J|A|C|S
COMMUNICATIONS

Published on Web 02/06/2008

Enantioselective Diels−Alder Reaction of Simple α,β-Unsaturated Ketones with a Cinchona Alkaloid Catalyst

Ravi P. Singh, Keith Bartelson, Yi Wang, Heng Su, Xiaojie Lu, and Li Deng*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110

Received October 29, 2007; E-mail: deng@brandeis.edu

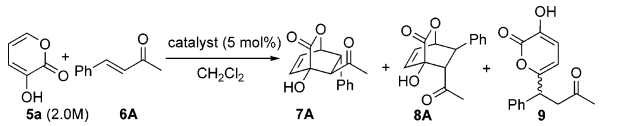
The extremely broad scope of both the dienes and dienophiles renders the Diels−Alder (D−A) reaction one of the most versatile reactions in organic synthesis. This in combination with the ability of asymmetric Diels−Alder reactions to directly transform achiral starting materials to stereochemically complex cyclic structures in a diastereoselective and enantioselective manner underscores the importance and necessity to continue the development of efficient catalytic enantioselective variants of the Diels−Alder reactions, especially those being promoted by practical catalysts and involving readily accessible yet synthetically valuable dienes and dienophiles.[1] Herein, we wish to describe the development of a highly general and efficient asymmetric Diels−Alder reaction of α,β-unsaturated ketones **6** and 2-pyrones **5** with a readily accessible cinchona alkaloid catalyst (**4**) that had not been previously explored for asymmetric Diels−Alder reactions.

Although α,β-unsaturated ketones **6** and 2-pyrones **5** have been extensively used as dienophiles and dienes, respectively, in Diels−Alder reactions, both prove to be challenging classes of substrates to be incorporated into asymmetric Diels−Alder reactions.[2−4] In fact, the first efficient asymmetric Diels−Alder reaction of a general scope with respect to α,β-unsaturated ketones **6** was reported only recently by MacMillan using chiral imminium catalysis.[2a,b] Our group recently disclosed the first highly enantioselective Diels−Alder reaction with 2-pyrones, which was realized with cinchona alkaloid-derived bifunctional catalysts such as **1** and **2**.[5] Although **1** and **2** afforded high diastereoselectivity and enantioselectivity for D−A reactions of 2-pyrones **5** and active dienophiles with the double bond substituted with two strongly electron-withdrawing functionalities, they were found to be ineffective for reactions of **5** and simple α,β-unsaturated ketones **6** (entries 1 and 2, Table 1). Additional cinchona alkaloids containing hydrogen bond donors and acceptors, such as quinine and **3**, were examined and were found to provide similarly low diastereoselectivity and enantioselectivity (entries 3 and 4, Table 1).

In light of the poor efficiency afforded by various cinchona alkaloids containing hydrogen bond donors and acceptors, we began to search for an alternative strategy to achieve efficient asymmetric catalysis for the D−A reaction of **5** and **6** (Figure 1). MacMillan demonstrated that chiral secondary amines could serve as effective catalysts to activate α,β-unsaturated ketones for asymmetric D−A reactions through imminium catalysis.[2a] Recent studies by Ishihara[6] established that chiral primary amines could activate α,β-unsaturated aldehydes for highly enantioselective D−A reactions. Although only electron-rich dienes were employed in these chiral primary and secondary amine-catalyzed D−A reactions of α,β-unsaturated ketones and aldehydes, we envisaged that the readily available 9-NH_2 cinchona alkaloids **4**[7,8] might be able to promote an efficient asymmetric D−A reaction via its ability to simultaneously activate **5** and **6** with its primary amine and quinuclidine motifs, respectively.

Accordingly, we began an investigation of the D−A reaction of **5** and **6** at room temperature in dichloromethane with 5 mol % of the 9-NH_2 cinchona alkaloid Q-**4**. In the absence of any acid, the reaction with Q-**4** readily proceeded to near completion but provided the Michael adduct **9** as the major product. The D−A adduct was formed not only as a minor product but also in very poor diastereoselectivity and enantioselectivity (entry 5, Table 1). The D−A adduct/Michael adduct ratio could be improved significantly when the **4**-catalyzed reaction was performed in the presence of certain acids. We were particularly pleased to find that, with 20 mol % of trifluoroacetic acid (TFA), the reaction with Q-**4** afforded the *exo*-D−A adduct **7A** as the major product in good enantiomeric excess (entry 11, Table 1). The *exo*-selectivity and the enantioselectivity could be further enhanced by lowering the reaction temperature to 0 °C, at which the D−A adduct/Michael adduct ratio as well as the *exo*-selectivity reached a synthetically useful level, while the *exo*-adduct **7A** was produced in 97% ee (entry 12, Table 1). Under the optimized condition, QD-**4** furnished comparable diastereoselectivity and enantioselectivity (entry 13, Table 1). Importantly, the primary amine functionality in catalyst **4** is critical

