

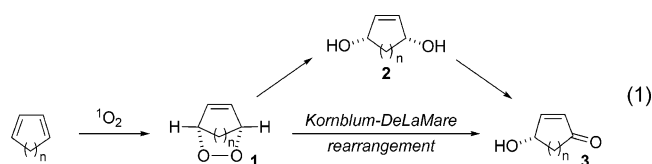
Enantioselective Synthesis of γ -Hydroxyenones by Chiral Base-Catalyzed Kornblum DeLaMare Rearrangement

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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-catalyzed² or biocatalytic³ 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

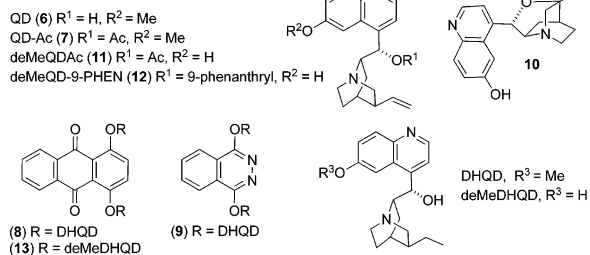


On the basis of the observation that the Kornblum DeLaMare rearrangement may be promoted by trialkylamines (i.e., Et₃N), we examined a series of chiral nonracemic amines as catalysts for this reaction. While the majority of amines tested promoted very little rearrangement and poor enantioinduction (for 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 desymmetrization 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) ₂ AQN (8)	EtOAc	16 h	67	72
4	(DHQD) ₂ PHAL (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 ₂ Cl ₂	6 h	99	99
8	deMeQD-9-PHEN (12)	CH ₂ Cl ₂	6 h	99	99
9	(deMeDHQD) ₂ AQN (13)	CH ₂ Cl ₂	6 h	99	97
10	deMeQAc (14)	CH ₂ Cl ₂	6 h	99	–97



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

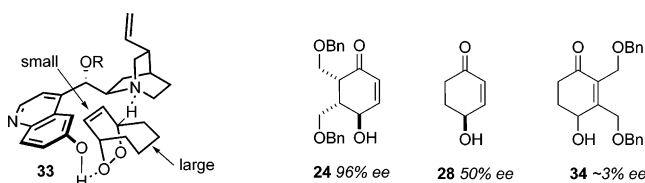
Seven-membered ring γ -hydroxyenones are available in excellent yield and enantioselectivity from desymmetrization of substituted dioxabicyclo[3.2.2]nonenes catalyzed by 5 mol % **11** (entries 3–5). Dioxabicyclo[2.2.2]octenes are also viable substrates for the base-catalyzed enantioselective reaction. 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 E2 elimination.^{12,13} The increased enantioselectivity (and rate of reactivity) observed with the demethylated catalysts supports dual-Brønsted base/Brønsted

Table 2. Scope of Enantioselective Kornblum-DeLaMare Reaction

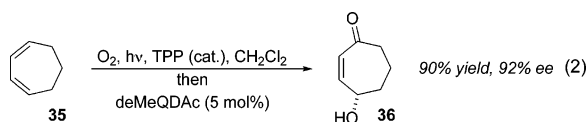
entry	endoperoxide	reaction conditions ^a	product	%yield	%ee
1		R = H (4)		97	99
2		5% 11, rt, 10 h		99	99
3		(17)		95	91
4 ^b		R = H (19)		99	87
5		R = TBS (21)		83	99
6		R = Bn (23)		90 ^c	96
7		R = -C(Me) ₂ - (25)		76	89
8		R = H (27)		89	50
9		R = OMOM (29)		76 ^d	70
10		(31)		99 ^e	73

^a Reactions run at 0.1–2.0 M in CH₂Cl₂. ^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 solvent⁹ 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 *E2*-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

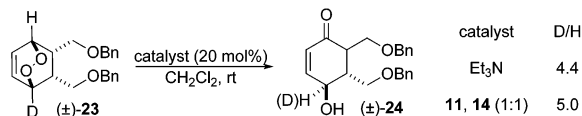


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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) With the exception of methanol (10 h, 99% yield, 80% ee), 10% **11** catalyzed the formation of **5** in other solvents (PhCH₃, 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 (\pm)-**23-d** with both triethylamine and a 1:1 mixture of deMeQDac: deMeQAc (D/H = 4.4 and 5.0, respectively).



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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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