JOC*Note*

Lewis Acid Catalyzed Dipolar Cycloadditions of an Activated Imidate

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Abstract: An evaluation of simple Lewis acids revealed that *N*-malonylimidates undergo catalyzed [3+2] cycloaddition reactions with aldehydes, imines, and activated olefins to form oxazolines, imidazolines, and pyrrolines, respectively. Reactions proceed optimally at ambient temperature with the addition of 5 mol % of $MgCl_2$ in CH_3CN. Experiments aimed at elucidation of the reactive intermediate undergoing cycloaddition suggest that the Lewis acid promotes a 1,2-prototropic shift to give a metal-coordinated azomethine ylide, rather than ionization and proton transfer to give a nitrile ylide.

Azomethine ylides are important intermediates in many [3+2] cycloadditions and have enjoyed much success in the synthesis of pyrrolidines and other nitrogen-containing heterocycles.[1−3] Continuing interest in such reactions has prompted a number of research groups to investigate *N*-metalated azomethine ylides formed via "soft enolization" of (imino)glycine esters as alternatives to ylides generated from the same compounds in the classic thermal [1,2]-prototropy manifold.[4,5] Ylides generated by the former method require a weak base working in concert with a metal salt.[6−10] Most substrates included in these cycloadditions are electron poor olefins which form functionalized pyrrolidines, in some cases with high levels of enantiocontrol.[11−13] [3+2] cycloadditions in which heterodipolarophiles are employed to intercept reactive azomethine ylide intermediates represent a useful entry into functionalized, protected α-amino acids.[14,15]

SCHEME 1. Lewis Acid Catalyzed [3+2] Cycloaddition

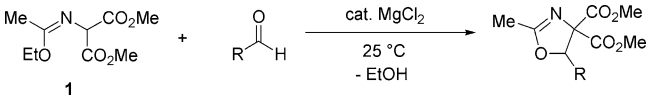
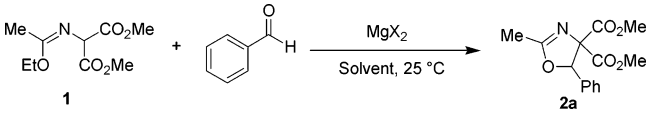


TABLE 1. Evaluation of Mg(II) Catalysts and Reaction Solvents



MgX_2 (equiv)	solvent	PhCHO (equiv)	time (h)	yield (%)
$Mg(OTf)_2$ (1.1)	THF	2.0	22.75	not complete
$MgCl_2$ (1.1)	THF	2.0	16.5	36
$Mg(OTf)_2$ (1.1)	CH_2Cl_2	2.0	5	49
$MgCl_2$ (1.1)	CH_2Cl_2	2.0	5.5	60
$MgCl_2$ (1.1)	toluene	2.0	20	not complete
$MgCl_2$ (0.2)	CH_2Cl_2	5.0	2.25	63
$MgCl_2$ (0.1)	CH_2Cl_2	10.0	1	76
$MgCl_2$ (0.1)	DMF	10.0	1	not complete
$MgCl_2$ (0.1)	CH_3CN	10.0	1.25	93

Recently, our group reported a Zn(II)-catalyzed heterolytic carbon−carbon bond cleavage of aziridines in which the intermediate azomethine ylide underwent cycloaddition with electron-rich dipolarophiles.[16] A geminal diester was needed to favor carbon−carbon bond cleavage relative to scission of the carbon−nitrogen bond, presumably allowing for stabilization of the nascent anion and chelation of the Lewis acid. In the context of this work we became interested in malonic imidate **1**, which, through the work of Bazureau, is known to undergo thermal dipolar cycloaddition with heterodipolarophiles.[6,17] The presence of the geminal ester groups suggested to us that this process may also be amenable to catalysis. In this Note we document mild, base-free, Lewis acid-catalyzed [3+2] cycloadditions of 2-(1-ethoxyethylideneamino)malonic acid dimethyl ester **1** and electron poor dipolarophiles (Scheme 1) and report our observations germane to the mechanism of this transformation.

Catalyst Evaluation and Scope. An examination of several Lewis acids ($SnCl_2$, $Sn(OTf)_2$, $ZnCl_2$, $Zn(OTf)_2$, $TiCl_4(THF)_2$, $TiCl_4$, $AlCl_3$, $Cu(OTf)_2$, $La(OTf)_3$, $Mg(OTf)_2$) revealed magnesium(II) triflate as the most promising promoter of oxazoline formation in the reaction between malonic imidate **1** and benzaldehyde (THF, 25 °C). Further investigation into the impact of the counterion showed $MgCl_2$ to be a more efficient catalyst. Finally, examination of reaction solvent demonstrated that CH_3CN was optimal (Table 1).

