New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition

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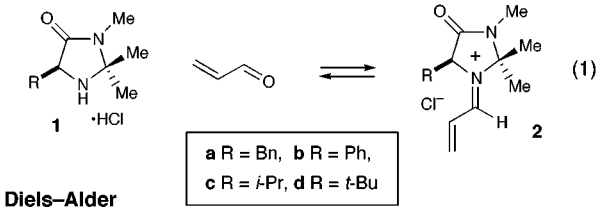
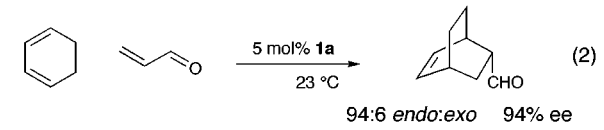
Our laboratory has been engaged in the design of broadly useful new strategies for enantioselective catalysis that utilize organic chemicals as reaction catalysts. In our recent study, we reported that the LUMO-lowering activation of α,β-unsaturated aldehydes using the reversible formation of iminium ions with chiral imidazolidinones **1** (eq 1) is a valuable platform for the development of enantioselective organocatalytic Diels−Alder reactions (eq 2).[1] In this work, we reveal that this catalytic strategy is also amenable to [3 + 2] cycloadditions between nitrones and α,β-unsaturated aldehydes to provide isoxazolidines (eq 3), useful synthons for the construction of biologically important amino acids, β-lactams, amino carbohydrates, and alkaloids.[2] To our knowledge, this is the first example of an organocatalytic 1,3-dipolar cycloaddition.[3] Moreover, this study further documents that chiral amines can be employed as asymmetric catalysts for a range of transformations that traditionally utilize metal salts.

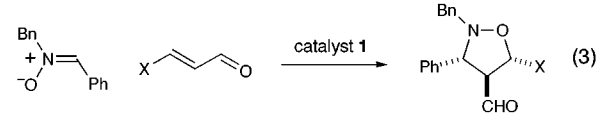
LUMO-Lowering Organocatalysis



Diels–Alder

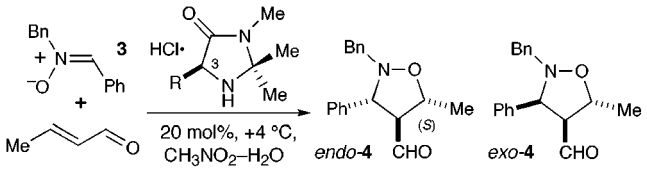


[3 + 2] Nitrone Cycloaddition



Given the operational and economical advantages associated with organocatalysis, we recently sought to further demonstrate the value of our iminium-activation strategy through the development of reaction variants that are currently unavailable using Lewis acid catalysts. In this context, it has been established that

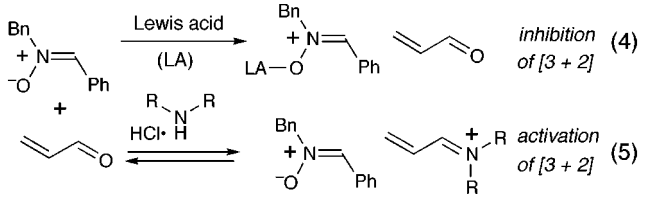
Table 1. Effect of Catalyst Structure on the Dipolar Cycloaddition between Crotonaldehyde and Nitrone **3**



entry	R–(catalyst)	Time (h)	% yield	*exo*:*endo*	% ee (*endo*)[a,b]
1	CH_2Ph (**1a**)	72	70	88:12	93
2	Ph (**1b**)	70	73	78:22	44
3	*i*-Pr (**1c**)	60	68	58:32	42
4	*t*-Bu (**1d**)	70	45	33:66	20
5	CH_2-2-napthyl (**1e**)	48	62	78:22	86
6	$CH_2C_6H_4OMe$-4 (**1f**)	48	77	79:21	89
7	CH_2CH_2Ph (**1g**)	48	72	50:50	69

[a] Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with $NaBH_4$. [b] Absolute and relative configurations assigned by chemical correlation or by analogy (Supporting Information).

α,β-unsaturated aldehydes are poor substrates for metal-catalyzed nitrone cycloadditions, presumably due to the preferential coordination of Lewis acids to nitrone oxides in the presence of monodentate carbonyls (eq 4).[4] In contrast, we expected amine catalysts to be inert to nitrone association, thereby enabling α,β-unsaturated aldehydes to undergo iminium activation (eq 5) and subsequent [3 + 2] cycloaddition.



