Asymmetric Catalysis

Stereocontrolled Creation of Adjacent Quaternary and Tertiary Stereocenters by a Catalytic Conjugate Addition**

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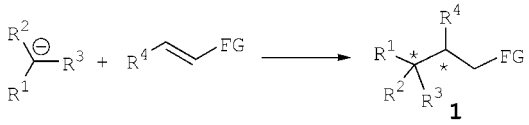
Adjacent quaternary and tertiary stereocenters as in structure **1** are common structural motifs in complex natural products. In principle, the stereocontrolled conjugate addition of a prochiral trisubstituted carbon nucleophile to a prochiral β-substituted Michael acceptor with a chiral catalyst could provide a one-step construction of such highly congested motifs from simple precursors [Eq. (1)]. However, this



(1)

requires the catalyst to impart both high enantioselectivity and diastereoselectivity in a sterically demanding, intermolecular C–C bond formation that simultaneously creates both the quaternary and tertiary stereocenters. This task has proven to be a formidable challenge. Among numerous literature examples,[1–3] to our knowledge there are only two catalytic asymmetric conjugate additions that afford the 1,4-adducts containing adjacent carbon-substituted quaternary and tertiary stereocenters in excellent enantioselectivity and with a diastereomeric ratio (d.r.) of greater than 10:1 for a substantial number of trisubstituted carbon Michael donors.[2] Herein, we report an asymmetric conjugate addition mediated by a chiral bifunctional organocatalyst that affords high enantioselectivity and diastereoselectivity for several structurally distinct classes of trisubstituted carbon nucleophiles. This reaction allows the direct and stereocontrolled construction of a wide variety of adjacent carbon- or heteroatom-substituted quaternary and tertiary stereocenters.

Readily accessible cinchona alkaloids **2** have been identified recently as effective catalysts for the enantioselective conjugate addition of dimethyl malonate and ethyl acetoacetate to nitroalkenes.[4,5] These results prompted us to examine

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conjugate additions involving trisubstituted carbon nucleophiles, especially those that could be conveniently generated in situ from readily available racemic carbonyl compounds. Screening of catalysts **2** for the addition of cyclic ketoester **3A** to nitroalkene **4a** in THF at room temperature revealed that Q-**2b** affords excellent enantioselectivities (94 and 95% *ee*) for both diastereomers of the 1,4-adducts, which were, however, generated in only a 4.5:1 ratio (Scheme 1). Interestingly, the reaction temperature was found to have a dramatic impact on the diastereoselectivity. Conjugate addition at −60°C afforded a d.r. of 18:1 with 99% *ee* for the major diastereomer.

Following this encouraging result, we examined a wide variety of trisubstituted carbon Michael donors in conjugate additions to nitroalkenes **4** mediated by Q-**2** (Table 1, Figure 1). Outstanding diastereoselectivity and enantioselectivity were obtained with various cyclic and acyclic β-ketoesters (**3A**–**D**). Similarly high enantioselectivity was also observed for the 2-substituted 1,3-diketone **3E**; the diastereoselectivity decreased noticeably but is yet of synthetic utility. Importantly, high diastereoselectivity and enantioselectivity can also be attained with trisubstituted carbon Michael donors that are not 1,3-dicarbonyl compounds (**3F**–**H**), including even those bearing a heteroatom substituent (**3F**–**G**). It is noteworthy that catalysts Q-**2** accept this unprecedented scope of trisubstituted carbon Michael donors and still tolerate a wide range of nitroalkenes (**4a**–**f**) bearing aryl, heteroaryl, and alkyl groups with varying electronic and steric properties.