A catalyst loading of 5 mol % of $MgCl_2$ and 10 equiv of dipolarophile was found to provide convenient reaction

(1) Lown, J. W. In *1,3-Dipolar Cycloaddtion Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 653−732.
(2) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−177.
(3) Harwood, L. M.; Vickers, R. J. In *The Chemistry of Heterocyclic Compounds*: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley and Sons: New York, 2002; Vol. 59, pp 169−252.
(4) Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109−111.
(5) Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1978**, 2885−2888.
(6) Amornraksa, K.; Barr, D.; Donegan, G.; Grigg, R.; Ratananukul, P.; Sridharan, V. *Tetrahedron* **1989**, *45*, 4649−4668.
(7) Ayerbe, M.; Arrieta, A.; Cossio, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795−1805.
(8) Garcia Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981−987.
(9) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174−10175.
(10) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043−5046.
(11) Grigg, R. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2475−2486.
(12) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236−4238.
(13) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400−13401.
(14) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919−1939.
(15) Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, L. F. *Tetrahedron*: *Asymmetry* **1992**, *3*, 1127−1130.
(16) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294−2295.
(17) Lerestif, J. M.; Toupet, L.; Sinbandhit, S.; Tonnard, F.; Bazureau, J. P.; Hamelin, J. *Tetrahedron* **1997**, *53*, 6351−6364.

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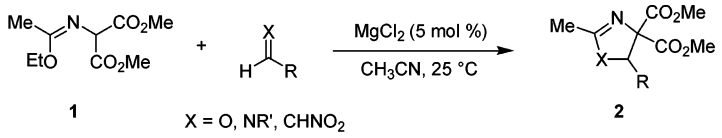
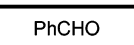
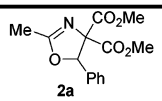
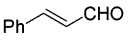
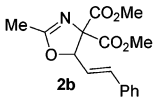
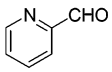
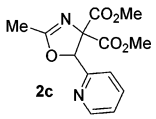
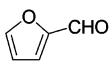
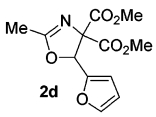
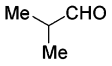
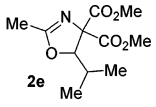
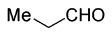
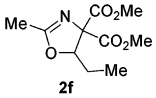
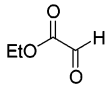
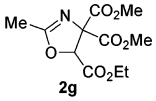
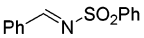
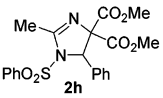
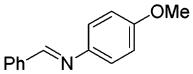
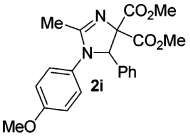
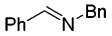
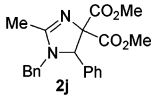
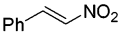
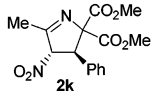
TABLE 2. Dipolarophile Scope



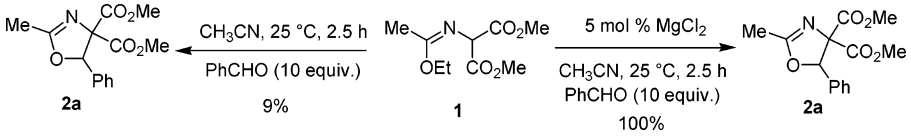
1 X = O, NR', $CHNO_2$ 2

Entry	Dipolarophile	Product	Time (h)	%Yield[a]
1		 2a	2.5	89
2		 2b	8	84
3		 2c	2	90
4		 2d	7	91
5		 2e	> 12	80
6		 2f	1.5	95
7[b]		 2g	2.5	72
8[b]		 2h	1.5	80
9		 2i	6	93
10		 2j	13	57
11		 2k	12	64

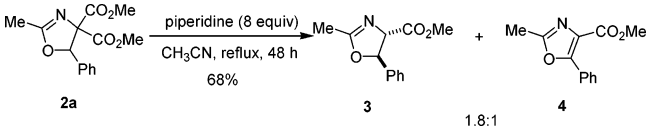
[a] Isolated yield. [b] 5 equiv of dipolarophile used.

rates. With an optimized catalyst−solvent system we began investigating electron-poor dipolarophiles (Table 2). Aldehydes were the most reactive dipolarophiles examined, forming oxazolines in moderate to excellent yields (entries 1−7). Ketones and esters were found to be completely unreactive in the heterocycloaddition. Activated imines also underwent cycloaddition to form imidazolines (entries 8−10). The cycloaddition tolerated aliphatic substitution on the *N*-terminus of the imine; however, aldimines derived from aliphatic aldehydes

SCHEME 2. Lewis Acid Catalyzed Cycloaddition vs Uncatalyzed Cycloaddition



SCHEME 3. Decarboxylation of Cycloadduct 2a



were unreactive. This method has also been extended to pyrroline synthesis with the cycloaddition of olefins activated by a nitro group[18] (entry 11); however, aliphatic substitution on the olefin was again not feasible.

