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Asymmetric Approach toward Chiral Cyclohex-2-enones from Anisoles via an Enantioselective Isomerization by a New Chiral Diamine Catalyst

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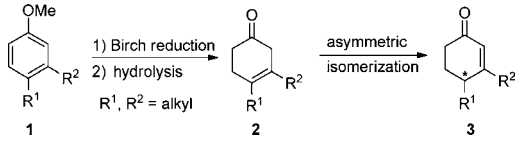
Supporting Information

ABSTRACT: A 3-step asymmetric approach toward the optically active chiral cyclohex-2-enones from anisoles has been developed. The crucial asymmetric induction step is an unprecedented catalytic enantioselective isomerization of β,γ-unsaturated cyclohex-3-en-1-ones to the corresponding α,β-unsaturated chiral enones. This new asymmetric transformation was realized by cooperative iminium-base catalysis with an electronically tunable new organic catalyst. The synthetic utility of this methodology is highlighted by the enantioselective total synthesis of (−)-isoacanthodoral.

Chiral 6-membered carbocycles are among the most common structural motifs in functional organic molecules.[1] Consequently, the development of efficient methods for the construction of 6-membered carbocycles represents a fundamentally important task in organic synthesis. Chiral cyclohex-2-enones[1k−p,2] constitute arguably the most versatile synthon for 6-membered carbocycles due to their ability to participate in stereoselective 1,4- and 1,2-additions with numerous nucleophiles and pericyclic reactions with a broad range of partners. Here we report the development of a concise catalytic enantioselective route for the transformation of substituted anisoles to optically active cyclohex-2-enones and its application to the first asymmetric synthesis of the natural product (−)-isoacanthodoral.

We became interested in the application of asymmetric proton transfer catalysis to the development of an isomerization of alkyl cyclohex-3-enones **2** to cyclohex-2-enones **3**, as it would provide the stereochemistry-defining transformation for a 3-step route[3] from anisoles **1** to optically active enones **3** (Scheme 1). Although the isomerizations of β,γ-unsaturated ketones to their α,β-unsaturated counterparts have been reported to be catalyzed by both enzymes and small-molecule-based acids, bases, and amines,[4] an enantioselective variant has not been reported to date.[5a,b] Building on our recent progress in the development of an asymmetric olefin isomerization of β,γ-butenolides,[5b] we initially attempted the isomerization of β,γ-unsaturated cyclohexenone **2A** with known cinchona alkaloid derivatives bearing a H-bond donor (**4**–**6**, Figure 1).[5b−f] Although these cinchona

Scheme 1. Asymmetric Synthesis of Cyclohex-2-enones from Anisoles 1



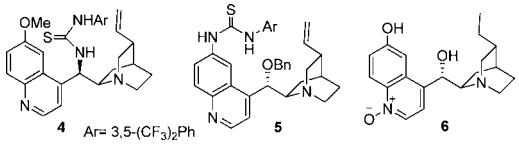
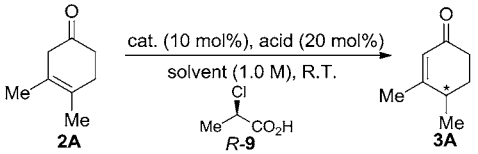


Figure 1. Some H-bonding organocatalysts from cinchona alkaloids.

Table 1. Asymmetric Isomerization of 2A to 3A



entry[a]	cat.	acid	solvent (x M)	time (h)	%conv.[c]	%ee[d]
1	**4**		$CHCl_3$ (1.0 M)	18	NR	
2	**5**		$CHCl_3$ (1.0 M)	18	NR	
3	**6**		$CHCl_3$ (1.0 M)	18	4	
4	QD-**7**	TFA	$CHCl_3$ (1.0 M)	18	95	30
5	QD-**8a**	TFA	$CHCl_3$ (1.0 M)	18	9	65
6	QD-**8b**	TFA	$CHCl_3$ (1.0 M)	18	65	67
7	QD-**8c**	TFA	$CHCl_3$ (1.0 M)	18	99	40
8	QD-**8b**	AcOH	$CHCl_3$ (1.0 M)	1 d	83[b]	57
9	QD-**8b**	$PhCO_2H$	$CHCl_3$ (1.0 M)	3	57[b]	52
10[f]	QD-**8b**	*rac*-**9**	$CHCl_3$ (1.0 M)	2 (24)	98	70 (50)
11	QD-**8b**	*S*-**9**	$CHCl_3$ (1.0 M)	2	86	71
12[f]	QD-**8b**	*R*-**9**	$CHCl_3$ (1.0 M)	2 (24)	98	73 (55)[g]
13[f,h]	QD-**8b**	*R*-**9**	$CHCl_3$ (1.0 M)	6 (24)	75 (>98)	79 (78)
14[i]	QD-**8b**	*R*-**9**	$CHCl_3$ (1.0 M)	48	60	84
15[i]	QD-**8b**	*R*-**9**	$PhCH_3$ (1.0 M)	48	96	84
16[i]	QD-**8b**	*R*-**9**	$PhCH_3$ (0.33 M)	72	87	87
17[i]	Q-**8b**	*R*-**9**	PhF (0.33 M)	10 d	58	-77
18[i]	Q-**8c**	$ClCH_2CO_2H$	PhF (0.33 M)	6 d	96	-84

