCN:H_2O$ (9:1, 1.0 mL) at 0 °C for 10 min. (ii) Toluene (1 mL) at 0 °C and then **2e** (0.005 mmol, 5 mol %). [b] Isolated yield. [c] Step 2 was carried out at rt. [d] Step 2 was carried out at −20 °C. [e] Step 2 was carried out at 40 °C. [f] After single recrystallization. [g] The *ee*'s were determined by chiral HPLC analysis.

Replacement of the phenyl ring with bi-phenyl (**3l,** 97% *ee*) and 1-naphthyl rings (**3m**, 90% *ee*) was equally successful. Instead of an aryl moiety, heteroaryl groups such as 2-furyl (**3n**) and 2-thiophenyl (**3o**) moieties underwent cyclization and gave high enantioselectivities (90% *ee* and 95% *ee*, respectively). Furthermore, substitutions on the phenol ring were also tolerated, for example, the corresponding 2,6-di-*tert*-butyl and 2,6-dibromo substituted phenols provided the corresponding products **3p** (84% *ee*) and **3q** (93% *ee*), respectively. Not only aryl and heteroaryl ketones but also aliphatic ketones such as methyl ketone (**3r**) worked well under these reaction conditions and provided 90% *ee* with a 75% yield. Notably, the ester (**3s**) and thioester (**3t**) functionalities were also equally effective and gave 98% *ee* and 95% *ee*, respectively. Finally, compound (**3b**) was synthesized in a higher scale (2 mmol scale) with only a small loss of selectivity (from 97% *ee* to 93% *ee*).

The absolute configuration of the spiro-dienone **3j** was unambiguously determined to be (*S*) by single-crystal X-ray diffraction analysis (Figure 2).

This protocol can also be applied to the asymmetric synthesis of substituted tetrahydropyrans (THP, Scheme 3). The electronic and steric effects on the α,β-enone moiety of **4** were examined; for example, Ph (**5a**), *p*-tol (**5b**), biphenyl (**5c**), 2- thiophenyl (**5d**), and 2-furyl (**5e**) provided good yields and high enantioselectivities (78–93% *ee*). Substitution

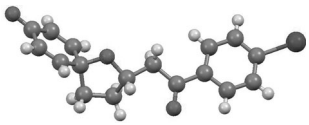
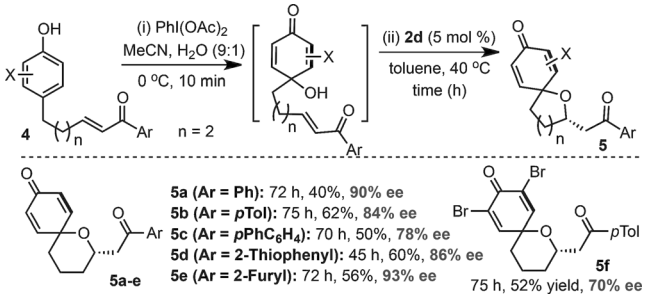
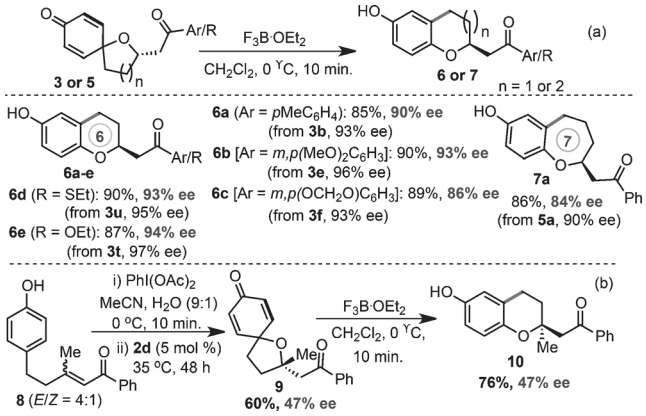


Figure 2. Crystal structure of compound **3j** (CCDC 1488175 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge by The Cambridge Crystallographic Data Centre).



Scheme 3. Substrate scope for CHD-spiro-pyrans.[a] [a] Reaction conditions remained the same as given in Scheme 2.

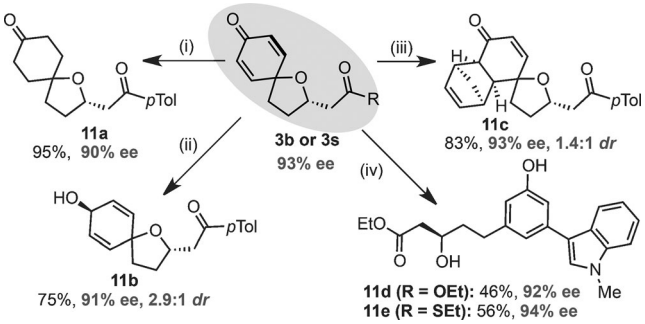
on the phenol moiety (for example, Br in **5f**) was well tolerated. To illustrate the further synthetic utility of the developed method, chiral spiro-oxocycle **3** and **5** were tested for an efficient Lewis-acid-mediated ring expansion into the chiral chromans (**6a–6e**) and homochroman (**7a**), respectively (Scheme 4a). To our delight, the desired chromans were obtained in good yields, albeit a slight decrease in enantioselectivity. To the best of our knowledge, this is the first synthesis of a chiral homochroman with good enantioselectivity. Chromans are an important structural motif in several natural products such as nebivolol, vitamin-E, and Trolox (Figure 1b).[13] However, the reports on the enantioselective synthesis of such motifs are very limited.[1a,2j,14] The prevalence of α-tertiary centers to oxygen in chromans (as shown in Figure 1b) prompted us carry out the current oxidative oxa-Michael addition of substrate **8** (Scheme 4b).