Electron-rich dipolarophiles were examined for efficacy; however, dihydropyran, 2-methoxypropene, norbornylene, and cyclohexenyl-1-pyrrolidine did not undergo cycloaddition. Other electron-poor dipolarophiles that were found to be unreactive were oximes, hydrazones, benzylidene, and alkylidene malonates, diethyl fumarate and maleate, and dimethylacetylene dicarboxylate.

To observe the extent of catalysis versus the background cycloaddition, a control experiment was carried out in the absence of $MgCl_2$. After 2.5 h, 9% conversion was observed by ^1H NMR spectroscopy; conversely, under otherwise identical conditions, the metal-catalyzed cycloaddition showed 100% conversion after the same period of time (Scheme 2).

Decarboxylation of cycloadduct **2a** to **3** is accomplished with use of 8 equiv of piperidine in refluxing acetonitrile for 48 h.[17,19] The decarboxylation affords a 1.8:1 mixture of oxazoline **3** and oxazole **4** in a 68% combined yield (Scheme 3). Only the trans oxazoline isomer was observed. The use of rigorously deoxygenated and dried solvent does not significantly impact the ratio of **3**:**4**, and to date, we have not found decarboxylation conditions that successfully avoid the undesired aromatized byproduct **4**.

Mechanism. Two limiting reaction mechanisms can be envisioned involving either an azomethine or nitrile ylide acting as the key reactive intermediate (Scheme 4). In path A, chelation of the malonyl imidate to $MgCl_2$ would lower the activation barrier for formation of azomethine ylide **5** via [1,2]-prototropy.[4] The derived metal-coordinated ylide could then engage benzaldehyde in [3+2] cycloaddition to form oxazolidine **6**. Spontaneous loss of ethanol would afford oxazoline **2a**.

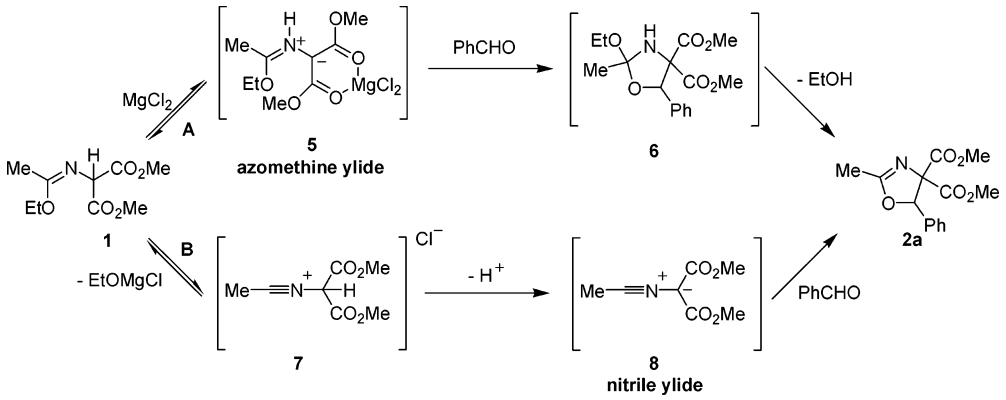
In path B, $MgCl_2$ could facilitate loss of ethoxide to form nitrilium ion **7**.[20] Subsequent deprotonation of the acidic malonyl proton by magnesium ethoxide would deliver nitrile ylide **8**, which can also undergo [3+2] cycloaddition with benzaldehyde to form oxazoline **2a**. A set of experiments was undertaken to elucidate which pathway might be operative.

When catalyzed cycloadditions were conducted in the presence of MeOH (20 equiv), ethoxy/methoxy exchange in the starting material does not occur competitively with cycloaddition: imidate **9** was not observed by ^1H NMR spectroscopy for reactions that had achieved partial conversion to product oxazoline. In the absence of dipolarophile, transimidation is quite slow (**9**:**1** = 1.5:1 after 16 h). If nitrilium ion **7** or nitrile ylide **8** were formed, transimidation to afford methyl acetimidate **9** should at the very least be competitive with cycloadduct formation (Scheme 5).[21]