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



entry	catalyst	acid (0.2 equiv)	temp (°C), time (h)	conv. (%)	dr[b] (**7A**:**8A**)	ee (%)[c] of **7A**	DA:MA[b] (**7** + **8**:**9**)
1[d]	Q-**1**	−	rt, 24	92	1.1:1	−3	100:0
2[d]	Q-**2**	−	rt, 24	98	1.4:1	53	59:1
3[d]	quinine	−	rt, 24	95	1:1.5	2	100:0
4[d]	QD-**3**	−	rt, 24	59	2.3:1	34	100:0
5[d]	Q-**4**	−	rt, 24	96	1.2:1	−3	1:2.5
6	Q-**4**	*p*-TSA	rt, 24	5	1:2.9	−	−
7	Q-**4**	CF_3SO_3H	rt, 24	29	1:4.2	−3	100:0
8	Q-**4**	$C_6H_5CO_2H$	rt, 24	63	1:1.3	−21	1:2.3
9	Q-**4**	*N*-Boc-Phenyl glycine-D	rt, 24	74	1.4:1	14	2:1
10	Q-**4**	*N*-Boc-Phenyl glycine-L	rt, 24	73	1:1.1	40	1.6:1
11	Q-**4**	TFA	rt, 24	91	3.6:1	−89	6:1
12	Q-**4**	TFA	0, 96	95	4.8:1	−97	11:1
13	QD-**4**	TFA	0, 96	99	4.1:1	98	10:1
14	Q-**2**	TFA	rt, 24	<5	−	−	−

[a] Unless noted, reactions were run with 0.15 mmol of **5a**, 0.30 mmol of **6** in 75 μL of CH_2Cl_2; see Supporting Information for details. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis. [d] Reaction was run with 10 mol % catalyst.

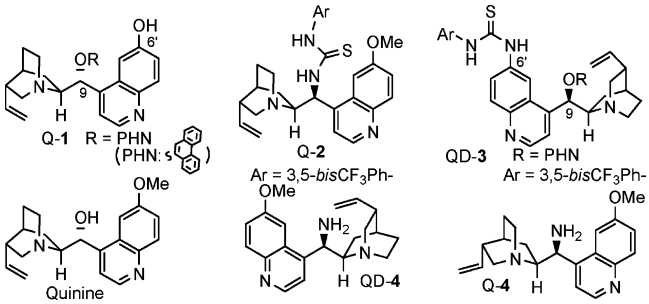
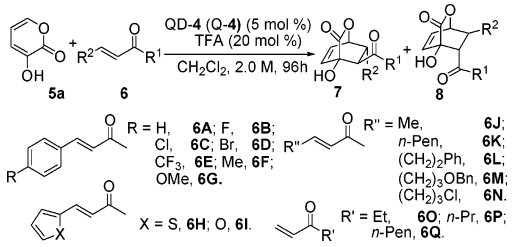


Figure 1. The structures of cinchona alkaloids.

10.1021/ja078251w CCC: $40.75

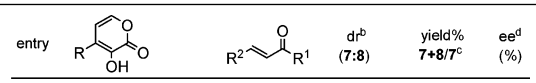
Table 2. D−A Reaction with 2-Pyrones[a]



entry	dienophile	temp (°C)	dr[c] (**7**:**8**)	yield % **7**+**8**/**7**[d]	ee[e] (%)
1	**6A**	0	80:20	87/69	98
		0	(82:18)	(91)/(74)	(96)[b]
2	**6B**	0	81:19	92/74	98
3	**6C**	0	79:21	89/69	98
		0	(79:21)	(95)/(74)	(96)[b]
4[g]	**6D**	0	81:19	96/76	97[f]
		0	(81:19)	(95)/(76)	(97)[b]
5	**6E**	−20	84:16	99/81	97
6	**6F**	0	80:20	81/63	97
7	**6G**	0	84:16	68/57	97
8	**6H**	0	80:20	85/67	99
9	**6I**	0	80:20	71/56	99
10	**6J**	−30	84:16	92/77	99
11	**6K**	−30	75:25	95/70	99
12	**6L**	−20	94:6	99/93	99
13[b]	**6M**	−20	76:24	92/70	99
14[h]	**6N**	−20	76:24	83/63	96
15[g]	**6O**	−20	97:3	99/96	99
16[g]	**6P**	−20	92:8	90/82	99
17[g]	**6Q**	−20	93:7	98/91	96

[a] Unless noted, reactions were run with 0.25 mmol of **5a**, 0.50 mmol of **6** in 125 μL of CH_2Cl_2. [b] The results in parentheses were obtained with Q-**4**; see Supporting Information for details. [c] Determined by ^{1}H NMR analysis. [d] Isolated yields of pure *exo*-**7**. [e] Enantiomeric excess of **7** as determined by HPLC analysis. [f] The absolute configuration was established by X-ray crystallographic analysis (see Supporting Information). [g] Reaction was run for 72 h. [h] Reaction was run for 120 h.

