

Readily Accessible 9-epi-amino Cinchona Alkaloid Derivatives Promote Efficient, Highly Enantioselective Additions of Aldehydes and Ketones to Nitroolefins

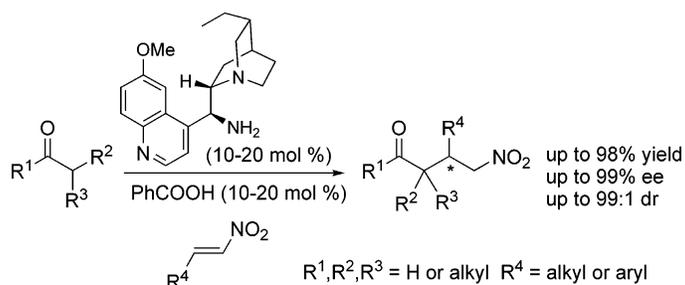
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ABSTRACT



Simple cinchona alkaloid derivatives, available via a one-pot procedure from commercially available starting materials, have been shown to promote highly enantio- and diastereoselective Michael-type addition reactions between enolizable carbonyl compounds and nitroalkenes of broad scope. The influence of both the absolute and relative stereochemistry at C-9 on catalyst performance has also been assessed.

Recent years have witnessed a dramatic upsurge in awareness among chemists of the potential utility of asymmetric organocatalysis as a tool for the synthesis of enantiopure molecules under mild, environmentally benign conditions.¹ The Michael addition of nucleophiles to nitroolefins² is proving a particularly attractive target for organocatalyst design, due largely to (a) the ready availability and high reactivity of nitroalkenes, (b) the ability of the nitro functionality to accept hydrogen bonds from suitably designed catalyst systems, and (c) the high synthetic utility of the nitroalkane adducts.

(1) Recent general reviews: (a) List, B. *Chem. Commun.* **2006**, 819. (b) Berkessel, A.; Gröger, H. In *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (c) Jayasree, S.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (e) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 487.

Existing organocatalysts for these nitro-Michael processes can be (ad hoc) categorized as promoting the addition of either acidic pronucleophiles^{3,4} or enolizable carbonyl compounds.^{5–7} Since the first reports of an amine-catalyzed asymmetric addition of ketones to nitroalkenes in 2001,^{5a–c} extraordinary progress has been made with respect to both stereoselectivity and substrate scope using both secondary^{5,6} and primary⁷ chiral amine catalysts. However, latitude for further development remains, in particular with regard to the design of readily accessible and inexpensive (in both antipodal forms) catalyst systems capable of promoting efficient, enantio/diastereoselective nitro-Michael additions involving both ketones and aldehydes (both straight-chain and α,α -disubstituted) of general utility.

(2) Recent reviews: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

With this in mind, we wished to design simple, readily available, and tunable 1,2-diamine catalyst templates based on the cinchona alkaloid backbone as mediators of asymmetric “enamine” organocatalysis for the first time (Figure 1). Such a strategy was appealing primarily for two rea-

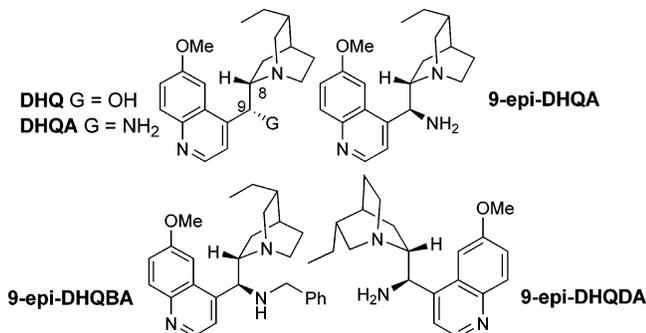


Figure 1. Novel cinchona alkaloid-derived catalysts.

sons: (a) availability – the alkaloid starting materials are inexpensive and available in both pseudoenantiomeric forms, thereby avoiding reliance on either amino-acid-derived

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Table 1. Initial Catalyst Screening and Optimization

entry	catalyst	acid	mol % H ₂ O	t (d)	conv (%) ^{a,b}
1	DHQA	CH ₃ COOH	100	5.8	7 (19)
2	9-epi-DHQA	CH ₃ COOH	100	5.8	24
3	9-epi-DHQBA	CH ₃ COOH	100	5.8	0
4	9-epi-DHQA		0	3.8	>98 ^c
5	9-epi-DHQBA		0	3.8	0
6	9-epi-DHQA		100	3.8	>98 ^c
7	9-epi-DHQA	CH ₃ COOH	0	3.8	31 (63)
8 ^d	9-epi-DHQA	CH ₃ COOH	0	3.7	24
9 ^d	9-epi-DHQA	CF ₃ COOH	0	3.7	15
10 ^d	9-epi-DHQA	PhCOOH	0	3.7	68 (45)
11 ^d	DHQA	PhCOOH	0	3.8	12
12 ^d	9-epi-DHQBA	PhCOOH	0	3.8	0
13 ^d	9-epi-DHQDA	PhCOOH	0	3.8	91 (–49)
14 ^d	9-epi-DHQDA	PhCOOH	0	3.8	90 ^e (–59)
15 ^d	9-epi-DHQDA	PhCOOH	0	6.9	73 ^f (–71)