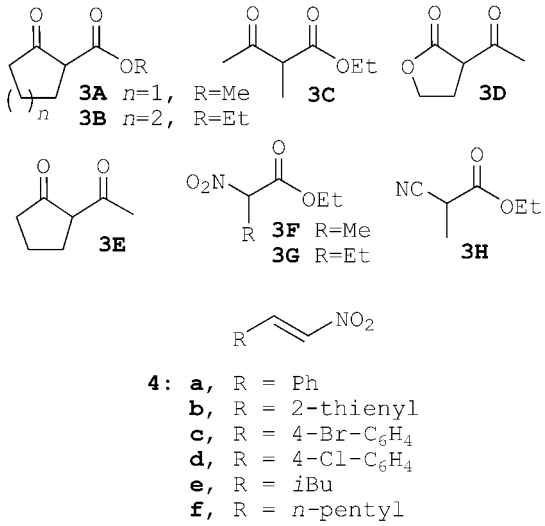
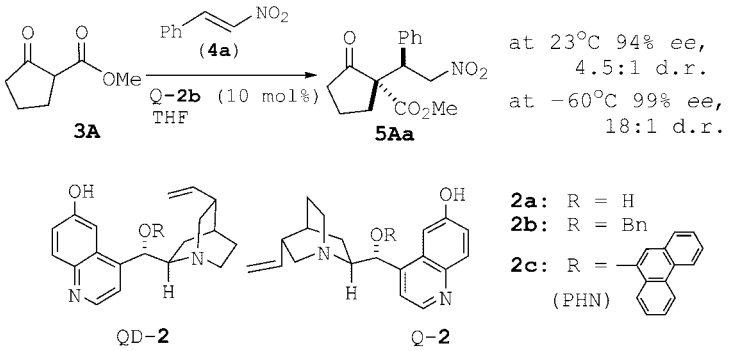
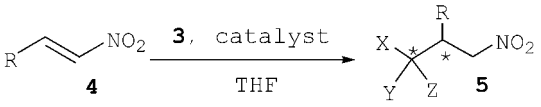


Figure 1. Carbon nucleophiles **3** and Michael acceptors **4** from Table 1.



Scheme 1. Michael addition of **3A** to **4a**.

Table 1: Diastereoselective and enantioselective 1,4-addition catalyzed by Q-**2**.[a]



Entry	3	4	Cat.	*T* [°C]	*t*	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3A**	**4a**	Q-**2b**	−60	48 h	94	95:5	99
2	**3A**	**4e**	Q-**2b**	−60	4 d	87	>98:2	99
3	**3B**	**4a**	Q-**2a**	−20	72 h	93	>98:2	99
4	**3B**	**4b**	Q-**2a**	−20	74 h	91	>98:2	99
5	**3B**	**4c**	Q-**2a**	−20	74 h	95	>98:2	>99
6	**3B**	**4e**	Q-**2c**	23	4 d	83	>98:2	99
7	**3C**	**4a**	Q-**2c**[e]	−20	63 h	73[g]	91:9	>99
8	**3D**	**4d**	Q-**2b**	−60	44 h	87	98:2	99
9	**3D**	**4e**	Q-**2c**	−60	48 h	82	98:2	99
10	**3E**	**4a**	Q-**2b**	−60	48 h	76[g]	86:14	99
11	**3F**	**4a**	Q-**2a**	−20	60 h	78[g]	92:8	92
12	**3F**	**4f**	Q-**2a**	−20	84 h	78[g]	93:7	92
13	**3G**	**4a**	Q-**2a**[f]	−50	6 d	77	95:5	96
14	**3H**	**4a**	Q-**2b**[f]	−50	6 d	77[g]	>98:2	>99
15	**3H**	**4f**	Q-**2a**	−20	84 h	75	93:7	98

[a] Unless noted, reactions were conducted on a 0.2-mmol scale in 0.2 mL THF with 10 mol% Q-**2**. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of crude product. [d] Determined by HPLC analysis. [e] Here 15 mol% catalyst was used. [f] Here 20 mol% catalyst was used. [g] Yield of the pure major diastereomer.