[a]Unless noted, reactions were run with 0.1 mmol of **2A** at rt in $CHCl_3$ (1.0 M). [b]Determined by ^1H NMR. [c]Determined by GC. [d]Determined by HPLC. [f]Data in parentheses were obtained when the reactions were conducted for 24 h. [g]Absolute configuration was determined as *R*.[9] [h]Reaction was run at 0 °C. [i]Reaction was run at −25 °C.

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alkaloid derivatives showed considerable catalytic activity for the isomerization of β,γ-butenolides, they failed to afford meaningful activity for the isomerization of the enone **2A** (Table 1, entries 1−3) at room temperature. The failure of these catalysts in activating enone **2A** for the isomerization could be attributed to the low acidity of the α-H of enone **2A** relative to that of 5-membered β,γ-butenolides.[6]

Although cooperative acid−base catalysis by the Δ^5-3-ketosteroid isomerase is implicated by extensive mechanistic studies for the isomerization of β,γ- to α,β-unsaturated steroidal ketones,[4a−d] the same isomerization has also been shown to readily occur with cooperative iminium-base catalysis by primary amines and catalytic antibodies, respectively.[4g−i] With respect to the former, Kayser and Pollack first demonstrated that an aqueous solution of 2,2,2-trifluoroethylamine could promote the isomerization of 3-methyl cyclohex-3-enone to its α,β-unsaturated isomer. The same authors also reported a particularly insightful kinetic result, namely the determination of a second-order dependence of the rate of isomerization on the amine concentration, which provided strong support for an enamine pathway initiated by deprotonation of the α-H in 3-methyl-cyclohex-3-enone via cooperative iminium-base catalysis.[4g]

We thus initiated an investigation of the 9-NH_2 cinchona alkaloid QD-7 (Figure 2) as a catalyst for the isomerization of the

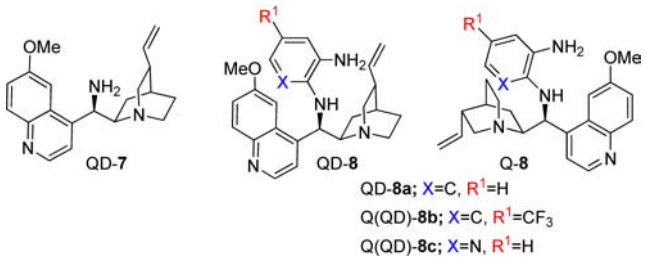
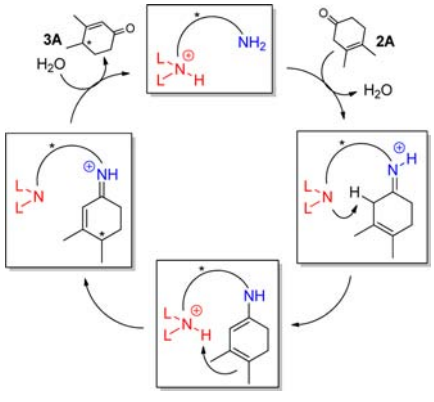


Figure 2. Electronically tunable primary amine catalysts derived from cinchona alkaloids.

enone **2A**. Presumably, the chiral diamines such as QD-7 could mediate the enantioselective isomerization of the enone **2A** via the enamine pathway with cooperative iminium-base catalysis (Scheme 2). In the presence of TFA as a cocatalyst, the isomerization of **2A** progressed to near completion and produced the desired α,β-unsaturated enone **3A** in 30% ee (Table 1, entry 4). These results verified that chiral diamines such as QD-7 could afford the desired activity for the isomerization of **2A** to **3A**.

