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Enantioselective Synthesis of γ-Hydroxyenones by Chiral Base-Catalyzed Kornblum DeLaMare Rearrangement

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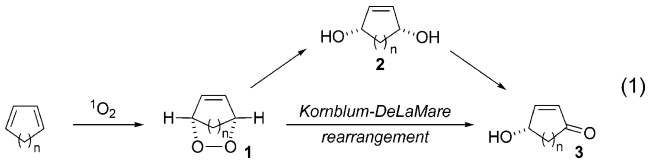
4-Hydroxyenones (**3**) are important building blocks for asymmetric organic synthesis.[1] Enantioselective synthesis of this class of molecules generally relies on metal-catalyzed[2] or biocatalytic[3] desymmetrization of diols (**2**) or their derivatives (eq 1). Given that these diols are most commonly prepared by photooxygenation of 1,3-dienes, we envisioned desymmetrization of the intermediate *meso*-endoperoxide (**1**) as a more direct means for the overall asymmetric 1,4-dioxygenation of cyclic 1,3-dienes.[4] While enantioselective transforms of endoperoxides are rare,[5] we anticipated the possibility of achieving a desymmetrization of bicyclic endoperoxides to enantioenriched γ-hydroxyenones via chiral base-catalyzed Kornblum DeLaMare rearrangement.[6]

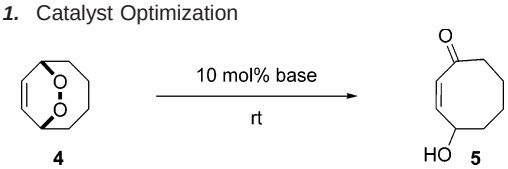


(1)

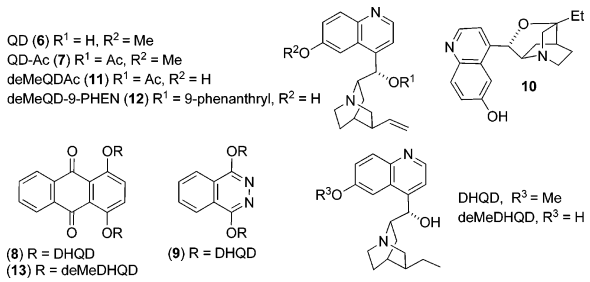
On the basis of the observation that the Kornblum DeLaMare rearrangement may be promoted by trialkylamines (i.e., Et_3N), we examined a series of chiral nonracemic amines as catalysts for this reaction. While the majority of amines tested promoted very little rearrangement and poor enantioinduction (for example, 10 mol % (−)-sparteine gave **5** in 90% yield and <5% ee after 3 days),[7] the use of cinchona alkaloids as catalysts resulted in a dramatic increase in both reactivity and enantioselectivity (Table 1). Although monomeric cinchona alkaloids provided **5** with modest enantiomeric excess (entries 1,2), dimeric cinchona catalyst $(DHQD)_2AQN$ (**8**) catalyzed the desymmetrizaton of **4** with an improvement in enantioselectivity to 72% ee (entry 3). Disappointingly, further examination of other dimeric catalyst systems proved unfruitful (i.e., entry 4). Inspired by recent reports,[8] we tested bifunctional cinchona alkaloids bearing a 6′-hydroxy group on the quinoline ring. To our delight, demethylated catalyst **11** provided a notable increase in enantioselectivity, affording **5** in quantitative yield and 99% ee (compare entries 2 and 6). Additionally, switching the solvent from ethyl acetate to methylene chloride allowed for the reaction to reach completion in only 6 h (entry 7).[9] Moreover, treatment of **4** with a sub-stoichiometric amount of pseudoenantiomeric quinine-derived catalyst (deMeQAc (**14**)) provided *ent*-**5** with similar enantioselectivity (entry 10). In contrast to our earlier findings, dimeric catalyst **13** provided the product in slightly lower enantioselectivity than monomeric version **11** (compare entries 8 and 9).

