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COMMUNICATIONS

Published on Web 04/13/2004

Chiral Lewis Acid Catalysis in Nitrile Oxide Cycloadditions

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Nitrile oxide cycloaddition to olefins is an important synthetic transformation.[1,2] Diastereoselective nitrile oxide cycloadditions have been investigated extensively, and successful methods are at hand.[3] However, the development of enantioselective variants using chiral Lewis acids has been hampered by the use of coordinative amine bases for the generation of the nitrile oxide, by the high donor ability of the oxygen atom of the dipole,[4] and by the propensity of the dipole to dimerize.[2] Ukaji and Inomata have reported examples of enantioselective nitrile oxide cycloadditions with allylic alcohols using chiral catalysts.[5] In this contribution we describe examples of highly regio- and enantioselective nitrile oxide cycloadditions to electron-deficient alkenes using substoichiometric amounts of a chiral Lewis acid.

We began our investigation with the goal of identifying achiral templates "Z" that would provide optimal regioselectivity in nitrile oxide cycloadditions to crotonates, since regioselectivity is often difficult to control (Scheme 1).[6] We reasoned that regioselectivity might result if the pathway leading to the *O*-adduct **4** could be suppressed by steric interactions of the R_1 group with either bulky templates and/or bulky Lewis acids. During template screening (Table 1), we used a chiral Lewis acid prepared from magnesium iodide and a bisoxazoline derived from amino indanol (**6a**) (30 mol % catalytic loading). Preformed mesityl nitrile oxide (**7a**), a stable dipole, was chosen as the reagent since this would obviate the use of an amine base for its generation. To aid us in the assessment of regio- and stereoselectivity, the product isoxazoline amides were reduced to alcohols **10** and **11**,[7] such that the same products would result regardless of initial template. Reaction with the oxazolidinone crotonates **5a**−**5c** proceeded with low regioselectivity and varying enantioselectivity (entries 1−3). Use of the 3,5-dimethylpyrazole template (**5d**) reversed the regioselectivity (entry 4). We have recently reported on a novel class of achiral pyrazolidinone templates, which contain a fluxional nitrogen atom and which have proven to be very effective in several enantioselective transformations.[8] Three such templates (**5e**−**5g**) differing in the size of the N1 substituent were investigated (entries 5−7). Reactions using each of the pyrazolidinone templates were both highly regio- and enantioselective providing the C-adduct exclusively. The size of the R group had minimal impact. *These results demonstrate that chiral Lewis acid-mediated nitrile oxide cycloadditions proceed with high enantioselectivity and high regioselectivity*.

The effect of the chiral Lewis acid on the nitrile oxide cycloadditions using template **5f** was evaluated next (Table 2). A remarkable impact of ligand is shown in entries 1−5. Reactions using MgI_2 and ligands **6b**−**6e** in place of **6a** gave adducts with poor C/O selectivity and negligible enantioselectivity. The nature of the magnesium counterion had limited influence, with magnesium perchlorate and triflimide giving results almost as good as with MgI_2 (entries 1, 6−8). Nickel salts (entries 9 and 10) also gave the C-adduct in high enantioselectivity, although with lower C/O regioselectivity as compared to MgI_2. These results show that several chiral Lewis acids are effective in providing C-adducts with high selectivity. The combination of ligand **6d** and $Cu(OTf)_2$, which has provided excellent enantioselectivity for various transformations, proved to be ineffective (entry 13). Lowering the catalytic loading of **6a** and MgI_2 from 30 to 10 to 5 mol % reduced both regioselectivity and enantioselectivity (compare entry 1 with entries 14 and 15).

