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Asymmetric Diels−Alder Reactions of 2-Pyrones with a Bifunctional Organic Catalyst

Yi Wang, Hongming Li, Yong-Qiang Wang, Yan Liu, Bruce M. Foxman, and Li Deng*
Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110

Received February 6, 2007; E-mail: deng@brandeis.edu

The Diels−Alder reaction of 2-pyrones provides a direct and versatile access to synthetically valuable multifunctional bicyclic chiral building blocks.[1,2] However, as electron-deficient dienes of aromatic character, 2-pyrones are known to be reluctant diene partners for Diels−Alder reactions.[1,3] This presents a distinct challenge for the development of a catalytic asymmetric variant for this synthetically useful class of Diels−Alder reactions. Thus, it comes as no surprise that, in spite of the great strides made on the development of asymmetric Diels−Alder reactions, a highly diastereoselective and enantioselective catalytic Diels−Alder reaction with 2-pyrones has not yet been realized.[1,4] In fact, to our knowledge, even for chiral auxiliary-directed asymmetric Diels−Alder reactions with 2-pyrones, only a single example was reported.[4b] Herein, we wish to describe the development of an efficient asymmetric Diels−Alder reaction of 2-pyrones using cinchona alkaloid-derived bifunctional organic catalysts.

Nakatani and co-workers explored the use of natural cinchona alkaloids to promote a Diels−Alder reaction of 3-hydroxy-2-pyrone (**3a**) with *N*-methylmaleimide.[4a] However, the enantioselectivity afforded by natural cinchona alkaloids was modest. Nakatani proposed that the mode of action by natural cinchona alkaloids was to activate and orient **3a** only in the Diels−Alder reaction. We recently demonstrated that 6′-OH cinchona alkaloids **1** (Figure 1) are effective organic catalysts for asymmetric conjugate additions,[5] aldol reactions,[6] and Friedel−Crafts reactions.[7] Mechanistic studies from our laboratories indicate that the hydrogen bond donor and acceptor motifs in **1** activate and orient the nucleophiles and electrophiles, respectively, through multiple hydrogen bonding interactions.[5a,b] This mechanistic insight in turn implies that **1** might function as efficient bifunctional catalysts for asymmetric Diels−Alder of pyrones **3** with electron-deficient dienophiles by simultaneously raising the energy of the HOMO of the former and lowering the energy of the LUMO of the latter while orienting the two reactants to exert stereochemistry control (Figure 1).[8−10]

Guided by this hypothesis, we investigated the reaction of 3-hydroxy-2-pyrone **3a** and *trans*-3-benzoylacrylic ester **4A** with various cinchona alkaloids as catalysts. As summarized in Table 1, the reaction readily proceeded to completion with the expected sense of chemoselectivity to afford cycloadducts *endo/exo*-**5aA** as a mixture of diastereomers (Table 1). Importantly, the 6′-OH cinchona alkaloids QD-**1** afforded significantly better catalytic efficiency than that by natural cinchona alkaloids, the monofunctional cinchona alkaloid DHQD-PHN, and the conformationally

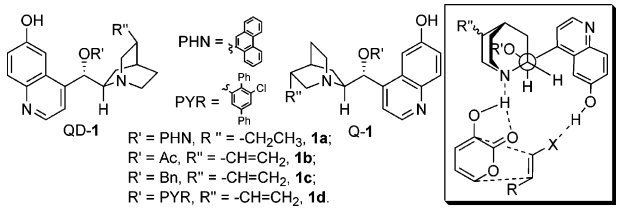
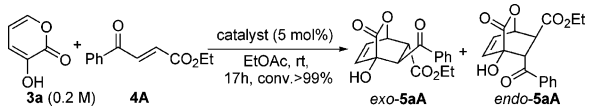


Figure 1. Bifunctional catalysis for D−A reactions of 2-pyrone **3**.