Scheme 2. Proposed Mechanism for Isomerization of 2A via an Enamine Pathway by a Chiral Primary−Tertiary Diamine



Unfortunately, attempts to improve the enantioselectivity of QD-7 were met with no success.

Although catalyst **7** has been successfully applied as an efficient catalyst for a range of asymmetric transformations,[7] one disadvantage of **7** is the lack of a handle for catalyst tuning. In order to develop an effective catalyst to afford highly enantioselective cooperative iminium-base catalysis for the isomerization of **2A**, we designed a novel class of cinchona alkaloid-derived catalysts **8** that bears an aniline moiety at the C9 position. This design intended to take advantage of the electronically tunable features of the aniline for catalyst optimization, which we expect to have an impact on how facile the deprotonation step would occur and on how enantioselective the protonation step could be along the enamine pathway. Importantly, as described in detail in the Supporting Information, cinchona alkaloid derivatives **8a−c** presenting differing substituted anilines could be readily prepared in two steps from **7**.[8]

The tunable nature of **8** proved to be critical to the development of an efficient catalyst for the enantioselective isomerization of **2A**. Compared to QD-**7**, catalyst QD-**8a** was found to be less active but afford significantly higher enantioselectivity (Table 1, entry 5, 18 h, 9% conv., 65% ee). Importantly, in comparison to QD-**8a**, catalyst QD-**8b** presenting an aniline substituted with an electron-withdrawing trifluoromethyl group at the *para* position provided much improved activity without deterioration in enanioselectivity (Table 1, entry 6, 18 h, 65% conv., 67% ee). Bearing an even more electron-deficient aromatic amine, QD-**8c** furnished the highest activity but also the lowest enantioselectivty (Table 1, entry 7, 18 h, 99% conv., 40% ee). Building on the overall most promising result obtained with QD-**8b**, we next focused on the identification of the optimal acid cocatalyst, which led to the identification of chiral *R*-2-chloropropionic acid (*R*-**9**) as the optimal cocatalyst for both reactivity and selectivity (Table 1, entry 12, 2 h, 98% conv., 73% ee).[10]

Similar to our observations in the studies of other catalytic asymmetric isomerizations,[5b] erosion of optical purity of the product via racemization occurred gradually at room temperature (Table 1, entry 12, 24 h, 55% ee from 73% ee). Fortunately, this undesirable racemization could be nearly eliminated when the reaction was carried out at 0 °C (Table 1, entry 13, 79% ee). Upon further optimization of reaction temperature, solvent and concentration, a highly enantioselective isomerization of **2A** could be attained in toluene at −25 °C (Table 1, entry 16).[10] To our surprise, the quinine-derived Q-**8b** under the optimized condition did not perform nearly as well as QD-**8b** did (Table 1, entry 17). Fortunately, after substantial catalyst screening and reaction optimization studies, we established that Q-**8c** catalyzed the isomerization of **2A** to afford the other enantiomer of the chiral product in high optical purity (Table 1, entry 18).[10]

Having achieved a highly enantioselective isomerization with enone **2A**, we turned our attention to the investigation of the substrate scope. The catalyst demonstrated a great deal of latitude in tolerating the alkyl groups at both the β- and γ-positions. Variations of the length of the alkyl chain at either position have no or little influence on either the catalytic activity or enantioselectivity. The sterically bulkier isopropyl group was also readily tolerated at both positions (Table 2, entries 1−5, 79−94% yield, 87−90% ee). It is noteworthy that the presence of the corresponding cyclohexanones of **2**, a commonly observed side product from the Birch reduction,[3b] showed no negative impact, as β,γ-unsaturated cyclohexenones **2** ranging from 70 to 98% in