Under the optimized reaction conditions, 5 mol % **11** catalyzed the conversion of endoperoxide **4** to γ-hydroxyenone **5** in 97% yield and 99% ee after 6 h at room temperature (Table 2, entry 1). Furthermore, catalyst **11** was quantitatively recovered from the reaction mixture. Cinchona alkaloid **11** catalyzed the transformation of substituted dioxabicyclo[4.2.2]decene **15** with equal efficiency,

Table 1. Catalyst Optimization



entry	catalyst	solvent	time	% yield	% ee
1	QD (**6**)	EtOAc	12 h	51	10
2	QD-Ac (**7**)	EtOAc	4 d	50	14
3	$(DHQD)_2AQN$ (**8**)	EtOAc	16 h	67	72
4	$(DHQD)_2PHAL$ (**9**)	EtOAc	12 h	38	32
5	(**10**)	EtOAc	8 h	89	28
6	deMeQDAc (**11**)	EtOAc	16 h	99	99
7	deMeQDAc (**11**)	CH_2Cl_2	6 h	99	99
8	deMeQD-9-PHEN (**12**)	CH_2Cl_2	6 h	99	99
9	$(deMeDHQD)_2AQN$ (**13**)	CH_2Cl_2	6 h	99	97
10	deMeQAc (**14**)	CH_2Cl_2	6 h	99	−97



affording γ-hydroxyenone **16** in quantitative yield and 99% ee (entry 2).

Seven-membered ring γ-hydroxyenones are available in excellent yield and enantioselectivity from desymmetrization of substituted dioxabicyclo[3.2.2]nonenes catalyzed by 5 mol % **11** (entries 3−5). Dioxabicyclo[2.2.2]octenes are also viable substrates for the base-catalyzed enantioselective reaction. Thus, **23** was converted to **24** with concomitant creation of three consecutive chiral centers in 96% ee (entry 9). Importantly, potentially base labile β-hydroxy-, siloxy-, and alkoxy- leaving groups remained stable under the mild reaction conditions (entries 2−7, 9), although some epimerization of the α-stereocenter is observed. Disappointingly, steric reduction of substituents (i.e., entry 8, R = H or entry 9, R = OMOM) led to a corresponding reduction in enantioenrichment of the products. The absolute stereochemistry of the γ-hydroxyenones derived from the asymmetric Kornblum DeLaMare rearrangement was assigned by comparison of optical rotation with known enone **28**[2a] and the acetate derivatives of **22** and **36**.[10] The absolute stereochemistry of the remaining of enones was assigned by analogy.

In analogy to the tertiary amine-promoted rearrangement of endoperoxides,[6c] we propose that the cinchona alkaloid catalyst functions as a base in an enantioselective *E*2 elimination.[12,13] The increased enantioselectivity (and rate of reactivity) observed with the demethylated catalysts supports dual-Brönsted base/Brönsted

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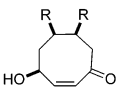
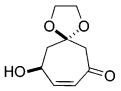
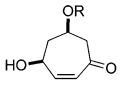
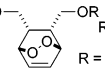
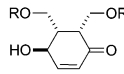
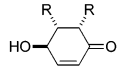
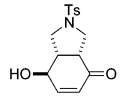
Table 2. Scope of Enantioselective Kornblum-DeLaMare Reaction

entry	endoperoxide	reaction conditions[a]	product	%yield	%ee
1	 R = H (**4**)	5% **11**, rt, 6 h	 (**5**)	97	99
2	R,R = $OC(Me)_2O$ (**15**)	5% **11**, rt, 10 h	(**16**)	99	99
3	 (**17**)	5% **11**, 0 °C, 24 h	 (**18**)	95	91
4[b]	 R = H (**19**)	5% **11**, 0 °C, 24 h	 (**20**)	99	87
5	R = TBS (**21**)	5% **11**, rt, 12 h	(**22**)	83	99
6	 R = Bn (**23**)	10% **11**, rt, 24 h	 (**24**)	90[c]	96
7	R = -C(Me)$_2$- (**25**)	10% **11**, rt, 36 h	(**26**)	76	89
8	 R = H (**27**)	10% **11**, rt, 48 h	 (**28**)	89	50
9	R = OMOM (**29**)	10% **11**, rt, 3 d	(**30**)	76[d]	70
10	 (**31**)	10% **11**, rt, 20 h	 (**32**)	99[e]	73

[a] Reactions run at 0.1−2.0 M in CH_2Cl_2. [b] Starting endoperoxide and product a 3.5:1 mix of hydroxyepimers. [c] Isolated as a 6:1 mix of α-diastereomers.[11] [d] Isolated as a 4:1 mix of α-diastereomers. [e] Isolated as a 8:1 mix of α-diastereomers.