We have carried out a short breadth and scope study by both varying the enoyl portion of the substrate and varying the nitrile oxide (Table 3). The *N*-benzyl pyrazolidinone template and the chiral Lewis acid derived from MgI_2 and **6a** were held constant. Four substrates were examined using **7a** as the dipole (entries 1−4). All of these reactions were highly efficient, providing the products in good yields and high regio- and enantioselectivity. Even the less reactive cinnamate acceptor **5i** gave excellent results (entry 3). The nitrile oxide was also varied (entries 1, 5−10). To avoid potential problems involving coordination of the Lewis acid by amine bases, we have devised a novel method for the generation of unstable nitrile oxides from hydroximinoyl chlorides using Amberlyst 21 as the base.[9] Cycloaddition with several aryl nitrile oxides gave

Scheme 1

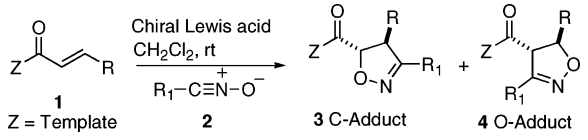
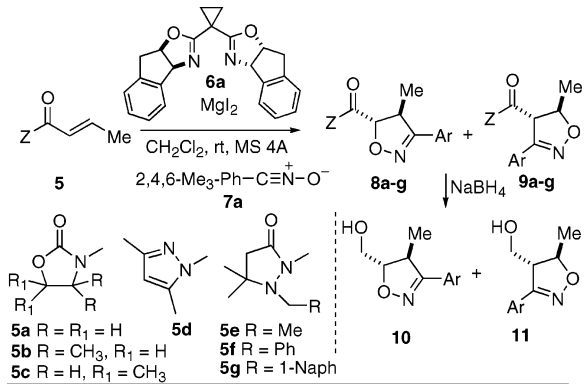


Table 1. Evaluation of Templates in Nitrile Oxide Cycloadditions[a,b]

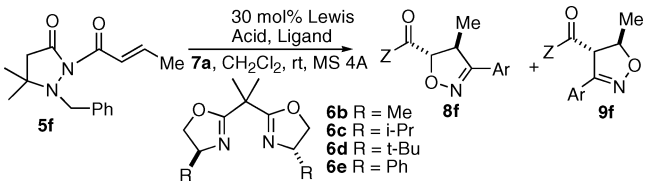


ent	subs.	yield, %[c]	time, h	**10**:**11** ratio[d]	**10** (ee), %[e]	**11** (ee), %[e]
1	**5a**	67	24	2.2:1 (**8a**:**9a**)	82	14
2	**5b**	41	24	1.6:1 (**8b**:**9b**)	28	00
3	**5c**	69	24	3:1 (**8c**:**9c**)	86	08
4	**5d**	61	96	1:5 (**8d**:**9d**)	37	03
5	**5e**	88	12	99:1 (**8e**:**9e**)	95	−
6	**5f**	84	2.5	99:1 (**8f**:**9f**)	99	−
7	**5g**	98	24	99:1 (**8g**:**9f**)	99	−

[a] For details of the reaction conditions see Supporting Information. [b] 30 mol % Lewis acid. [c] Isolated yield. [d] Regioisomer ratio determined by ^{1}H NMR (500 MHz). [e] Chiral HPLC.

10.1021/ja0318636 CCC: $27.50

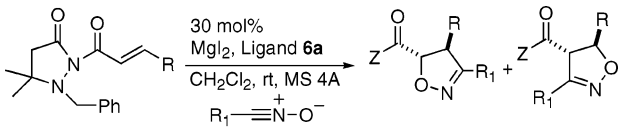
Table 2. Evaluation of Chiral Lewis Acids



ent	LA	ligand	yield, %[a]	8:9[b]	8 ee, %[c]	9 ee, %[c]
1	MgI_2	**6a**	84	99:1	99	–
2	MgI_2	**6b**	88	2:1	00	00
3	MgI_2	**6c**	89	4:1	19	04
4	MgI_2	**6d**	79	7:1	12	17
5	MgI_2	**6e**	88	11:1	40	14
6	$Mg(ClO_4)_2$	**6a**	89	32:1	98	–
7	$Mg(NTf_2)_2$	**6a**	83	21:1	97	33
8	$Mg(SbF_6)_2$	**6a**	92	17:1	72	57
9	$Ni(ClO_4)_2$	**6a**	74	15:1	92	20
10	$Ni(SbF_6)_2$	**6a**	88	10:1	96	–
11	$Zn(OTf)_2$	**6a**	76	3:1	11	04
12	$Cu(OTf)_2$	**6a**	67	3:1	00	29
13	$Cu(OTf)_2$	**6d**	34	2:1	−07	27
14[d]	MgI_2	**6a**	90	13:1	97	59
15[e]	MgI_2	**6a**	85	4:1	16	02

[a] Isolated yield. [b] Regioisomer ratio determined by ^{1}H NMR (500 MHz). [c] Chiral HPLC. [d] 10 mol % Lewis acid. [e] 5 mol % Lewis acid.