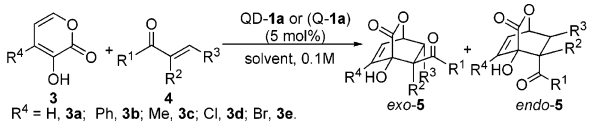
Table 1. D−A Reaction with Cinchona Alkaloids[a]

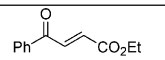
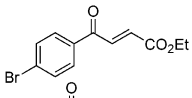
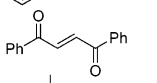
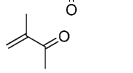


entry	catalyst	dr[b] *exo:endo*	ee (%)[b] of *exo*-**5aA**	entry	catalyst	dr[b] *exo:endo*	ee (%)[b] of *exo*-**5aA**
1	quinidine	66:34	5	6	QD-**1c**	87:13	80
2	cinchonine	62:38	−5	7	QD-**1d**	85:15	82
3	DHQD-PHN	66:34	33	8	QD-**1a**	88:12	88
4	β-ICD	94:6	22	9[c]	QD-**1a**	93:7	89
5	QD-**1b**	90:10	57	10[d]	QD-**1a**	93:7	91

[a] See Supporting Information for details. [b] In crude reaction mixtures. [c] Reaction was run in Et_2O. [d] Reaction was run in Et_2O; the concentration of **3a** was 0.1 M.

Table 2. D−A Reaction with QD-**1a** and Q-**1a** (in Parentheses)[a]



entry	pyrone	dienophile		solvent	temp (°C)	*exo:endo*	yield[b] (%)	ee[b] (%)
1	**3a**		**4A**	Et_2O	rt	93:7 (94:6)	87 (90)	94 (87)
2	**3a**		**4B**	Et_2O	rt	91:9 (94:6)	91 (93)	91 (83)
3	**3a**		**4C**	Et_2O	rt	93:7	100[c]	90
4[d]	**3a**		**4D**	Et_2O	rt	24:76 (26:74)	65 (63)	91 (90)
5	**3b**	**4A**		Et_2O	0	95:5	84	85
6	**3c**	**4A**		Et_2O	0	88:12	87	82
7	**3d**	**4A**		EtOAc	rt	86:14	77	84
8	**3e**	**4A**		EtOAc	rt	85:15	75	83

[a] See Supporting Information for details. [b] For major diastereomers. [c] Yield of **5**. [d] 10 mol % of catalyst was used instead.

rigid 6′-OH cinchona alkaloid β-ICD (Table 1, entries 5−8 vs 1−4). These results illustrated that both the structure of the tunable 9-substituent and the bifunctional nature of catalysts **1** are critically important to their catalytic efficiency for the asymmetric Diels−Alder reaction. After further optimizations, we achieved a highly diastereoselective and enantioselective reaction with 5 mol % of QD-**1a** to afford *exo*-**5aA** in 93:7 dr and 91% ee.

Catalyst QD-**1a** was found to tolerate a significant degree of alterations in both pyrones **3** and dienophiles **4** (Table 2). The reactions between pyrone **3a** and dienophiles of different substitution patterns (**4A**−**D**) proceeded in 76:24 to 93:7 dr, and the major diastereoisomers were generated mostly in greater than 90% ee. It is noteworthy that even the relatively unreactive dienophile **4D** could be employed in this reaction, thereby generating optically active chiral

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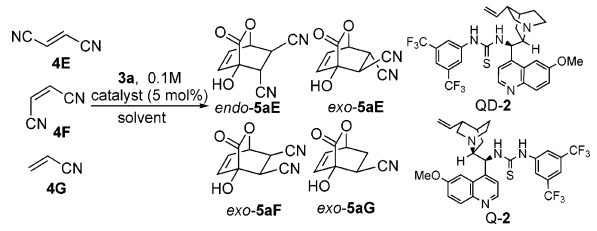
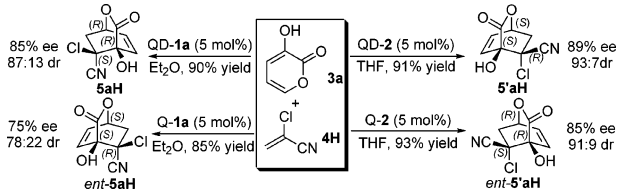
Table 3. D−A Reactions with **4E,F** Catalyzed by QD-**2** and Q-**2** (in Parentheses)[a]