Mechanistic studies were carried out to gain insight into the transition-state assembly of this reaction. The absolute configuration of **5Dd** generated using Q-**2b** and the relative configuration of **5De** has been determined by X-ray crystallography.[6] We established that the asymmetric Michael addition follows a first-order dependence on the catalyst, the donor, and the acceptor.[6] We also found that the reaction proceeds at significantly higher stereoselectivities in aprotic solvents (THF, ether, and toluene) rather than protic solvents (MeOH, EtOH), which could form hydrogen bonds with either the catalyst or the substrates. To delineate the active conformer for the flexible catalysts **2** in the transition state, we compared their stereoselectivities with those of **6** (Figure 2),[7] a conformationally rigid catalyst, in Michael additions utilizing a variety of combinations of donors and acceptors. The remarkably similar d.r. and *ee* profiles thus exhibited by QD-**2** and **6** provide powerful evidence to support a *gauche*-open active conformer for catalysts **2** in the transition state (Table 2).[8–9] These results are also noteworthy for establishing QD-**2** and **6** as efficient catalysts for the asymmetric Michael addition.

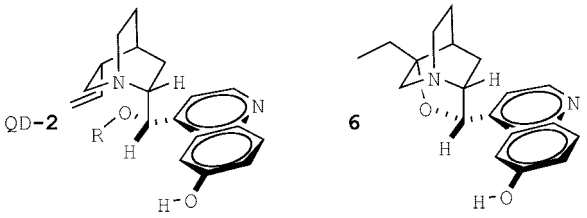
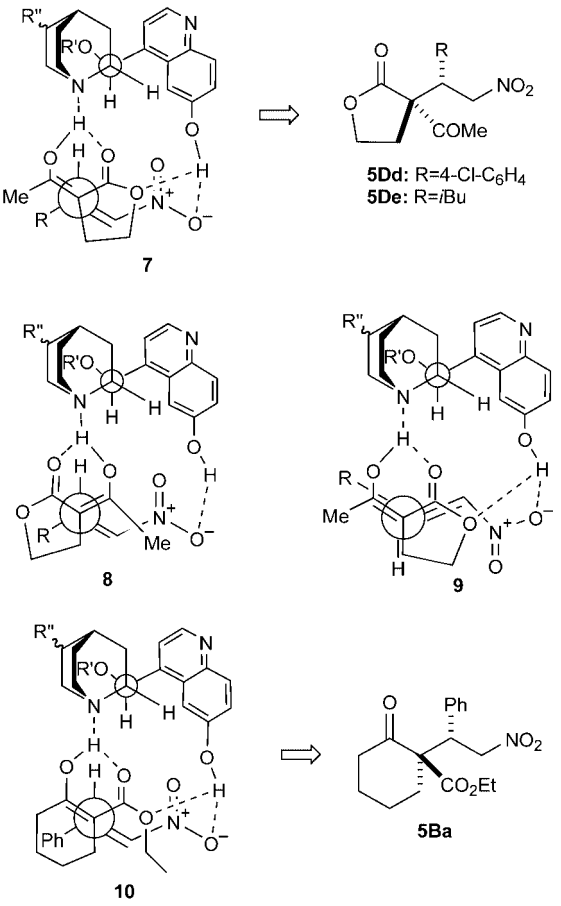


Figure 2. Catalyst QD-**2** shown as its *gauche*-open conformer and catalyst **6**.

With this key insight into the active conformer of the catalysts **2**, the kinetic results consistent with an acid–base bifunctional catalysis mode, and the observed solvent effect indicating an important role played by hydrogen-bond interactions between the catalyst and the substrates, we propose the transition-state model **7** to rationalize the stereochemical outcome of the asymmetric Michael addition (Scheme 2). In this model cinchona alkaloids **2** and **6** adopt a *gauche*-open conformer to simultaneously activate and orient the Michael donor and the acceptor by means of a network of hydrogen-bonding interactions. The substituents of the two bond-forming carbons are in a staggered rather than eclipsed arrangement. Alternative transition states generating the other stereoisomers are relatively disfavored due to either the loss of hydrogen-bond interaction between the chiral catalyst and the substrates (as in **8**) or the engagement of unfavorable eclipsed interactions between the substitutents of the bond-forming carbons (as in **9**). Application of this model (as in **10**) predicts that the adduct **5Ba** should have the relative configuration shown in Scheme 2. Gratifyingly, this was confirmed by X-ray structure analysis.[6]



Scheme 2. Stereochemical model for Michael additions catalyzed by QD-**2** or **6**.