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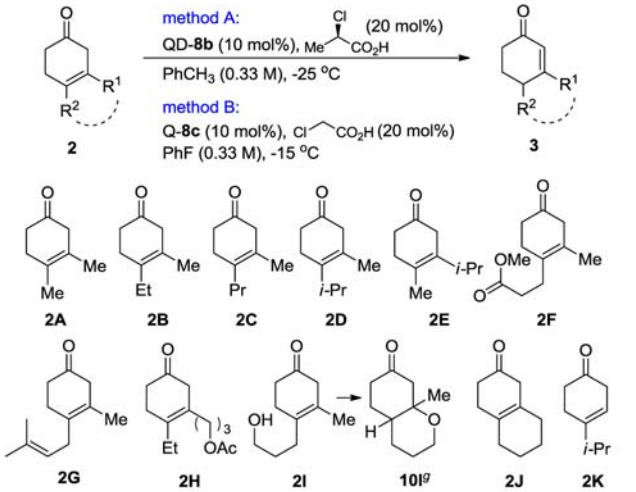
Table 2. Isomerization of β,γ-Unsaturated to α,β-Unsaturated Enones Catalyzed by QD-8b and Q-8c



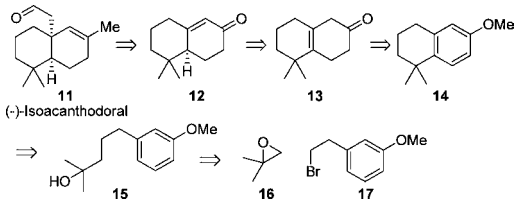
entry[a]	2	catalyst	3 or 10	time (h)	temp.(°C)	yield (%)[b]	ee (%)[c]
1	2A	QD-8b (Q-8c)	3A	96 (72)	-25 (-15)	83 (73)	88 (-79)
2	2B	QD-8b (Q-8c)	3B	96 (72)	-25 (-15)	85 (80)	88 (-83)
3	2C	QD-8b (Q-8c)	3C	96 (96)	-25 (-25)	94 (66)	87 (-87)
4[d]	2D	QD-8b (Q-8c)	3D	96 (96)	-25 (-25)	79 (72)	87 (-86)
5	2E	QD-8b (Q-8c)	3E	96 (72)	-25 (-15)	83 (75)	90 (-87)
6	2F	QD-8b (Q-8c)	3F	96 (72)	-25 (-15)	75 (58)	88 (-80)
7	2G	QD-8b (Q-8c)	3G	96 (72)	-25 (-15)	79 (84)	89 (-83)
8	2H	QD-8b (Q-8c)	3H	96 (72)	-25 (-15)	76 (58)	87 (-81)
9	2I	QD-8b (Q-8c)	10I	48 (48)	-25 (-25)	83 (71)	84 (-51)[f]
10	2J	QD-8b (Q-8c)	3J	96 (96)	-25 (-15)	67 (60)	85 (-78)
11[e]	2K	QD-8b	3K	72	R.T.	44	72

[a]Unless noted, reactions were run with 0.1 mmol of **2** with QD-**8b** by method A. Results in parentheses were obtained with Q-**8c** by method B. [b]Isolated yield. [c]Determined by HPLC. [d]Reaction was run with QD-**8b** in PhF. [e]10 mol% acid used. [f]Determined by GC. [g]Only one diastereomer was obtained.

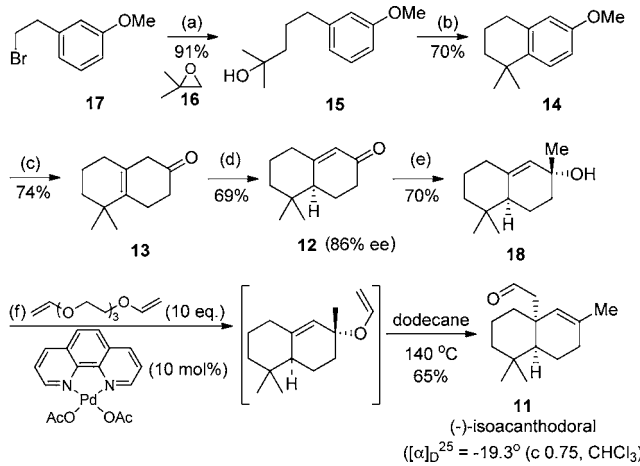
purity were successfully applied in the asymmetric isomerization. Moreover, enones **2** bearing functional groups such as prenyl and carboxylic ester were converted into the desired product in useful yield and enantioselectivity (Table 2, entries 6–8, 75–79% yield, 87–89% ee). Consequently, the asymmetric synthesis of the optically active γ-prenyl cyclohex-2-enone **3G** (Table 2, entry 7), an intermediate for the total synthesis of garsubellin A,[11] was readily accomplished from the corresponding anisole precursor. In addition, the presence of an unprotected hydroxyl group is also compatible with the reaction, rendering it possible to directly generate the chiral chromen-7-one **10I** from **2I** via an asymmetric tandem isomerization-conjugate addition reaction. To our delight, the bicyclic substrate **2J** was found to undergo the QD-**8b** catalyzed isomerization to furnish the $\Delta^{1,9}$-octalone-2 **3J** in 85% ee and 67% yield (Table 2, entry 10).[11] We also examined a γ-substituted cyclohex-3-en-1-one **2K**, which was converted into the expected product **3K** in 44% yield and 72% ee (Table 2, entry 11).