Our catalytic [3 + 2] addition strategy was first evaluated using *N*-benzylidenebenzylamine *N*-oxide (**3**) with (*E*)-crotonaldehyde and a series of chiral imidazolidinone·HCl salts **1**.[5] As revealed in Table 1, this reaction was successful with a variety of amine catalysts (entries 1−7, 45−77% yield, 20−93% ee) in CH_3NO_2−H_2O at +4 °C. A survey of catalyst architecture reveals that incorporation of benzylic substituents at the C(3) position on the imidazolidinone framework provides the highest levels of enantiofacial discrimination (**1a**, R = CH_2Ph, 93% ee; **1e**, R = CH_2-2-naphthyl, 86% ee; **1f**, R = $CH_2C_6H_4OMe$-4, 89% ee). In accord with our Diels−Alder studies,[1] the phenylalanine-derived catalyst **1a** was found to be most general with respect to reaction substrates (vide infra).

Variation in the Brønsted acid component of the benzyl imidazolidinone catalyst was next examined (Table 2). A number of imidazolidinone acid salts were found to catalyze the formation

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(1) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(2) For a recent review on the utilty of amino-oxy synthons, see: Fredrickson, M. *Tetrahedron* **1997**, *53*, 403.

(3) For reviews of [3 + 2] cycloadditions, see: (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: Chichester, 1984; Vol. 2, p 83. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(4) Chiral Lewis acid mediated [3 + 2] cycloadditions involving bidentate dipolarophiles have been reported: (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710. (c) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947. (d) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547. (e) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, *J. Org. Chem.* **1997**, *62*, 2471. (f) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (g) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.

(5) Derived in two steps from the respective amino acid (see Supporting Information).

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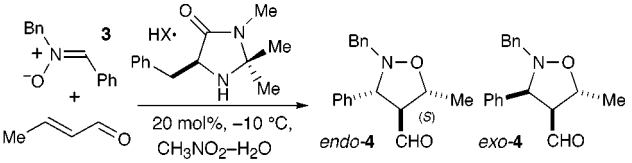
Table 2. Effect of the Brønsted Acid Cocatalyst on the Dipolar Cycloaddition between Crotonaldehyde and Nitrone **3**



entry	HX co-catalyst	Time (h)	% yield	*endo*:*exo*	% ee (*endo*)[a]
1	HCl (**1a**)	108	70	88:12	95
2	TfOH (**5**)	101	88	89:11	90
3	TFA (**6**)	80	65	72:28	86
4	HBr (**7**)	80	77	94:6	93
5	$HClO_4$ (**8**)	80	86	94:6	90
6	$HClO_4$ (**8**)	100	98	94:6	94[b]

[a] Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with $NaBH_4$. [b] Reactions performed at −20 °C.

of isoxazolidine (4*S*)-**4** in good yield and in greater than 86% ee (entries 1−6). An enantioselectivity/temperature profile documents that optimal stereochemical control and reaction efficiency is achieved at −10 °C with catalysts **1a**, **5**−**7** (entries 1−5), while the $HClO_4$ salt **8** is most effective at −20 °C (entry 6). Preliminary investigations suggest that the observed variation in enantioselectivity as a function of cocatalyst can be attributed to the extent of iminium activation in preference to achiral Brønsted acid promotion. As such, it is important to note that the HCl- and $HClO_4$-derived catalysts successfully partition the [3 + 2] cycloaddition toward the iminium pathway with >94% selectivity (>94% ee). The superior levels of asymmetric induction and diastereocontrol exhibited by the $HClO_4$ salt **8** to afford isoxazolidine (*S*)-**4** in 94% ee, 94:6 dr, and 98% yield (20 mol % catalyst, −20 °C) prompted us to select this catalyst for further exploration.

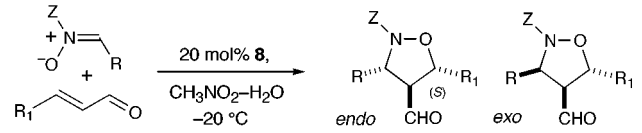
The scope of the organocatalytic 1,3-dipolar cycloaddition between α,*β*-unsaturated aldehydes and various nitrones has been investigated (Table 3).[6] The reaction appears quite general with respect to the nitrone structure (entries 1−8, 66−98% yield, 92:8 to 98:2 *endo*:*exo*, 91−99% ee). Variation in the *N*-alkyl group (R_1 = Me, Bn, allyl, entries 1−3) is possible without loss in enantioselectivity (*endo* 94−99% ee). As revealed with 4-chlorophenyl- and 4-methoxyphenyl-substituted nitrones (entries 4−6), the reaction is tolerant to a range of aromatic substituents on the dipole (76−93% yield, 92:8 to 98:2 *endo*:*exo*, 91−95% ee). Moreover, excellent levels of diastero- and enantioselectivity can be achieved with alkyl-substituted nitrones (entry 9, 99:1 *endo*:*exo*, 99% ee). To demonstrate the preparative utility, the addition of nitrone **3** to crotonaldehyde was performed on a 25 mmol scale with catalyst **8** to provide (4*S*)-**4** (94% ee, 98% yield).