Table 2: Asymmetric Michael additions catalyzed by QD-**2** and **6** (in brackets).[a]

Entry	3	4	Cat.	*T* [°C]	Yield [%]	d.r.	*ee* [%]
1	**3A**	**4a**	QD-**2c** (**6**)	−60	97 (97)	94:6 (97:3)	>99 (98)
2	**3B**	**4c**	QD-**2a** (**6**)	−20	96 (97)	>98:2 (>98:2)	99 (98)
3	**3C**	**4a**	QD-**2c** (**6**)	−20	70 (75)	82:18 (89:11)	99 (96)
4	**3D**	**4d**	QD-**2c** (**6**)	−60	92 (92)	97:3 (97:3)	98 (98)
5	**3E**	**4a**	QD-**2c** (**6**)	−60	70 (80)	88:12 (90:10)	98 (96)
6	**3F**	**4a**	QD-**2a** (**6**)	−20	74 (80)	89:11 (95:5)	89 (88)
7	**3H**	**4a**	QD-**2a** (**6**)	−20	76 (74)	86:14 (86:14)	95 (88)

[a] Reactions were run under the same conditions as described in Table 1 (see the Supporting Information).

In summary, we have developed a highly enantioselective and diastereoselective catalytic conjugate addition for a direct, stereocontrolled construction of adjacent carbon- or heteroatom-substituted quaternary and tertiary stereocenters from readily available starting materials. With exceptionally wide scopes for both the trisubstituted carbon Michael donors and the Michael acceptors, this experimentally simple new method should be useful for the synthesis of many multifunctional chiral building blocks containing adjacent quaternary and tertiary stereocenters that were previously not easily accessible. The stereochemical outcome of the reaction can be rationalized by a transition-state model, which is derived from mechanistic studies that clarify the active conformer of the bifunctional cinchona alkaloid catalyst in the transition state.

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[1] For reviews see: a) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171; c) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; d) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; e) J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862; f) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; g) M. Yamaguchi in *Comprehensive Asymmetric Catalysisis* (Eds.: E. N. Jacobsen, A. Pfaltz,

H. Yamamoto), Springer, Heidelberg, **2003**, Suppl. 1, Supplement to chap. 31.2, p. 151.
[2] a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204; b) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci USA*, **2004**, *101*, 5482.
[3] For other notable studies of intermolecular, diastereoselective, and enantioselective catalytic conjugate additions for the construction of vicinal quaternary and tertiary stereocenters see: a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240; b) M. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527.
[4] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.
[5] For other recent examples of highly enantioselective Michael additions catalyzed by cinchona alkaloid derivatives see: a) P. McDaid, Y. Chen, L. Deng, *Angew. Chem.* **2002**, *114*, 348; *Angew. Chem. Int. Ed.* **2002**, *41*, 348; b) M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672.
[6] See the Supporting Information for details.
[7] Catalyst **6** was first reported by Hatakeyama et al. See: a) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219; b) S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 3103.
[8] For the use of conformationally rigid cinchona alkaloids to probe the active conformer of cinchona alkaloids as ligands for Os-catalyzed Sharpless asymmetric dihydroxylations see: a) E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1993**, *115*, 12579; b) E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1996**, *118*, 11038.
[9] For a study of the active conformer of cinchona alkaloids in applications as an organic catalyst see: G. S. Cortez, S. H. Oh, D. Romo, *Synthesis* **2001**, 1731.