To illustrate the synthetic utility of this new asymmetric transformation, we embarked on the first asymmetric total synthesis of (−)-isoacanthodoral (**11**),[12] featuring a new strategy for the construction of the *cis*-fused bicyclo[4.4.0]dec-1-ene ring via the enantioselective isomerization of enone **13**. The enone **13** was to be prepared from a Birch reduction of anisole **14**, which in turn could be synthesized from anisole **17** (Scheme 3). Notably, to our knowledge, only two racemic syntheses of **11** have been reported, requiring 15 and 11 steps, respectively.[13a,b]

Scheme 3. Retrosynthetic Analysis



Scheme 4. Asymmetric Synthesis of (−)-Isoacanthodoral[a]



[a]Reagents and conditions: (a) Mg; CuI, THF, −20 °C; **16**, 91%. (b) Polyphosphoric acid, 10 °C, warm to rt, 70%, 13% regioisomer. (c) Li/NH_3/Et_2O; $(CO_2H)_2$, 74%. (d) QD-**8b** (10 mol%), *R*-2-chloropropionic acid (20 mol%), $PhCH_3$/PhF (5/1, 0.33 M), −20 °C, N_2(g), 5 d, 69%, 86% ee, **13** (16%). (e) MeLi·LiBr, −78 °C, 70%. (f) Dodecane (3.5 M), 65 °C, 5 d; dodecane (0.4 M), 140 °C, 20 h, 65%.

Our synthesis commenced with nucleophilic addition of the cuprate derived from **17** to dimethyl oxirane **16** (Scheme 4).[14] The resulting alcohol **15** readily underwent Freidel–Crafts cyclization in the presence of polyphosphoric acid[15] to furnish anisole **14** as the major isomer, which was subjected to Birch reduction followed by hydrolysis to form β,γ-unsaturated enone **13**. To our delight, upon minor modifications of the standard protocol,[10] the key asymmetric isomerization was accomplished in a highly enantioselective manner to afford the chiral bicyclic enone **12** in 86% ee and 69% yield. However, attempted 1,4-additions with vinyl cuprate to **12** invariably produced the 1,2-addition product along with unreacted enone **12**.[16] We then explored an alternative strategy featuring an intramolecular Claisen rearrangement to install the *cis*-fused bicyclic γ,δ-unsaturated aldehyde. Accordingly, enone **12** was subjected to 1,2-addition with MeLi·LiBr to yield alcohol **18** in 70% yield.[17] After considerable experimentations, a tandem vinylation–Claisen rearrangement reaction sequence following modifications of the protocol reported by Wei[18] was realized for the direct conversion of alcohol **18** into (−)-isoacanthodoral **11** in 65% yield. Thus, enantioselective total synthesis of (−)-isoacanthodoral was achieved in *seven* steps and 18% overall yield from commercially available starting materials **17** and **16**.

In summary, by exploring cooperative iminium-base catalysis with a newly designed class of electronically tunable organic catalysts derived from cinchona alkaloid, we have realized an

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unprecedented highly enantioselective asymmetric isomerization of β,γ-unsaturated cyclohexenones to their chiral α,β-unsaturated isomers. Consequently, optically active cyclohex-2-enones are accessible from anisoles. The synthetic potential of this new reaction was demonstrated in the design and the implementation of the first enantioselective synthesis of (−)-isoacanthodoral **11**. Notably, this enantioselective route not only is conceptually distinct in strategy from but also shorter and of higher yield than the existing racemic routes. It is noteworthy that the tunable nature of the aniline-containing cinchona alkaloid catalysts **8** proved to be critical for the development of an effective catalyst for the current asymmetric isomerization. More importantly, this feature of catalysts **8** should make them attractive candidates for the development of useful catalysts for other asymmetric transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, additional optimization studies, analytical data, and spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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