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The First General Enantioselective Catalytic Diels−Alder Reaction with Simple α,β-Unsaturated Ketones

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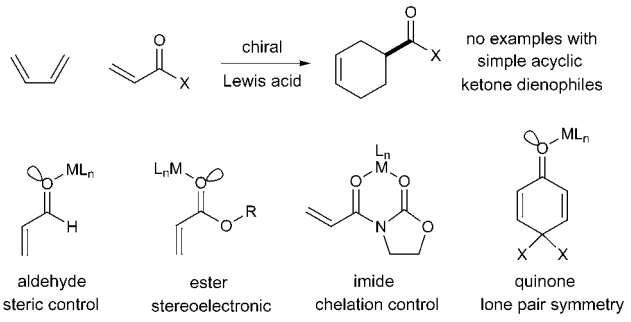
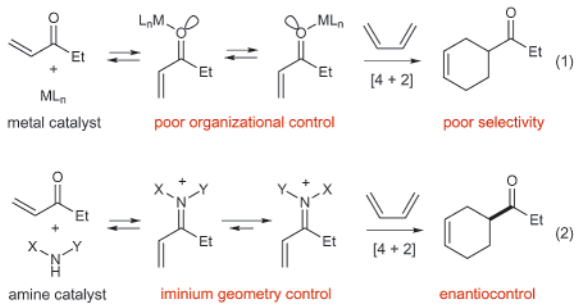
For more than 70 years, the Diels−Alder reaction has remained arguably the most powerful organic transformation in chemical synthesis.[1] In particular, asymmetric catalytic variants of this venerable reaction[2] have received unprecedented attention,[3] presumably due to their capacity to rapidly provide complex enantioenriched carbocycles from simple substrates. It is remarkable, therefore, that simple acyclic ketone dienophiles have yet to be successfully employed in enantioselective catalytic [4 + 2] cycloadditions,[4] a synthetic deficiency that is underscored by the prevalence of enantiopure ketones throughout natural product architecture. In our recent studies, we reported that the LUMO-lowering activation of α,β-unsaturated aldehydes using chiral imidazolidinones **1** is a valuable platform for the development of a wide range of enantioselective carbon−carbon bond-forming reactions. In this communication, we extend this organocatalytic strategy[5] to the activation of α,β-unsaturated ketones using a new chiral amine catalyst. In this context, we document the first enantioselective catalytic Diels−Alder reaction with simple ketone dienophiles.



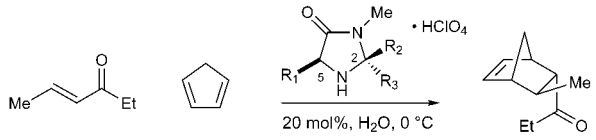
The success of chiral Lewis acid mediated Diels−Alder reactions is founded upon the use of dienophiles such as aldehydes, esters, quinones, and bidentate chelating carbonyls that achieve high levels of lone pair discrimination in the metal association step, an organizational event that is essential for enantiocontrol. In contrast, Lewis acid coordination is traditionally a nonselective process with ketone dienophiles since the participating lone pairs are positioned in similar steric and electronic environments (eq 1). The capacity for diastereomeric activation pathways in this case often leads to poor levels of enantiocontrol and ultimately has prevented the use of simple ketone dienophiles in asymmetric catalytic Diels−Alder reactions.

Having demonstrated the utility of iminium activation to provide LUMO-lowering catalysis outside the mechanistic confines of lone pair coordination,[6] we hypothesized that amine catalysts might also enable simple ketone dienophiles to function as useful substrates for enantioselective Diels−Alder reactions. In this case, the capacity to perform substrate activation through specific lone pair coordination is replaced by the requirement for selective π-bond formation (eq 2), a precedented task with respect to iminium construction.[6,7]



Our enantioselective catalytic ketone-Diels−Alder was first evaluated with 4-hexen-3-one and cyclopentadiene and a series of amine·$HClO_4$ salts **1**−**5** (Table 1). Surprisingly, this cycloaddition

Table 1. Effect of Amine Architecture on the Diels−Alder Reaction between 4-Hexen-3-one and Cyclopentadiene



entry	cat.	R_1	R_2 (R_3)	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	**1**	Bn	Me (Me)	48	20[c]	7:1	0
2	**2**	Bn	*t*-Bu (H)	48	27[c]	9:1	0
3	**3**	Ph	Ph (H)	22	88	21:1	47
4	**4**	Bn	Ph (H)	42	83	23:1	82
5	**5**	Bn	5-Me-furyl (H)	22	89	25:1	90

