New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels−Alder Reaction

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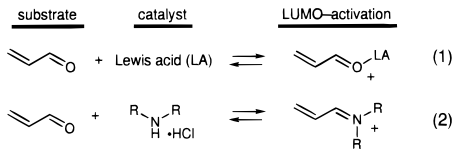
Over the past 30 years, enantioselective catalysis has become one of the most important frontiers in exploratory organic synthetic research. During this time, remarkable advances have been made in the development of organometallic asymmetric catalysts that in turn have provided a wealth of enantioselective oxidation, reduction, π-bond activation, and Lewis acid-catalyzed processes.[1] Surprisingly, however, relatively few asymmetric transformations have been reported which employ organic molecules as reaction catalysts,[2] despite the widespread availability of organic chemicals in enantiopure form and the accordant potential for academic, industrial, and economic benefit. Herein, we introduce a new strategy for organocatalysis that we expect will be amenable to a range of asymmetric transformations. In this context, we document the first highly enantioselective organocatalytic Diels−Alder reaction.[3]

We recently embarked upon the development of a general strategy for organocatalytic reactions based upon design features derived from the arena of Lewis acid catalysis. Specifically, we reasoned that (i) LUMO-lowering activation and (ii) the kinetic lability toward ligand substitution that enables Lewis acid-catalyst turnover (eq 1) might also be available with a carbogenic system that exists as a rapid equilibrium between an electron-deficient and a relatively electron-rich state. With this in mind, we hypothesized that the reversible formation of iminium ions from α,β-unsaturated aldehydes and amines (eq 2) might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis, thereby providing a new platform for the design of organocatalytic processes. Significantly, this analysis reveals the attractive prospect that chiral amines might function as enantioselective catalysts for a range of transformations that traditionally utilize metal salts.



Scheme 1

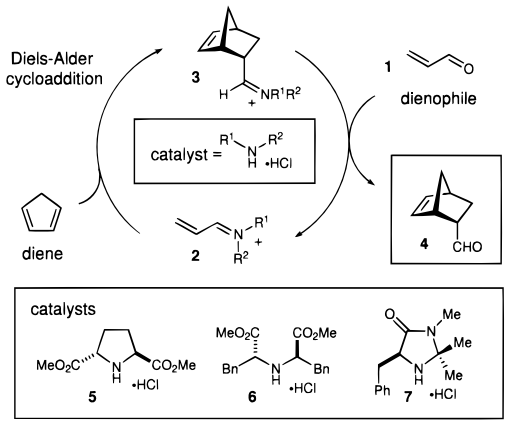
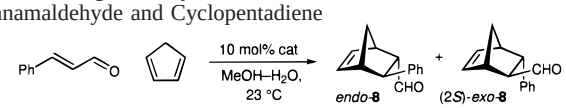


Table 1. Organocatalyzed Diels−Alder Reaction between Cinnamaldehyde and Cyclopentadiene



entry	catalyst	time (h)	yield (%)	*exo*:*endo*	*exo* ee (%)[a,b]
1	(*S*)-Pro-OMe•HCl	27	81	2.7:1	48 (2*R*)
2	(*S*)-Abr-OMe•HCl	10	80	2.3:1	59 (2*S*)
3	**5**	23	92	2.6:1	57 (2*R*)
4	**6**	84	82	3.6:1	74 (2*R*)
5	**7**	8	99	1.3:1	93 (2*S*)[c]

[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information). [c] Using 5 mol % catalyst.

To test this hypothesis we investigated the capacity of chiral amines to enantioselectively catalyze the Diels−Alder reaction between α,β-unsaturated aldehydes and various dienes.[4,5] As outlined in Scheme 1, we envisioned that condensation of aldehyde **1** with an enantiopure amine would lead to the formation of an iminium ion (**2**) that is sufficiently activated[6] to engage a diene reaction partner. Accordingly, Diels−Alder cycloaddition would lead to iminium ion **3**, which upon hydrolysis would provide the enantioenriched cycloaddition product (**4**) while reconstituting the chiral amine catalyst.

Our enantioselective catalytic Diels−Alder strategy was first evaluated using cyclopentadiene with (*E*)-cinnamaldehyde and a series of chiral secondary amine•HCl salts. As revealed in Table 1, this LUMO-lowering strategy was successful using only catalytic quantities of both (*S*)-proline and (*S*)-abrine-methyl esters (10 mol %), providing the Diels−Alder adduct in excellent yield

(1) For leading references, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Heidelberg, 1999. (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed; Wiley: New York, 1994. (c) *Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.