^a Determined by ¹H NMR spectroscopy. ^b Enantioselectivity (% ee, determined by CSP-HPLC) in parentheses. ^c Multiple products. ^d 10 equiv of acetone used. ^e Isolated yield: reaction at 8 °C with 20 mol % catalyst. ^f Isolated yield: reaction at 0 °C with 20 mol % catalyst

stereogenicity or resolution techniques; in addition the catalysts would be accessible from available alkaloid derivatives in a one-pot procedure, and (b) tunability – we^{3e,k} and others^{3f,8} have recently demonstrated the potential advantages associated with tuning the chiral environment of modified cinchona alkaloid organocatalysts through the inversion of configuration at C-9; this together with an ability to design both primary and secondary prototype amine catalysts affords an exceptional degree of scope for catalyst optimization from simple starting materials.⁹ We therefore prepared the 9-amino derivative of dihydroquinine quinidine (DHQA) together with C-9 inverted and *N*-benzylated analogues (Figure 1)¹⁰ and evaluated them as organocatalysts of a challenging (from

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an asymmetric catalysis standpoint¹¹) Micheal reaction, the addition of acetone to (*E*)- β -nitrostyrene **1**.

The results of this preliminary study (Table 1) were instructive. Initial experiments demonstrated that the primary amine derivatives of **DHQ** (**DHQA** and **9-epi-DHQA**) were capable of promoting the reaction when utilized at 10 mol % loading. Although the employment of a Brønsted acid additive resulted in clean reactions (which gave multiple products otherwise), contrary to recent reports concerning primary amine catalysts for this reaction, we did not find the use of water as an additive to be beneficial in this system (entries 1–7).^{7a–c} Interestingly, inversion of the “natural” alkaloid stereochemistry at C-9 (i.e., **9-epi-DHQA**) resulted in a catalyst considerably more active than **DHQA** (entries 1, 2, 10, and 11) without alteration of the sense of stereinduction observed (i.e., both **DHQA** and **9-epi-DHQA** promote the formation of (*R*)-**2**), whereas the secondary amine analogue of this material (**9-epi-DHQBA**) proved completely inactive (entries 3, 5, and 12). Further experimentation allowed the identification of optimal, solvent-free conditions under which the quinidine derivative **9-epi-DHQDA** (Figure 1) could promote the efficient formation of (*S*)-**2** with good enantioselectivity¹¹ in the presence of benzoic acid (entries 7–15).

With an active catalyst system in hand, attention was now turned to the key question of reaction scope. **9-epi-DHQDA** promoted the smooth, high-yielding addition of a variety of ketones to **1** to give *syn* adducts **3–7** in good to outstanding enantio- and diastereoselectivity (Table 2). The clear supe-

Table 2. Addition of Ketones to **1**

entry	mol % cat.	product	t (d)	yield (%) ^a	<i>dr</i> (%) ^b	<i>ee</i> (%) ^c
1	20		3	71 ^d	4.8:1	96
2	20		8	87	10:1	99
3	10		3	90	8.3:1	72
4 ^e	15		10	91	10:1	78
5 ^f	10		11	88	11:1	69
6	10		3	91	7.1:1	84

^a Isolated yield. ^b Determined by ¹H NMR spectroscopy; the *syn* diastereomer is preferentially formed in all cases. ^c Determined by CSP-HPLC; see Supporting Information. ^d 23% yield of the regioisomer also isolated. ^e At 0 °C. ^f 100 μ L of toluene added, reaction on 0.4 mmol scale.

riority of acyclic to cyclic ketone substrates and the isolation of **3** and **4** in >95% ee (the highest enantioselectivity for these substrates thus far reported) is gratifying. Although several amine catalysts capable of promoting the enantioselective addition of **5–7** to **1** are known,^{5–7} to the best of our knowledge only one report^{6m} detailing a *syn*-selective catalyst system has thus far appeared¹² for the analogous transformation of more challenging, acyclic ketones such as **3–4** with >80% ee.