[a] Product ratios determined by chiral GLC. [b] Absolute configuration assigned by chemical correlation to a known compound. [c] Less than 30% conversion of starting material after 48 h.

strategy was unsuccessful with amine salts that have previously been identified[4] as valuable catalysts for aldehyde activation (entries 1 and 2, 20−27% yield, 0% ee). In contrast, the *cis*-2,5-diphenyl-substituted amine **3** provided useful reaction rates in conjunction with moderate enantiocontrol (entry 3, 88% yield, 21:1 *endo*:*exo*, 47% ee).[8] Efforts to increase enantioselectivity through iminium geometry control were successful with the introduction of a benzyl group at the C(2) catalyst site[9] (entry 4, 83% yield, 82% ee). Moreover, a survey of aryl and heteroaromatic architecture at the C(5) position has established that the 2-(5-methylfuryl)-derived imidazolidinone[10] **5** affords superior levels of enantiofacial discrimination while maintaining reaction efficiency (entry 5, 89% yield, 25:1 *endo*:*exo*, 90% ee).

Experiments that probe the scope of the dienophile component are summarized in Table 2. Variation in the alkyl ketone group

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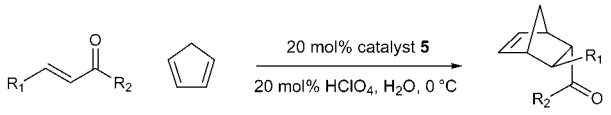
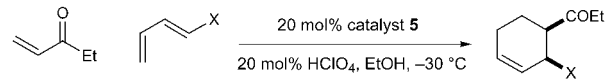
Table 2. Organocatalyzed Diels−Alder Cycloadditions between Cyclopentadiene and Representative Acyclic Enones

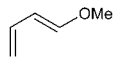
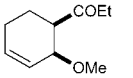
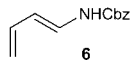
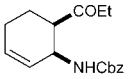
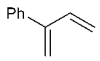
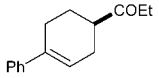
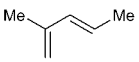
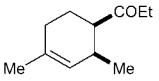
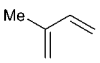
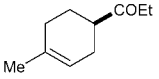


entry	R_1	R_2	% yield	*endo*:*exo*	% ee[a,b]
1	Me	Me	85	14:1	61
2	Me	Et	89	25:1	90
3	Me	*n*-Bu	83	22:1	92[c]
4	Me	*i*-Am	86	20:1	92
5	Me	*i*-Pr	24	8:1	0
6	*n*-Pr	Et	84	15:1	92
7	*i*-Pr	Et	78	6:1	90

[a] Product ratios determined by chiral GLC. [b] Absolute configuration determined by chemical correlation to a known compound or by analogy. [c] Reaction performed without solvent.

Table 3. Organocatalyzed Diels−Alder Cycloadditions between Ethyl Vinyl Ketone and Representative Dienes



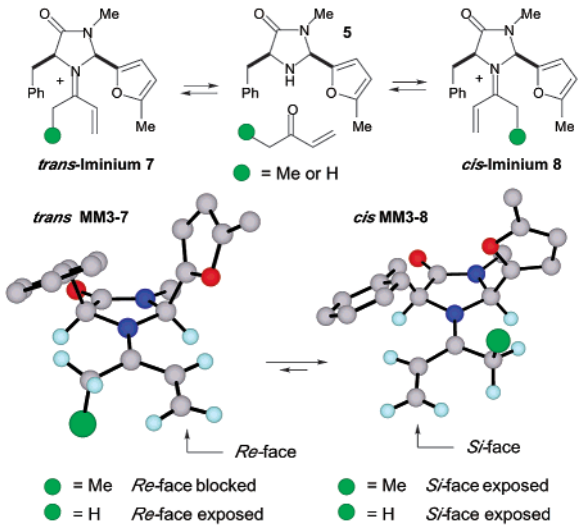
entry	diene	product	*endo*:*exo*	% yield	% ee[a,b]
1			>200:1	88	96
2	 **6**		>100:1	91	98
3[c]			>200:1[d]	92	90
4			>200:1	90	90
5[e]			>200:1[d]	79	85[f]

[a] Product ratios determined by chiral GLC or HPLC. [b] Absolute configuration determined by chemical correlation to a known compound or by analogy. [c] Reaction conducted at −40 °C. [d] Regiomeric ratio. [e] Reaction conducted at −20 °C. [f] Reaction performed without solvent.