(2) For notable examples, see the following. Aldol reaction: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Agami, C.; Meyneir, F.; Puchot, C. *Tetrahedron* **1984**, *40*, 1031. (d) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.*, in press. Phase-transfer catalysis: (e) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (f) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287. (g) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1999**, *120*, 13000. (h) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. Epoxidation: (i) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (j) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wnag, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (k) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (l) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. Bayliss-Hillman reaction: (m) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *120*, 10219.

(3) Asymmetric base-catalyzed Diels−Alder reactions between anthrone and maleimide have been achieved with moderate selectivity (6−61% ee): Riant, O.; Kagan, B. *Tetrahedron Lett.* **1989**, *30*, 7403.

(4) For recent reviews of enantioselective Diels−Alder reactions involving chiral Lewis acids, see: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (c) Oh, T.; Reilly, M. *Org. Prep. Proc. Int.* **1994**, *26*, 129. (d) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289.

(5) (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (c) Isihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (d) Isihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (e) Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (f) Corey, E. J.; Guzman-Perez, A.; Loh, T. P. *J. Am. Chem. Soc.* **1994**, *116*, 3611. (g) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

(6) It has been established that α,β-unsaturated iminium ions are significantly more reactive as dienophiles than the corresponding α,β-unsaturated aldehydes: Baum, J. S.; Viehe, H. G. *J. Org. Chem.* **1976**, *41*, 183.

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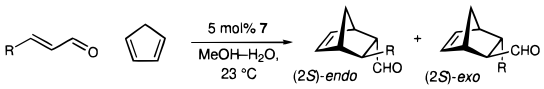
Table 2. Organocatalyzed Diels−Alder Cycloadditions between Cyclopentadiene and Representative Dienophiles



entry	R	time (h)	yield (%)	*exo*:*endo*[a,b]	*exo* ee (%)	*endo* ee (%)
1	Me	16	75	1:1	86 (2*S*)	90 (2*S*)
2	Pr	14	92	1:1	86 (2*S*)	90 (2*S*)
3	*i*-Pr	14	81	1:1	84 (2*S*)	93 (2*S*)
4	Ph	21	99	1.3:1	93 (2*S*)	93 (2*S*)
5	Furyl	24	89	1:1	91 (2*S*)	93 (2*S*)

[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information).

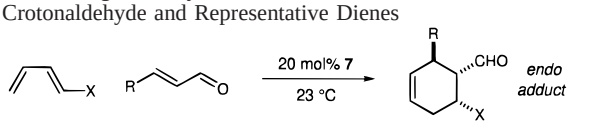
and moderate stereoselectivity (entries 1 and 2, >80%, 2.3−2.7:1 *exo*:*endo*, 48−59% ee). With the C_2-symmetric amines **5** and **6**, an increase in enantiocontrol was observed (entries 3 and 4, >82% yield, 2.6−3.6:1 *exo*:*endo*, 57−74% ee). Importantly, control of iminium ion geometry[7] through the use of steric constraints on the catalyst architecture **7** was found to provide the highest levels of enantioselectivity (93% ee) while maintaining reaction efficiency (entry 5, 5 mol %).[8−10] Consequently, amine salt **7** was identified as the optimal catalyst for further exploration.

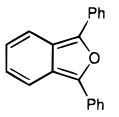
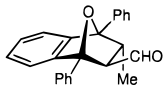
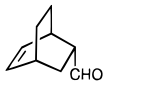
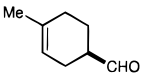
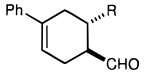
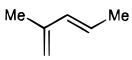
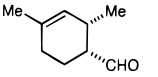
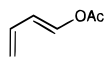
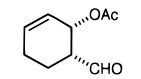
Experiments that probe the scope of the dienophile reaction component are summarized in Table 2. Variation in the steric contribution of the olefin substituent (R_1 = Me, Pr, *i*-Pr, entries 1−3) is possible without loss in yield or enantioselectivity (>75% yield, *endo* >90% ee, *exo* >84% ee). The reaction is also tolerant of aromatic groups on the dienophile component (entries 4 and 5, 89% yield, *endo* >93% ee, *exo* >91% ee). To demonstrate the preparative utility of this methodology, the addition of cyclopentadiene to cinnamaldehyde was performed on a 50-mmol scale utilizing catalyst **7** (5 mol %) to afford 12 g of (2*S*)-**8** (99% yield, *exo* 93% ee).