Table 3. Reactions with Various Dipolarophiles and Nitrile Oxides



ent	sub. R	nitrile oxide R_1	prod	yld, %[a]	8:9[b]	8 ee, %[c]
1	R = Me **5f**	**7a**	**8f**, **9f**	84	99:1	99
2	R = Et **5h**	**7a**	**8h**, **9h**	86	99:1	99
3	R = Ph **5i**	**7a**	**8i**, **9i**	85	99:1	99
4	R = CO_2Et **5j**	**7a**	**8j**, **9j**	75	99:1	99
5	R = Me **5f**	R_1 = Ph **7b**	**8k**, **9k**	75	99:1	99
6	R = Me **5f**	R_1 = 2-Cl−Ph **7c**	**8l**, **9l**	78	99:1	86
7	R = Me **5f**	R_1 = 4-Cl−Ph **7d**	**8m**, **9m**	70	99:1	96
8	R = Me **5f**	R_1 = 4-MeOPh **7e**	**8n**, **9n**	61	10:1	99
9	R = Me **5f**	R_1 = *t*-Bu **7f**	**8o**, **9o**	44	99:1	92
10	R = Me **5f**	R_1 = *i*-Bu **7g**	**8p**, **9p**	63	33:1	79

[a] Isolated yield. [b] Regioisomer ratio determined by ^{1}H NMR (500 MHz). [c] Chiral HPLC.

the C-adduct preferentially in high enantioselectivity and good yields (entries 5−8). Aliphatic nitrile oxides also provided the C-adducts with good selectivity, although the reactions were slower and proceeded in lower yields (entries 9 and 10).

The absolute stereochemistry of adduct **8k** was determined to be *S*,*S* by converting it to a known compound.[10] In general, control reactions in the absence of Lewis acid were slower than Lewis-acid-catalyzed reactions.[11] Thus, the superior results using the combination of bulky ligand **6a** and bulky templates **5e**−**5g** reflect shielding effects rather than superior rate acceleration. A tentative model for the cycloaddition is shown in Figure 1. In our model, a five- or six-coordinate magnesium is bound to the ligand and to the bidentate substrate in an *s-cis* conformation. Shielding by the ligand blocks the bottom face of the alkene.[12] The high enantioselectivity with templates **5e**−**5g** requires the bulky ligand **6a**; ligands

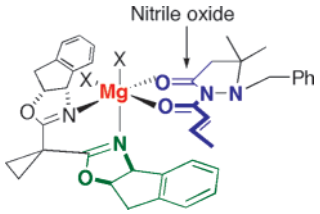


Figure 1. Stereochemical model

6b−**6e** are apparently too small. While MgI_2/**6a** provides good enantioselectivity even with oxazolidinone templates **5a** and **5c**, high regioselectivity requires the bulky pyrazolidinone templates **5e**−**5g**. We believe these templates may clutter the rear quadrant above the alkene such that the carbon end of the dipole prefers approach from the front quadrant for steric reasons. In contrast to some other reactions,[8] the size of the R group on the pyrazolidiones **5e**−**5g** had little observable influence on enantioselectivity.

Acknowledgment. This work was supported by NSF-CHE-0316203 and NSF-EPS-0132289.

Supporting Information Available: Characterization data for compounds **5**−**16** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The nitrile oxide can be generated using in situ Amberlyst 21, or by passing the hydroximinoyl chlorides through an external bed of Amberlyst 21 immediately prior to injection into the reaction mixture. See Supporting Information for details of the reaction setup.
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(11) Competing background reaction does explain entry 15 of Table 2 (5 mol % of MgI_2 as catalyst). Copper triflate also appears to be ineffective as a catalyst (Table 2, entries 12 and 13).
(12) MgX_2/**6a** gives the same sense of facial selectivity in other conjugate additions (amine, radical) with various templates (imide, pyrazolidione, oxazolidinone), see: (a) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796. (b) Reference 8c. (c) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472.

JA0318636