Scheme 4. Ring expansion: synthesis of chiral chromans and homochromans.[a–c] [a] Reaction conditions: a) **3** or **5** (0.1 mmol), $BF_3{\cdot}OEt_2$ (8.0 equiv), dry CH_2Cl_2, 0 °C, 10 min. [b] Isolated yield. [c] The *ee*'s were determined by chiral HPLC analysis.

Unfortunately, a lower selectivity was obtained for product **9** owing to the inseparable *E*/*Z*-isomers (4:1) in the parent substrate **8**.[14a] However, the enantioselectivity remained unchanged during the rearrangement step. This provides an excellent opportunity to expand the synthesis of hindered spiro-cyclic ethers having both α-tertiary carbons.

To expand further the synthetic utility of our method, functionalization of the cyclohexadienone moiety of **3b** or **3s** was performed without losing much enantioselectivity (Scheme 5). Pd/C-catalyzed hydrogenation of **3b** (93% *ee*)



Scheme 5. Functionalization of cyclohexadienone moiety.[a–c] [a] **3b** or **3s** (0.1 mmol, 1 equiv), (i) Pd/C (10 mol%), H_2 gas (1 atm), MeOH (2 mL), rt, 12 h. (ii) DIBAl-H (2.2 equiv), THF (1 mL), −78 °C, N_2 atm, 20 min. (iii) cyclopentadiene (10 equiv), CF_3CH_2OH (2 mL), rt, 16 h. (iv) *N*-methyl indole (1.2 equiv), $FeCl_3$ (10 mol%), CH_2Cl_2 (2 mL), rt, 18 h. [b] Isolated yield. [c] The *ee*'s were determined by chiral HPLC analysis.

gave the corresponding cyclohexanone derivative **11a** in excellent yield and nearly the same *ee* (90% *ee*). A ketone functionality of the cyclohexadienone moiety of **3b** was selectively reduced over benzyl ketone with DIBAL-H to provide **11b** with 2.9:1 d.r. and 91% *ee*. The unsaturation of **3b** was utilized as a dienophile in a Diels–Alder reaction with cyclopentadiene as a diene to provide **11c** with the same selectivity. Interestingly, nucleophilic addition of the indole to a cyclohexadienone moiety using a $FeCl_3{\cdot}6H_20$ catalyst resulted in a unique C–O bond breaking, which did not affect enantioselectivities to provide the β-hydroxy ester (**11d**) and thioester (**11e**) attached to a δ-phenol moiety.[15]

A bifunctional mechanism similar to those previously proposed for the squaramide/thiourea-based amino catalysts in the oxa-Michael reaction of enone[2,3] may be cited to explain the observed absolute stereochemistry.

In summary, a sequential dearomatization/enantioselective intramolecular oxa-Michael reaction of in situ generated 4-hydroxyl cyclohexadienones has been developed using a chiral bifunctional organocatalyst. This process provides the first and promising approach for the enantioselective synthesis of tetrahydrofurans and tetrahydropyrans, attached to a cyclohexadienone moiety in spiro-fashion, with excellent enantioselectivity and a broad substrate scope. Furthermore, a Lewis-acid-mediated ring expansion of the chiral spiro-THFs/pyrans has been demonstrated to provide the corresponding chromans and homochroman without disturbing the enantioselectivities. Overall, this methodology contributes to

the development of the enantioselective synthesis of sterically hindered ethers, which, though ubiquitous in natural products, were a long-standing challenge to the synthetic community.

Acknowledgements

This work has been funded by the Council of Scientific and Industrial Research (CSIR), New Delhi and IISER Bhopal.

Keywords: asymmetric synthesis · chromans · organocatalysis · oxa-Michael addition · tetrahydrofurans

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Received: July 20, 2016
Revised: August 24, 2016
Published online: ■■ ■■, ■■■■

Communications

Enantioselective Synthesis

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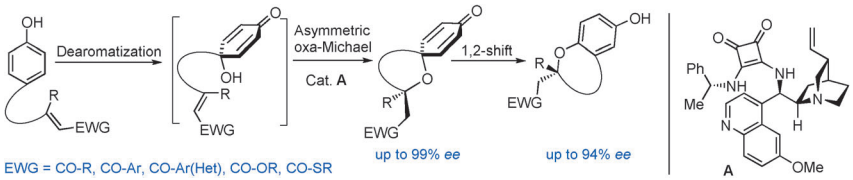
Organocatalytic, Enantioselective Synthesis of Cyclohexadienone Containing Hindered Spirocyclic Ethers through an Oxidative Dearomatization/Oxa-Michael Addition Sequence



An asymmetric oxa-Michael reaction of α-tertiary alcohols using chiral squaramide catalysts is reported. The reaction provided a broad array of sterically hindered tetrahydrofurans and tetrahydropyrans attached to a cyclohexadienone moiety in spiro fashion. Good yields and enantioselectivities were observed. The oxocycles obtained were transformed into chromans without disturbing the enantioselectivity.