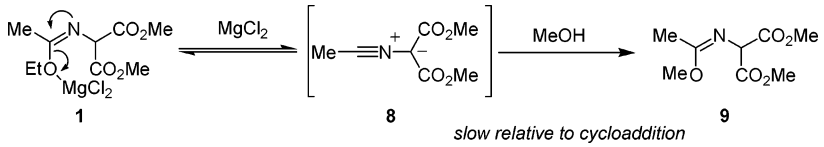
Further evidence suggesting an azomethine ylide intermediate was obtained by employing a scalemic catalyst. Oxazoline **2a** was obtained in low, but reproducible enantioselectivity when the cycloaddition between imidate **1** and benzaldehyde was carried out in the presence of enantiopure [bis(imine)]$MgCl_2$ complex **10** (Scheme 6). This verifies that a metal-bound intermediate must play an active role in the cycloaddition. If the $MgCl_2$ facilitates loss of ethoxide and nitrile ylide formation (Path B), then it is unlikely that any enantioinduction would be observed (although the [bis(imine)]$MgCl_2$ complex could coordinate the malonate after/during the deprotonation step). At a minimum, this suggests that a free nitrile ylide is unlikely. Importantly, this experiment also establishes the foundation for chirality transfer in this family of cycloadditions.

Conclusion. Dipolar cycloaddition of imidates via azomethine ylides can be catalyzed by $MgCl_2$, effecting the additions at ambient temperature. This process has

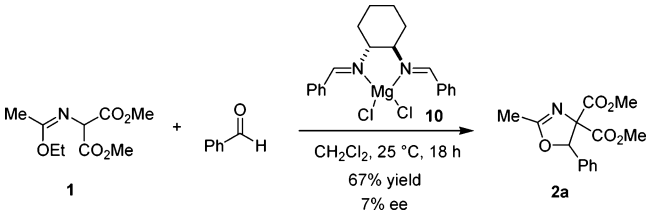
SCHEME 4. Azomethine vs Nitrile Ylide Formation



SCHEME 5. Transimidation of 1 Is Slow



SCHEME 6. [3+2]Cycloaddition Catalyzed by an Enantiopure Lewis Acid



been applied to several electron-poor dipolarophiles to form oxazolines, imidazolines, and pyrrolines. A series of control experiments are consistent with a metal-bound azomethine ylide intermediate, although a metal-coordinated nitrile ylide cannot be definitively excluded. The use of a scalemic metal complex to catalyze the cycloaddition allows for the possibility of enantioselective variants that are not possible thermolytically. Experimentation to optimize these findings is currently underway and will be reported in due course.

Experimental Section

General Procedure for Lewis Acid-Promoted Cycloaddition. In an inert atmosphere glovebox, a dry shell vial with a magnetic stir bar was charged with 0.369 mmol of imidate, 0.0185 mmol of $MgCl_2$, 2 mL of dry acetonitrile, and the dipolarophile (5−10 equiv). The shell vial was sealed with a septum and removed from the glovebox, placed under argon, and stirred for the required time at 25 °C. The reaction was filtered and washed with CH_2Cl_2. The solvent was removed with a rotary evaporator. The product was purified by flash chromatography, eluting with the indicated solvent system to afford pure oxazoline, imidazoline, or pyrroline product. TLC visualization was performed with a UV lamp or $KMnO_4$ solution.

5-Ethyl-2-methyloxazole-4,4-dicarboxylic Acid Dimethyl Ester (2f). The title compound was prepared according to the General Procedure, using 80 mg (0.369 mmol) of imidate **1**, 1.8 mg (0.0185 mmol) of $MgCl_2$, 2 mL of acetonitrile, and 214 mg (3.69 mmol) of propionaldehyde. After 1.5 h at ambient temperature the reaction was filtered to remove the catalyst. The product was purified by flash chromatography (EtOAc/CH_2Cl_2 1/1, R_f 0.45) to afford 81 mg (96%) of the product as a white solid (mp 70−72 °C). Analytical data for title compound **5f**: IR (thin film, cm^{-1}) 2956, 2883, 2850, 1743, 1662, 1436, 1390, 1340, 1292, 1245, 1107, 1084, 1051, 1026, 941; ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (dd, J = 10.3, 3.4 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.08 (s, 3H), 1.70−1.60 (m, 1H), 1.56−1.45 (m, 1H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.94, 168.91, 168.0, 85.4, 83.4, 53.4, 52.8, 24.2, 14.3, 10.8. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.24; H, 6.59; N, 6.07.

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

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(18) Nyerges, M.; Balazs, L.; Kadas, I.; Bitter, I.; Kovesdi, I.; Toke, L. *Tetrahedron* **1995**, *51*, 6783−6788.
(19) Texier, F.; Carrie, R. *Bull. Soc. Chim. Fr.* **1973**, *12* (Pt. 2), 3437−3442.
(20) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892−5899.
(21) Roberts, R. M.; Higgins, T. D.; Noyes, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 3801−3805.