Aldehyde substrates (both α -substituted and α,α -disubstituted analogues) were also found to be compatible with **9-epi-DHQDA** (Table 3), allowing the isolation of adducts

Table 3. Addition of Aldehydes to **1**

entry	mo % cat.	product	time (d)	yield (%) ^a	<i>dr</i> (%) ^b	<i>ee</i> (%) ^c
1	10		3.3	97	-	91
2	10		1.8	93	-	88
3 ^d	10		4.2	92	-	89
4	10		2.3	95	2:1	92
5	10		3.3	93	>20:1	66
6 ^d	15		4.1	94	>20:1	65
7	10		3.8	76	6.7:1	95
8 ^e	10		4.2	91	12.5:1	83

^a Isolated yield. ^b Determined by ¹H NMR spectroscopy; the *syn* diastereomer is preferentially formed in all cases (where relevant). ^c Determined by CSP-HPLC; see Supporting Information. ^d At 0 °C. ^e Repetition of the reaction at 0 °C had no effect on enantioselectivity.

8–13 in high yield and excellent enantioselectivity (with one exception, entry 5) using only 10 mol % of catalyst. While (as expected) the sense of stereinduction in these reactions is the opposite to that observed using ketone substrates (Table 1), high levels (up to >95% de) of *syn*-diastereoselectivity are preserved, with even 2-methyl butanal, a substrate with minimal steric differentiation between α -substituents), providing a 2:1 ratio of diastereomers in excellent yield (entry 4).

We propose that the observed enantio- and diastereoselectivity can be rationalized in terms of a synclinal transition state (Figure 2).¹³ In this case the in situ formed (*E*)-enamine

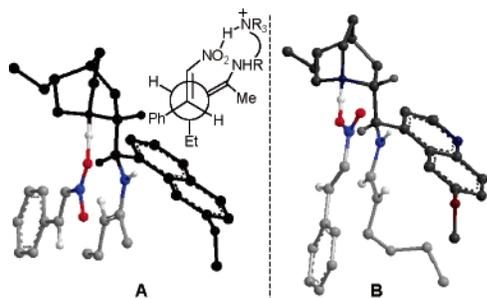


Figure 2. Rationale for the observed stereoselectivity in the formation of **3** (A) and **13** (B) promoted by **9-epi-DHQDA**.

directs its bulkier substituent (the alkyl group for ketones (A) and the olefinic moiety for aldehydes (B) away from the catalyst, resulting in a single enamine rotamer, one face of which is shielded by the catalyst's quinoline ring. Given the low steric requirement of the catalyst's tertiary amine moiety and the necessity of an acidic cocatalyst for efficient, clean reactions,¹⁴ it seems likely that a hydrogen bonding interaction between the nitroolefin electrophile and the protonated quinuclidine nitrogen atom contributes to the high levels of catalyst activity and selectivity observed.

Finally, investigation of the reaction scope with respect to the electrophile was examined. We were pleased to find that isobutyraldehyde could be efficaciously added to nitroolefins of variable steric and electronic characteristics in the presence of **9-epi-DHQDA** with the highest levels of enantioselectivity reported thus far for this aldehyde substrate (Table 4, entries 1–5).

In summary, cinchona alkaloid derived catalysts such as **9-epi-DHQDA** are capable of promoting efficient asym-

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(9) As this manuscript was being reviewed, a report appeared online detailing the use of 9-epi-DHQDA as an organocatalyst for promotion of Michael addition reactions via "iminium ion" catalysis: Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, early view.

(10) See Supporting Information for details.

(11) Only Tsogoeva (91% ee, ref 7a) and Jacobsen (99% ee, ref 7b) have reported amine-based catalysts capable of promoting this reaction with >55% ee.

(12) Tsogoeva (ref 7a) and Jacobsen (ref 7b) have recently reported bifunctional thiourea-based catalysts that promote highly enantioselective reactions with this substrate class with *anti* diastereoselectivity.

(13) For discussion, see ref 5e and references therein.

(14) Polymerization was the major fate of the nitroolefin substrate in the absence of a Brønsted acid co-catalyst.

Table 4. Reaction Scope with Respect to the Nitroolefin

entry	product	t (d)	yield (%) ^a	ee (%) ^b
1		3.5	91	94
2		1.8	95	91
3		2.0	96	82
4		2.6	95	85
5		2.1	56 ^c	94

^a Isolated yield. ^b Determined by CSP-HPLC; see Supporting Information. ^c Product isolated before complete consumption of starting material. Longer reaction times lead to side reactions and reduced yield.

metric *syn*-selective addition reactions of enolizable carbonyl compounds to nitroolefins. The catalysts are readily available in both pseudoenantiomeric forms and have been found (at relatively low loadings) to catalyze highly enantio- and diastereoselective nitro-Michael addition reactions of exceptionally broad scope: ketones (cyclic/acyclic), aldehydes (straight-chain/ α,α -disubstituted), and a variety of nitroolefins are tolerated. Studies aimed at the further investigation of the potential utility of these amine catalysts of "unnatural" configuration at C-9 are in progress.

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Supporting Information Available: General experimental procedures, ¹H and ¹³C NMR spectra, characterization data, HPLC assays. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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