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Enantioselective synthesis of hindered cyclic dialkyl ethers *via* catalytic oxa-Michael/Michael desymmetrization†

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Abstract

An asymmetric oxa-Michael/Michael cascade reaction of *p*-quinols and α,β-unsaturated aldehydes provides access to hindered dialkyl ethers. A highly enantioselective oxa-Michael addition of a tertiary alcohol precedes an intramolecular cyclohexadienone desymmetrization, which allows for the concomitant formation of four contiguous stereocenters in a single step. The highly functionalized bicyclic frameworks are rapidly obtained from simple starting materials with good diastereoselection and serve as valuable precursors for further manipulation.

Introduction

Sterically hindered ethers are ubiquitous in natural products and their asymmetric preparation is a long-standing challenge to the synthetic community. Limitations of classical methods for the preparation of tertiary ethers, such as the Williamson ether synthesis, include undesirable racemization and elimination pathways.[1] Current C–O bond forming methodologies to address these limitations include metal-mediated alkene functionalizations,[2] carbonyl ylide cycloadditions,[3] among others;[4] intramolecular C–O bond formation with creation of a single α-stereocenter is common. A more powerful method for complexity-building synthesis could arise from intermolecular C–O bond formation allowing the preparation of α-tertiary ethers where both α-stereocenters are set in a single operation, but examples of these are rare.[4j] Herein, we report a direct metal-free synthesis of hindered *tert/sec* ethers *via* an organocatalytic oxa-Michael/Michael sequence involving tertiary alcohols and α,β-unsaturated aldehydes with concomitant formation of four contiguous stereocenters.

As conceptualized in Scheme 1a, we sought to develop an asymmetric C—O bond construction involving achiral tertiary carbinols bearing enantiotopic groups that would undergo subsequent diastereoselective desymmetrization to establish the tertiary stereogenic center. The illustrated (3 + 2)-annulation[5] was targeted as an attractive embodiment of this strategy and would require initiation by oxa-Michael addition to an α,β-unsaturated carbonyl (Scheme 1b). Despite increasing attention in the literature, the oxa-Michael addition retains key challenges limiting its broad utility as a general method for the construction of hindered ethers: poor nucleophilicity, competitive acetal/ketal formation, and reversibility.[6] Consequently, phenols and oximes are typically employed in asymmetric intermolecular oxa-Michael additions due to their heightened reactivity.[7] Applications of secondary and

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tertiary alcohols in oxa-Michael reactions are scarce due to their α-stereogenicity and reduced nucleophilicity; generally limiting their application to intramolecular kinetic resolutions.[8] Based on recent work by Córdova, we believed carefully selected tertiary alcohols could be effective participants in oxa-Michael additions in conjunction with an ensuing intramolecular complexity building transformation.[8c]

The strategy described above implicitly relies on simple access to the achiral tertiary alcohol; dearomatization is a valuable method that is relevant in the present context.[9] In particular, oxidative dearomatization of 4-substituted phenols with an oxygen nucleophile provides access to *p*-quinols,[10] a unique cyclohexadienone subclass that has been applied in various desymmetrization processes.[11] Gaunt demonstrated the potential to perform direct enantioselective dearomatization reactions of phenols employing $PhI(OAc)_2$ in conjunction with enamine catalysis (Scheme 2a),[11d] while Rovis developed enantioselective synthesis of endoperoxide acetals by desymmetrization of the achiral hydroperoxides (Scheme 2b).[11j] *p*-Quinol **1** possesses both a tertiary alcohol capable of participating in intermolecular oxa-Michael addition and enantiotopic π-electrophiles for subsequent intramolecular desymmetrization. We proposed that these attributes could establish *p*-quinol **1** as a competent substrate class for iminium/enamine oxa-Michael/Michael cascade reactions under secondary amine catalysis.[12]