entry	substrate	catalyst	product	solvent	temp (°C)	*exo*:*endo*	yield[b] (%)	ee (%)[b]
1	**4E**	QD-**1a**	**5aE**	Et_2O	rt	64:36	97[c]	15
2	**4E**	**2**	**5aE**	TBME	−20	>97:3 (>97:3)	85[c] (87)[c]	92 (85)
3	**4F**	**2**	**5aF**	TBME	−20	93:7 (89:11)	81 (89)	97 (>98)
4	**4G**	**2**	**5aG**	TBME	rt	96:4 (93:7)	91 (87)	94 (93)

[a] See Supporting Information for details. [b] For *exo*-**5**. [c] Combined yield of *endo*- and *exo*-**5**.

Scheme 1. Catalyst-Controlled *exo/endo* Selectivity



building blocks containing two adjacent tetrasubstituted stereocenters. Moreover, catalyst QD-**1a** was able to furnish useful levels of enantioselectivity and diastereoselectivity for reactions of dienophile **4A** with pyrones **3b**−**e** bearing various substituents (entries 5−8, Table 2).

However, QD-**1a** was found to be ineffective for reactions of **3a** with fumaronitrile **4E** (Table 3, entry 1). Although the 9-thiourea cinchona alkaloids **2** were found to afford low diastereoselectivity and enantioselectivity for the reaction of **3a** with **4A**,[11] their high efficiency for the activation of acrylonitriles toward conjugate additions[12] led us to evaluate **2** as catalysts for reactions of **3a** with dienophiles **4E**−**G**. Gratifyingly, QD-**2** and Q-**2** afforded drastically improved enantioselectivity and diastereoselectivity, generating the corresponding *exo*-adduct in 85 to 98% ee and 89:11 to >97:3 dr (Table 3, entries 2−4). The results obtained with reactions involving fumaronitrile (**4E**) and maleonitrile (**4F**) illustrate the ability of **2** to tolerate dienophiles with either an *E*- or a *Z*-double bond. It is also noteworthy that these reactions are stereospecific with respect to the geometry of the double bond. These results are consistent with a concerted cycloaddition mechanism.[13]

We recently demonstrated that bifunctional organic catalysts containing the hydrogen bond donor and acceptor in different spatial relationships, such as **1a** and **2**, could afford complementary diastereoselectivities for asymmetric reactions creating two stereocenters.[5f,12] Prompted by this finding, we investigated the reaction of **3a** and α-chloroacrylonitrile **4H** with catalysts QD-**1a** and QD-**2**, respectively (Scheme 1). Indeed the former was found to be *endo*-selective and the latter *exo*-selective. Consequently, cinchona alkaloids **1a** and **2** derived from quinine and quinidine, respectively, afforded selective pathways to each of the four possible stereoisomers that could be generated from **3a** and **4H** (Scheme 1).[14]

In summary, by exploring cinchona alkaloid-based bifunctional organic catalysts, we have developed an unprecedented highly enantioselective and diastereoselective catalytic Diels−Alder reaction with pyrones. To our knowledge, the current study also provides the first example of an organic molecule as an efficient acid−base bifunctional catalyst for a Diels−Alder reaction. Furthermore, we demonstrated the possibility of using such catalysts to control the *endo*/*exo* selectivity in a Diels−Alder reaction. Studies are underway to expand the scope of this reaction and to explore its application in asymmetric synthesis.

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Supporting Information Available: Experimental procedures and characterization of the products. X-ray analysis data (CIF) for **5aH** and **5′aH**. This material is available free of charge via the Internet at http://pubs.acs.org.

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