(R_2) reveals that ethyl, *n*-butyl, and isoamyl substituents (entries 2−4) provide superior enantiocontrol (90−92% ee), while surprisingly the methyl ketone is subject to moderate levels of induction (entry 1, 61% ee). Furthermore, the isopropyl-substituted ketone leads to racemic cycloadducts in poor yield (entry 5, 0% ee, 24% yield), presumably as a result of steric inhibition of iminium formation and the attendant potential for Brønsted acid catalysis. In contrast, variation in the steric contribution of the olefin substituent (R_1) can be accomplished without loss in enantiocontrol or reaction efficiency (entries 2, 6, and 7, R_1 = Me, *n*-Pr, *i*-Pr, ≥78% yield, 6−25 to 1 *endo*:*exo*, 90−92% ee).

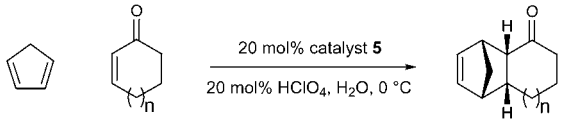
This organocatalytic Diels−Alder reaction is also quite general with respect to diene structure, allowing enantioselective access to a broad range of alkyl-, alkoxy-, amino-, and aryl-substituted cyclohexenyl ketones (Table 3, entries 1−5, 79−92% yield, >100 to 1 *endo*:*exo*, 85−98% ee). Of particular note is the fact that all entries in Table 3 produce a single regio- and diastereoisomer as determined by GLC (>200:1) or HPLC (>100:1) analysis. To highlight both the functional tolerance and the preparative utility of this new organocatalytic strategy, the cycloaddition of dienylamine **6** to ethyl vinyl ketone was performed on a 25 mmol scale to afford the corresponding Diels−Alder adduct in 98% ee and 91% yield (Table 3, entry 2).[11] Notably, recovery of amine catalyst **5** was accomplished in 91% yield after chromatography.

The sense of asymmetric induction observed in all cases is consistent with selective engagement of the diene substrate with the *si*-face of the *cis*-iminium isomer **8** (**MM3-8**). Indeed, computational models provide supporting evidence that the *trans*-iminium isomer **MM3-7** will be energetically disfavored on the basis of nonbonding interactions between the benzyl and CH_2−● (green) substituents.[12] Moreover, the calculated *cis*-iminium isomer **MM3-8** is selectively exposed to cycloaddition at the *si*-face, while both enantiofacial sites of the *trans*-isomer are shielded by structural impediment when R_2 = Et (**MM3-7**, green circle = Me), *n*-Bu or isoamyl. In the singular case of methyl ketone (R_2 = Me, green circle = H), it is apparent that the *trans*-iminium **MM3**−**7** will also be exposed at the olefin *re*-face, thereby allowing enantiodivergent pathways to compete in the [4 + 2] event. Significantly, this computational prediction is in complete accord with the disparity in enantiocontrol observed with methyl and ethyl ketone dienophiles (Table 2, R_2 = Me, 61% ee; R_2 = Et, 90% ee).



To test the validity of these models and the accompanying stereochemical analysis we conducted several experiments with cyclic dienophiles (Table 4). The principal issue in these studies is

Table 4. Organocatalyzed Diels−Alder Cycloadditions between Cyclopentadiene and Representative Cyclic Enones



entry	n	time (h)	% yield	*endo*:*exo*	% ee[a,b]
1	0	12	81	15:1	48
2	1	17	81	12:1	63
3	2	28	85	18:1	90
4	3	72	83	6:1	91
5	10	72	88[c]	5:1	93

[a] Product ratios determined by chiral GLC. [b] Absolute configuration determined by chemical correlation to a known compound or by analogy. [c] Reaction conducted with (*E*)-cyclopentadecene-2-one to provide the corresponding 1,2-*trans*-tricyclo[15.2.1.0]eicos-18-en-3-one.

that small rings (ring size = 5 or 6) were expected to exhibit selectivities in accord with methyl ketone dienophiles because the inherent conformational restrictions should allow participation of both *cis*- and *trans*-iminium isomers in the Diels−Alder event. However, as the dienophile ring size is expanded, we would expect enhanced torsional freedom about the N=C-alkyl bond, a trend that should increasingly shield the *trans*-iminium *re*-face (see **MM3-7**) and accordingly improve asymmetric induction. In agreement with this hypothesis, cyclopentenone and cyclohexenone provide modest enantiocontrol (12−15:1 *endo*:*exo*, 48−63% ee, 81% yield), while cycloheptenone ($n = 2$), cyclooctenone ($n = 3$), and (*E*)-cyclopentadecene-2-one ($n = 10$) are highly enantioselective (entries 3−5, 5−18:1 *endo*:*exo*, 90−93% ee, 83−88% yield).