Results and discussion

We commenced our investigation by examining the reaction of *p*-quinol **1a** with cinnamaldehyde (**2a**) employing Jørgensen–Hayashi diarylprolinol ether catalysts **3** due to their applicability in a variety of aldehyde functionalization reactions.[13] Gratifyingly, silyl ether **3b** in conjunction with benzoic acid as an additive provided **4a** in 61% yield with good diastereocontrol and excellent enantioselection (Table 1, entry 1). The use of basic additives like $NaHCO_3$ was found to be detrimental to the reaction (entry 2). Switching the solvent to toluene and utilizing 4-nitrobenzoic acid (PNBA) increased the yield to 82% with no loss in stereocontrol (entry 4). Although high levels of enantio-selectivity were observed in the initial oxa-Michael addition, efforts to increase the diastereoselection of the subsequent intramolecular Michael addition through structural modifications of the catalyst **3** were largely unsuccessful. Both free alcohol **3a** and 3,5-$(CF_3)_2$Ph-derived **3d** completely shut down the reaction (entries 5 and 7). Catalysts possessing a bulkier TES group (**3c**) or 3,5-Me_2Ph aryl groups (**3e**) provided **4a** in good yield, but lower levels of diastereoselection (entries 6 and 8). Optimized conditions were realized using commercially available **3b** with 1.5 equivalents of cinnamaldehyde affording **4a** in 81% yield with 15:1 dr and >99.5:0.5 er (entry 9).

The feasibility of employing other quinol and aldehyde reactants was examined as the reaction's scope was probed (Table 2). Excellent levels of enantioselection were observed for all substrates irrespective of the steric and electronic features of the nucleophile and electrophile. In addition to the parent product **4a**, products can be obtained bearing strongly electron-releasing and withdrawing *para*-substituents with slightly reduced diastereocontrol (**4b** and **4c**). Aromatic aldehydes bearing *ortho*-substituents were found to provide excellent levels of diastereocontrol regardless of electronic features (**4d**, **4e**, and **4f**). The bulky mesityl-group could be incorporated providing **4g** in good chemical yield and enantioselectivity, but with low diastereocontrol (4 : 1 dr). Thien-2-yl and indol-3-yl functionality was amenable to the reaction providing access to heteroaromatic substrates **4h** and **4i**. Aldehydes bearing a γ-enolizable site are also compatible under the reaction conditions as crotonaldehyde provides access to Me-substituted **4j** in 58% yield and 7 : 1 dr with 99 : 1 enantioselection. Only trace byproducts were observed from undesired dienamine formation. In addition to methyl-substituted **1a**, a variety of *p*-quinols were

tolerated bearing linear aliphatic substituents allowing for the incorporation of pendant siloxy and ester functionality (**4k**, **4m**, and **4n**). The bulkier ^{i}Pr-derived *p*-quinol provided **4l** in 71% yield, but with modest diastereoselection in the intramolecular Michael addition.

In order to further highlight the potential applicability of this methodology, the reaction of **1a** and **2d** was performed on 20 mmol scale employing commercially available catalyst **3b** with technical grade reagents under ambient atmosphere providing **4d** in 82% yield after a single recrystallization (Scheme 3).

In addition to providing complex fused bicyclic frameworks with good stereocontrol, the products contain synthetically useful aldehyde and enone functional handles for further orthogonal manipulations (Scheme 4). Chemoselective reduction of aldehyde **4a** afforded alcohol **5a** (92% yield), which was subsequently converted to the *p*-nitrobenzoate **6**. The absolute stereochemistry of the product was assigned by an X-ray diffraction study of **6** and others were assigned by analogy.[14] The illustrated X-ray structure reveals a rigidified structure that was projected to engender excellent stereocontrol in manipulations of π-functional groups. Indeed, Weitz–Scheffer reaction of **4d** afforded epoxide 7 as a single diastereomer bearing six contiguous stereocenters. Chemoselective Horner–Wadsworth–Emmons olefination of **4n** provided diester **8** in 96% yield. A one-pot TBS-cleavage/oxa-Michael cyclization of **4m** gave access to aldehyde **9** bearing a tricyclic framework found in the physalins.[15] Exposure of **4d** to benzylamine and $NaBH_3CN$ generated tricycle **10** presumably *via* sequential epimerization, reductive amination, and intramolecular aza-Michael addition from the concave surface of the bicyclic enone.[16]