This amine-catalyzed Diels−Alder cycloaddition is also general with respect to diene structure (Table 3). As revealed with 1,3-diphenylisobenzofuran and cyclohexadiene (entries 1 and 2), a wide range of diene reactivity can be accommodated without loss in stereocontrol (entry 1, 75% yield, 35:1 *exo*:*endo*, 96% ee; entry 2, 82% yield, 1:14 *exo*:*endo*, 94% ee). This methodology allows access to a number of cyclohexenyl building blocks that incorporate acetoxy, alkyl, formyl, and aryl substituents with high levels of regio- and enantioselectivity (entries 3−6, 72−89% yield, 1:5−1:11 *exo*:*endo*, 83−90% ee). Notably, all of the dienes employed in this study undergo cycloaddition with excellent diastereoselectivity (entries 1, 2, 6, and 7, 5−35:1 *endo*:*exo*), with the exception of cyclopentadiene (Table 1, 1:1−1.3 *endo*:*exo*). Finally, it is noteworthy that the reactions depicted in Tables 2 and 3 were performed under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst,[11] further illustrating the preparative advantages of organocatalysis.

The sense of asymmetric induction observed in all cases involving catalyst **7** is consistent with the calculated iminium ion

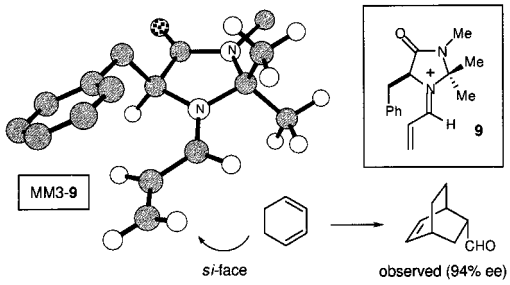
Table 3. Organocatalyzed Diels−Alder Reaction between Acrolein or Crotonaldehyde and Representative Dienes



entry	diene	R	product	yield	*exo*:*endo*	% ee[a,b]
1		Me		75	35:1	96[c]
2		H		82	1:14	94[d]
3		H		84	--	89
4		H		90	--	83
5		Me		75	--	90
6		H		75	1:5	90
7		H		72	1:11	85

[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information). [c] Using catalyst **5**. [d] Using 5 mol % catalyst.

model MM3-**9**.[12] Inspection of structure MM3-**9** reveals two salient stereocontrol elements: (i) selective formation of the (*E*)-iminium isomer to avoid nonbonding interactions between the substrate olefin and the geminal methyl substituents, and (ii) the benzyl group on the catalyst framework which effectively shields the *re* face of the dienophile, leaving the *si* face exposed to cycloaddition. Notably, catalyst **7** achieves high levels of organizational control with simple aldehydes, presumably due to the geometrical constraints that accompany formation of the iminium ion π-bond. Indeed, we expect that substrate activation by π-bond formation will provide a valuable organizational tool in asymmetric catalysis.



In conclusion, we have documented a new strategy for organocatalysis that has enabled the development of the first highly enantioselective amine-catalyzed Diels−Alder reaction. Further studies to address the scope of this new catalytic strategy will be forthcoming.

Acknowledgment. This research has been supported by kind gifts from Merck, Roche-Biosciences, and Warner-Lambert.

Supporting Information Available: Experimental procedures, spectral data for all compounds, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000092S

(7) Molecular modeling calculations suggest that iminium ion stereocontrol is essential for attaining high levels of enantiocontrol, as the (*E*)- and (*Z*)-iminium ion isomers are expected to undergo cycloaddition from opposite enantiofaces.

(8) Although MeOH−H_2O was typically employed in this study, other solvent combinations were found to be useful (Table 1, entry 5): DMSO−H_2O, *exo* 92% ee; DMF−H_2O, *exo* 90% ee; CH_3NO_2−H_2O, *exo* 90% ee.

(9) The addition of 5% H_2O to the reaction solvent results in increased reaction rates and enantioselectivities. The precise role of H_2O in this process has not been elucidated; however, we tentatively propose that this addend is facilitating the iminium ion hydrolysis step in the catalytic cycle.

(10) In a representative procedure the dienophile (0.5 mmol) and the diene (1.5 mmol) were added sequentially to the catalyst (0.025 mmol, 5 mol %) in the appropriate solvent (0.5 mL). Upon consumption of the aldehyde (3−24 h), the mixture was diluted with Et_2O and washed with H_2O and brine. The organics were dried (Na_2SO_4), concentrated, and then purified by flash chromatography.

(11) The estimated cost for the preparation of 50 g of catalyst **7** is $6.

(12) A Monte Carlo simulation using the MM3 force-field; Macromodel V6.5.