Last, with respect to the operational and environmental advantages of organocatalysis, it is important to note that all of the cycloadditions reported herein were conducted in aqueous (Tables 1, 2, and 4) or ethanolic (Table 3) media. While the capacity of protic solvents to accelerate [4 + 2] cycloadditions has long been established,[13] such reaction media are rarely amenable to chiral metal salt catalysis.[14] In this and in preceding reports,[6] we have demonstrated that iminium-catalysis and the accompanying imidazolidinone catalysts are robust to aqueous conditions. We hope this organocatalytic strategy will continue to provide a new platform for the development of enantioselective processes that utilize environmentally benign solvents.

In summary, the scope of LUMO-lowering organocatalysis has been extended to accomplish the first general enantioselective ketone Diels−Alder reaction. A full disclosure of these studies will be reported in due course.

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Note Added in Proof. Shortly prior to publication it came to the authors attention that an enantioselective boron-catalyzed ketone Diels−Alder reaction has been accomplished. This work will be submitted for communication in the near future. Joel M. Hawkins, Pfizer Global Research, personal communication.

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

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(3) A survey of the CAS database (Scifinder) reveals >500 manuscripts or patents related to asymmetric catalysis of the Diels−Alder reaction.

(4) Only quinone and chelating ketone dienophiles have been successfully utilized in asymmetric Diels−Alder reactions. Quinones: (a) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (c) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373. (d) Engler, T. A.; Letavic, M. A.; Lynch, K. O., Jr.; Takusagawa, F. *J. Org. Chem.* **1994**, *59*, 1179. (e) Engler, T. A.; Letavic, M. A.; Takusagawa, F. *Tetrahedron Lett.* **1992**, *33*, 6731. (f) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559. Chelating ketone dienophiles: (g) Honda, Y.; Date, T.; Hiramatsu, H.; Yamauchi, M. *Chem. Commun.* **1997**, 1411. (h) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238. (i) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798. (j) Schuster, T.; Bauch, M.; Durner, G.; Gobel, M. W. *Org. Lett.* **2000**, *2*, 179.

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(7) The Beilstein database reports 7924 examples of tetrasubstituted iminium ions. Prior to this investigation, only examples that involve intramolecular formation of tetrasubstituted iminium ions have been accomplished selectively.

(8) Only catalysts that bear an aryl substituent at C(5) of the imidazolidinone ring exhibit enantioselectivity in this reaction. Investigations are currently underway to determine the origins of this phenomenon.

(9) The C(2)−CH_2Ar motif in catalyst **1** is required for selective iminium formation; Ahrendt, K. A., unpublished results.

(10) Preparation of (2*S*,5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one (catalyst **5**): To $Sm(OTf)_3$ (1.20 g, 2.0 mmol) were added powdered 4 Å molecular sieves (4.0 g), followed by (*S*)-phenylalanine methyl amide (8.91 g, 50 mmol) in THF (80 mL). To the resulting mixture was added 5-methylfurfural (3.98 mL, 40 mmol). After stirring for 29 h at 23 °C, the mixture was filtered through a plug of silica gel, concentrated, and purified by silica gel chromatography to afford the title compound as a clear, colorless oil in 46% yield (4.93 g, 18.2 mmol). The faster eluting (2*R*,5*S*)-5-benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one isomer was isolated in 38% yield.

(11) Representative procedure: To a flask containing catalyst **5** (20 mol %) in H_2O (3−7 M) at 0 °C was added the α,β-unsaturated ketone (100 mol %) followed by aqueous perchloric acid (20 mol %). After stirring for 5 min, freshly distilled cyclopentadiene (150 mol %) was added dropwise. The resulting mixture was stirred at 0 °C until consumption of the unsaturated ketone as determined by TLC analysis. The reaction mixture was then diluted with the appropriate eluent and then purified by silica gel chromatography.

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

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