Conclusions

In conclusion, we have developed an asymmetric synthesis of hindered cyclic dialkyl ethers *via* intermolecular oxa-Michael addition of *p*-quinols and α,β-unsaturated aldehydes under secondary amine catalysis. The reaction provides rapid construction of complex bicyclic frameworks in uniformly high enantioselectivity and good to excellent levels of diastereoselectivity. The application of dearomatization/desymmetrization strategies for the conversion of simple starting materials to functionally-rich complex cores is of ongoing interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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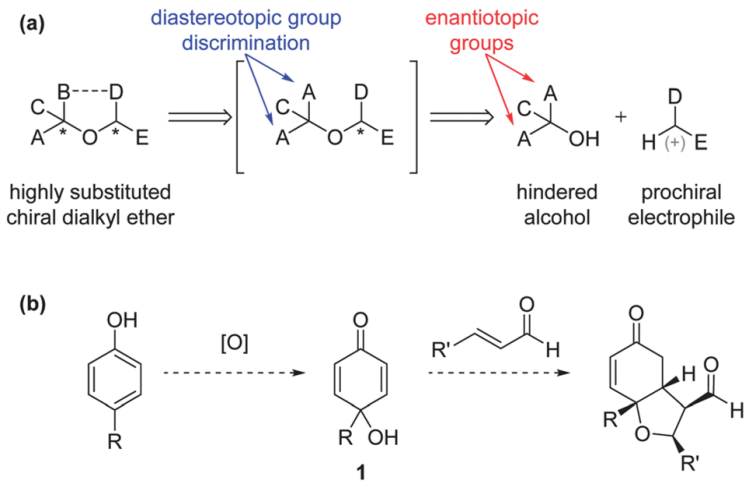
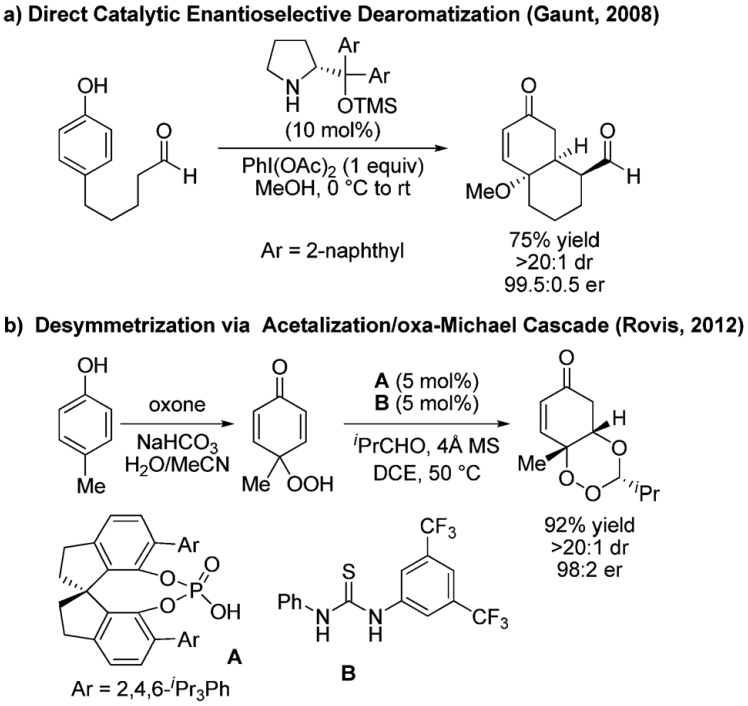
16. See the ESI† for further analysis

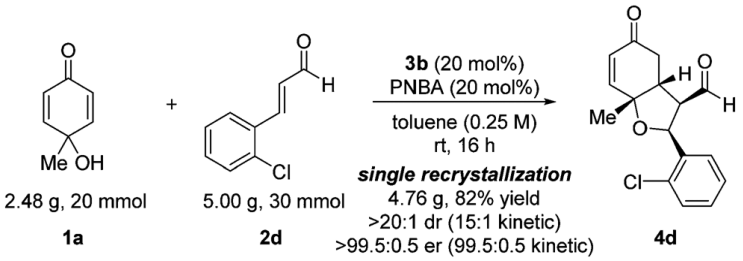
†Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra, and HPLC/SFC traces. CCDC 926927. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc51022k



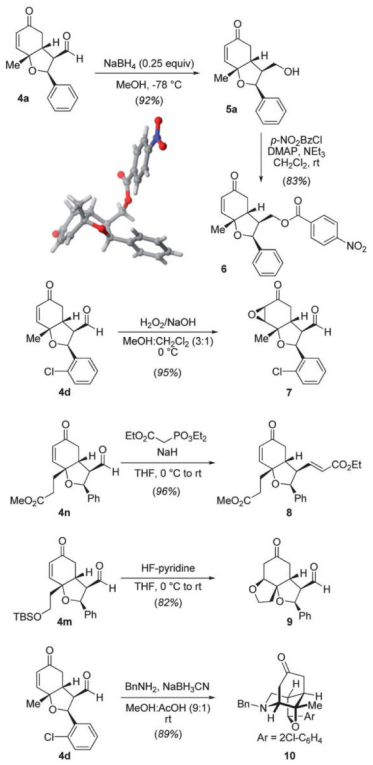
Scheme 1.
Asymmetric approach to hindered ether synthesis.