Table 3. D−A Reaction with Substituted Pyrones[a]



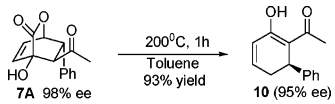
entry			dr[b] (**7**:**8**)	yield% **7**+**8**/**7**[c]	ee[d] (%)
1	**5b:** R=Ph	**6A**	83:17	83/63	96
2	**5c:** R=Me	**6A**	80:20	60/48	96
3	**5b**	**6J**	80:20	81/63	96
4	**5c**	**6J**	73:27	80/57	96
5	**5d:** R=Cl	**6D**	67:33	63/42	90[e]

[a] Unless noted, reactions were run with 0.15 mmol of **5**, 0.30 mmol of **6** in 75 μL of CH_2Cl_2 with 5 mol % of QD-**4** and 20 mol % of TFA for 96 h. [b] Determined by ^{1}H NMR analysis. [c] Isolated yields of pure *exo*-**7**. [d] Enantiomeric excess of **7** as determined by HPLC analysis. [e] The absolute configuration of the D−A adduct was established by X-ray crystallographic analysis (see Supporting Information).

to its activity, as replacing the amine with a thiourea group abolishes the catalytic activity (entry 14 vs 11, Table 1). Moreover, the presence of TFA is essential to the selectivity of **4** (entry 11 vs 5, Table 1), although TFA itself does not promote the D−A reaction.[9] These results suggest that **4** activates **6A** for the D−A reaction through imminium catalysis. We also found that, in contrast to **5a**, electron-rich dienes bearing neither a hydrogen bond acceptor nor donor such as cyclopentadiene and cyclohexadiene were inactive for the D−A reaction with **6A** in the presence of **4** and TFA.[9] These results indicate that the activation of **5a** by catalyst **4** is also required for the D−A reaction to occur.

Significantly, the high enantioselectivity afforded by catalyst **4** could be readily extended to β-aryl (**6A-I**), β-alkyl (**6J**-**N**), and β-unsubstituted (**6O**-**Q**) α,β-unsaturated ketones (Table 2). As illustrated in Table 3, the catalyst also tolerates substituted

Scheme 1. Decarboxylation of **7A**[4c]



2-pyrones. Notably, the diastereoselectivity and enantioselectivity of the reaction did not fluctuate significantly when the aromatic substituent was changed to an aliphatic substituent. The diastereoselectivity and enantioselectivity decreased with a 2-pyrone bearing an electron-withdrawing group (**5d**), although the corresponding *exo*-D−A adduct was still formed in 90% ee.

In summary, we have discovered a readily available cinchona alkaloid-derived catalyst for asymmetric Diels−Alder reactions. Notably, this catalyst proved to be highly effective for the asymmetric D−A reaction of simple α,β-unsaturated ketones **6** with 2-pyrones **5**, an unprecedented enantioselective D−A reaction involving two readily available but challenging classes of D−A reactants. This reaction should provide a useful asymmetric route to a wide range of bicyclic chiral building blocks amenable for further synthetic elaborations (Scheme 1).[4c,9]

Acknowledgment. We are grateful for financial support from NIH (GM-61591). We thank Bruce Foxman and Chen-Hsing (Josh) Chen for X-ray crystallographic analysis and the NSF for the partial support of this work through Grant CHE-0521047 for the purchase of a new X-ray diffractometer.

Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews of enantioselective Diels−Alder reactions, see: (a) Maruoka, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 467. (b) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, p 1177. (c) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.

(2) (a) For a discussion of challenging issues in the development of catalytic asymmetric D−A reactions with simple α,β-unsaturated ketones, see: Northrup, A. B.; MacMillian, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. For reviews of asymmetric imminium catalysis, see: (b) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (c) Erkkilä, A.; Majamder, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

(3) For chiral Lewis acid catalyzed asymmetric D−A reactions with simple α,β-unsaturated ketones, see: (a) Ryu, D. H.; Lee, T. L.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

(4) For reviews of D−A reaction with 2-pyrones, see: (a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. (b) Woodard, B. T.; Posner, G. H. *Adv. Cycloaddit.* **1999**, *5*, 47. For synthetic applications of Diels−Alder reactions of 2-pyrones, see: (c) Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, 2389. (d) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1118. (e) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. (f) Okamura, H.; Shimizu, H.; Nakamura, Y.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2000**, *41*, 4147. (g) Shimizu, H.; Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2001**, *57*, 1903. (h) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908.

(5) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364.

(6) (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (b) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229. (c) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457.

(7) Cinchona alkaloid **4** was first reported by: Brunner, H.; Bügler, J.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699.

(8) For **4**-catalyzed asymmetric conjugate addition reactions, see: (a) 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.* **2007**, *46*, 389. (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (d) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

(9) See Supporting Information for details.

JA078251W