Structural variation in the dipolarophile can also be realized (Table 3, entries 10−15). Significantly, both the $HClO_4$- and TfOH-derived catalysts are compatible with acrolein (entries 10 and 11, 90−92% ee), with amine **5** providing optimal reaction efficiency and stereocontrol (80% yield, 86:14 *endo*:*exo*). Finally, it is noteworthy that all of the reactions described in this study were performed under an aerobic atmosphere, using wet solvents and a readily available bench-stable catalyst, further outlining the operational advantages of organocatalysis.

Enantioselective formation of the *endo*-(4*S*)-isoxazolidine adduct was observed in all cases involving catalyst **8**. Significantly, this sense of asymmetric induction and diastereoselectivity are

(6) In a representative procedure, crotonaldehyde (1.2 mmol) was added to a solution of nitrone (0.3 mmol), catalyst **8** (0.04 mmol), and H_2O (1.8 mmol) in CH_3NO_2 (3 mL) at −20 °C. The resulting solution was maintained at this temperature until the nitrone was judged to be consumed by TLC analysis (35−160 h). The resulting solution was then passed through a plug of silica gel with EtOAc and concentrated. The resulting residue was then purified by silica gel chromatography.

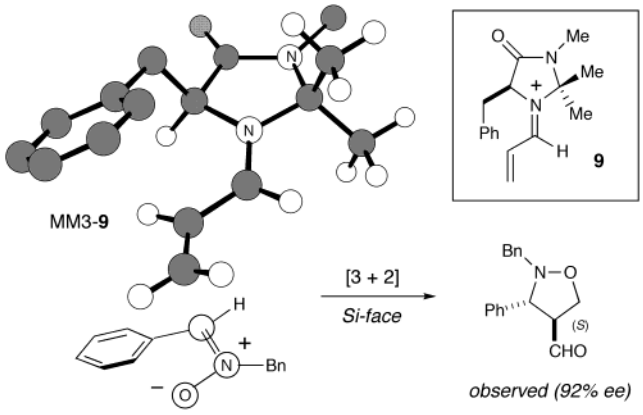
Table 3. Organocatalyzed Dipolar Cycloadditions between Representative Nitrones and Dipolarophiles



entry	Z	R	R_1	*endo*:*exo*	yield	% ee (*endo*)[a,b]
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Me	C_6H_4Cl-4	Me	93:7	76	94
6	Bn	C_6H_4OMe-4	Me	98:2	93	91
7	Me	C_6H_4Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	*c*-hex	Me	99:1	70	99
10	Bn	Ph	H	81:19	72	90
11	Bn	Ph	H	86:14	80	92[c]
12	Bn	C_6H_4Me-4	H	85:15	80	90[c]
13	Bn	C_6H_4Cl-4	H	80:20	80	91[c]
14	Bn	2-naph	H	81:19	82	90[c]
15	Bn	C_6H_4OMe-4	H	91:9	83	90[c]

[a] Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with $NaBH_4$. [b] Absolute and relative configurations assigned by chemical correlation or by analogy (Supporting Information). [c] Reactions conducted with catalyst **5**.

consistent with (*E*)-iminium isomer MM3-**9**[7] in direct analogy with our Diels−Alder studies.[1] By inspection, it is evident that enforced formation of the (*E*)-iminium isomer and the position of the benzyl group on the catalyst framework effectively promote cycloaddition from the *si*-face of the dipolarophile. Furthermore, cycloaddition through an *endo* topography effectively alleviates nonbonding interactions between the nitrone phenyl group and the neopentyl methyl substituent on the catalyst framework.



In conclusion, we have further established LUMO-lowering organocatalysis as a broadly useful concept for asymmetric catalysis in the context of [3 + 2] dipolar cycloadditions. A full account of this work will be forthcoming.

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

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(7) A Monte Carlo simulation, MM3 force-field; Macromodel V6.5.