Scheme 2.
Select cyclohexadienone desymmetrization strategies.



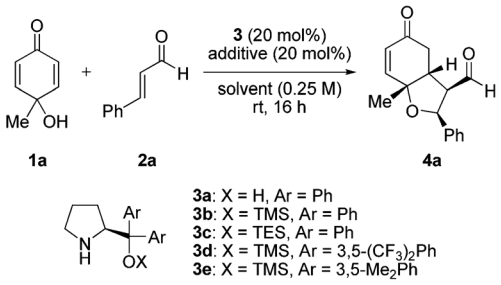
Scheme 3.
Gram scale synthesis.



Scheme 4.
Transformation of products.

Table 1

Reaction optimization[a]



Entry	3	Additive	Solvent	Yield (%)[b]	dr[c]	er[d]
1	**3b**	$PhCO_2H$	CH_2Cl_2	61	15 : 1	99.5 : 0.5
2	**3b**	$NaHCO_3$	CH_2Cl_2	Trace[c]	—	—
3	**3b**	$PhCO_2H$	Toluene	78	15 : 1	>99.5 : 0.5
4	**3b**	PNBA	Toluene	82	16: 1	>99.5 : 0.5
5	**3a**	PNBA	Toluene	0	—	—
6	**3c**	PNBA	Toluene	72	7 : 1	>99.5 : 0.5
7	**3d**	PNBA	Toluene	0	—	—
8	**3e**	PNBA	Toluene	75	9 : 1	>99.5 : 0.5
9[e]	**3b**	PNBA	Toluene	81	15 : 1	>99.5 : 0.5

[a] Reactions were performed on 0.30 mmol scale, using 3.0 equiv. aldehyde unless otherwise noted.

[b] Isolated yield of major diastereomer.

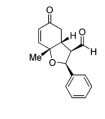
[c] Determined by ^1H NMR analysis of crude reaction mixture.

[d] Determined by chiral SFC analysis.

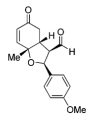
[e] Employing 1.5 equiv. aldehyde.

Table 2

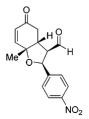
Substrate scope[a]



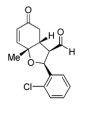
4a 81% yield
15 : 1 dr, >99.5 : 0.5 er



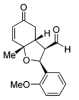
4b 80% yield
9 : 1 dr, 98 : 2 er



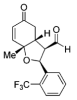
4c[b] 77% yield
7 : 1 dr, >99.5 : 0.5 er



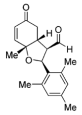
4d 93% yield
17 : 1 dr, >99.5 : 0.5 er



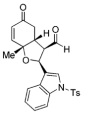
4e 86% yield
14 : 1 dr, >99.5 : 0.5 er



4f 91% yield
>20 : 1 dr, 99.5 : 0.5 er



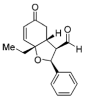
4g 76% yield
4 : 1 dr, 99 : 1 er



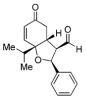
4h[b] 73% yield
5 : 1 dr, 98 : 2 er

4i 65% yield
7 : 1 dr, 97 : 3 er

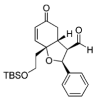
4j 58% yield
7 : 1 dr, 99 : 1 er



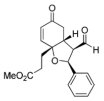
4k 77% yield
12 : 1 dr, >99.5 : 0.5 er



4l[c] 71% yield
6 : 1 dr, 99 : 1 er



4m 82% yield
13 : 1 dr, 99 : 1 er



4n 75% yield
6 : 1 dr, >99.5 : 0.5 er

[a] Reactions were performed on 1.00 mmol scale, using 1.5 equiv. aldehyde. Isolated yields of analytically pure major diastereomer are reported. Diastereomer ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures; enantiomer ratios were determined by chiral HPLC/SFC analysis.

[b] Toluene:CH_2Cl_2 (1 : 1) (0.25 M).

[a] Isolated yield of 10 : 1 dr mixture.