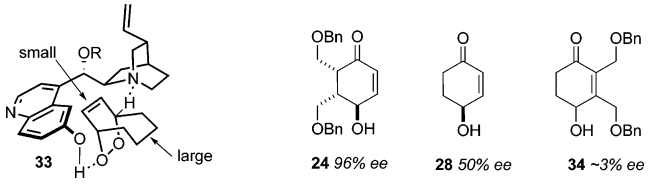
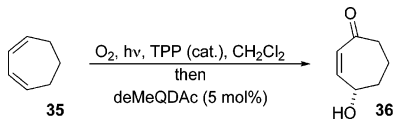


Figure 1. Proposed Model for Enantioinduction.

acid activation of the endoperoxide. Additionally, we noted that substituted cyclohexenone **24** was formed in significantly greater enantioselectivity than **28**; however, poor enantioselectivity was obtained in the synthesis of enones (e.g., **34**) with substituted olefins. On the basis of these observations we propose a model (**33**) in which the tertiary amine and hydroxyl group interact with the endoperoxide such that the olefin moiety is positioned in the sterically demanding pocket encompassed by the quinoline ring (Figure 1).[8a,f] The decrease in enantioselectivity observed when the reaction is conducted in a protic solvent[9] is also consistent with participation of the 6′-hydroxyl group in the enantiodetermining event.

In summary, the first enantioselective Kornblum DeLaMare rearrangement based on the desymmetrization of meso-endoperoxides by chiral base catalysis has been developed. A mechanism involving bifunctional catalysis of an *E*2-elimination is proposed and thus represents a rare example of cinchona-alkaloid catalyzed enantiodetermining deprotonation.[14] The reaction is amenable to a variety of substrates providing an expedient entry into enantioenriched γ-hydroxyenones from 1,3-dienes. This fact is exemplified by a one-pot asymmetric 1,4-dioxygenation of 1,3-cycloheptadiene (**35**) by sequential reaction with singlet oxygen and 5 mol % **11** providing γ-hydroxyenone **36** in 90% yield and 92% ee (eq 2).[15]



90% yield, 92% ee (2)

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) See Supporting Information for a complete list of amine bases examined as catalysts.

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(9) With the exception of methanol (10 h, 99% yield, 80% ee), 10% **11** catalyzed the formation of **5** in other solvents ($PhCH_3$, 12 h, 99%, 99% ee; THF, 20 h, 99%, 97% ee; acetone 12 h, 99%, 97% ee) with similar enantioselectivities but slower rates than in methylene chloride

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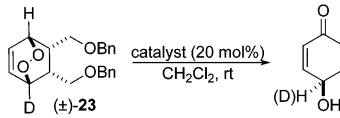
(11) Product **24** can be converted to the diastereomeric trans-epimer (4:1 dr) by treatment with triethylamine.

(12) Consistent with this hypothesis is a large primary kinetic isotope effect for the reaction of monodeuterated (±)-**23-d** with both triethylamine and a 1:1 mixture of deMeQDAc: deMeQAc (D/H = 4.4 and 5.0, respectively).



catalyst	D/H
Et_3N	4.4
11, **14** (1:1)	5.0

(13) For reviews of base-catalyzed enantioselective eliminations see: (a) Eames, J. *Eur. J. Org.* Chem. **2002**, 393. (b) Magnus, A.; Bertilsson, S. K.; Andersson, P. G. *Chem. Soc. Rev.* **2002**, *31*, 223. (c) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (d) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

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(15) Reaction of the purified intermediate endoperoxide, catalyzed by 5 mol % **11**, produced **36** in 97% yield and 91% ee.

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