J|A|C|S
COMMUNICATIONS

Published on Web 12/30/2003

Exo Selective Enantioselective Nitrone Cycloadditions

Mukund P. Sibi,* Zhihua Ma, and Craig P. Jasperse

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

Received October 16, 2003; E-mail: mukund.sibi@ndsu.nodak.edu

Dipolar cycloadditions of nitrones to alkenes have received much synthetic interest[1] because they generate three contiguous stereocenters, and the products can be converted by reductive cleavage to β-amino acids. A number of different chiral Lewis acids have been used to catalyze nitrone cycloadditions that are regioselective, diastereoselective, and enantioselective.[1,2] Highly enantioselective examples involving electrophilic olefins **1** have consistently produced endo diastereomers **4**.[2,3] At present, there are no reported methods which provide access to the exo isomers **3** with both high enantioselectivity and high chemical efficiency (Scheme 1).[4] In this paper, we describe examples of highly exo- and enantioselective nitrone cycloadditions using novel templates[5] developed in our laboratory.

When Lewis acids coordinate to substrates **1**, the pathway leading to exo product **3** is frequently destabilized because the R_2 group interacts with the metal complex. In keeping with literature precedents,[4] we reasoned that a square planar metal complex would reduce these steric interactions and be more amenable to an exo mode of nitrone attack.

Given our interest in pyrazolidinone templates,[5] we evaluated nitrone additions to substrate **5**, using catalytic amounts (30 mol %) of chiral Lewis acids derived from metal salts and bisoxazolines **9**−**12** (eq 1).[6] These results are tabulated in Table 1. Reaction using $Cu(OTf)_2$ and ligand **9** as a Lewis acid (entries 1−4) was effective and gave a high yield of the exo isomer in good ee (entry 1).[7] Increasing the bulk of the chiral ligand (**10**, **11**) did not lead to enhancement in ee (entries 1−3). The modest ee using *tert*-butyl ligand **11** is interesting because this ligand in combination with cupric salts often gives excellent selectivity in a variety of transformations.[8] Much better results were observed using the aminoindanol-derived ligand **12** (entry 4), which resulted in 98% ee for the exo isomer **7** in high yield and with 96:4 exo−endo diastereoselectivity. These results establish for the first time that the exo adduct can be obtained in high yield and enantioselectivity. Molecular sieves (MS) have been reported to play an influential role in a variety of nitrone cycloadditions.[9] In our reactions, addition of MS led to a dramatic reversal (entry 5 versus 1) or reduction (entry 6 versus 4) in exo/endo selectivity, but without compromising the enantioselectivity of the exo isomer.[10] A similar impact on exo/endo selectivity by MS was observed when $Cu(ClO_4)_2$ was used (compare entry 7 with 8). A series of other Lewis acids were also screened using ligand **9** (compare entries 9−12 with entry 1). Zinc triflate was modestly exo-selective, but with low enantioselectivity (entry 9). In contrast, magnesium and iron Lewis acids gave nearly equal amounts of the exo/endo adducts with low ee's (entries 10 and 11), while scandium triflate gave only the endo adduct with no selectivity (entry 12). These studies suggest that a square planar metal complex is best for providing high exo selectivity.[11]

Having identified a viable chiral Lewis acid for providing the exo adduct, we evaluated the role of the template with respect to enantioselectivity (eq 2, Table 2). The bisoxazoline **9** with the smallest shielding group was used in these experiments to better assess the importance of the substituents on the pyrazolidinone ring. In the presence of a chiral Lewis acid, the fluxional nitrogen in the template can adopt a preferred configuration such that the pyrazolidinone ring effectively becomes a chiral auxiliary which can at times amplify stereoselectivity. Initially, we investigated the effect of the N1-substituent (the "chiral relay" group) in substrate **5**, with R_1 fixed. The enantioselectivity for the major exo adduct correlated with the steric bulk of the N1-substituent: increasing the bulk of the relay group from ethyl to benzyl to naphthylmethyl led to an increase in ee from 78% to 86% (entries 1−3). Decreasing the reaction temperature to 3 °C led to a small improvement in ee from 86% to 91% (compare entry 3 with 4). The nature of R_1 also impacted the ee of the major exo adduct. With benzyl as the N1-substituent, varying R_1 from methyls to cyclohexyl to benzyls also led to a systematic increase in the ee for the exo adduct (compare

Scheme 1

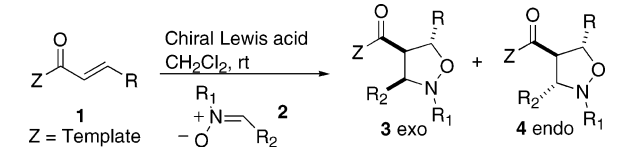
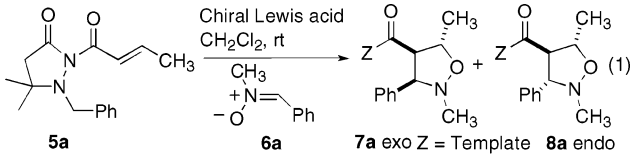
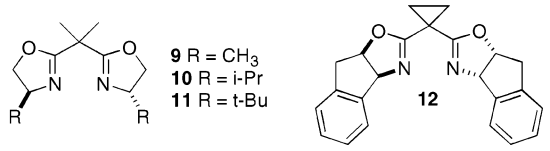


Table 1. Exo Selective Nitrone Additions: Effect of Chiral Lewis Acids[a]



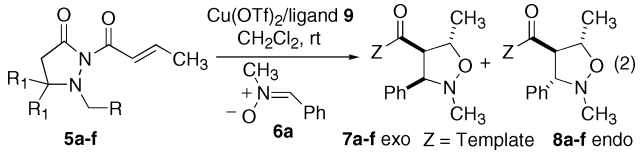


ent	Lewis acid[b]	lig	% yield[d] (SM)	exo/endo[c]	exo %(ee)[e]	endo %(ee)[e]
1	$Cu(OTf)_2$	**9**	96	90/10	75	
2	$Cu(OTf)_2$	**10**	91 (5)	79/21	71	50
3	$Cu(OTf)_2$	**11**	24 (71)	83/17	73	
4	$Cu(OTf)_2$	**12**	94 (4)	96/4	98	
5[f]	$Cu(OTf)_2$	**9**	88 (9)	19/81	72	47
6[f]	$Cu(OTf)_2$	**12**	92 (6)	63/37	98	80
7	$Cu(ClO_4)_2 \cdot 6H_2O$	**9**	93	83/17	71	
8[f]	$Cu(ClO_4)_2 \cdot 6H_2O$	**9**	96	32/68	67	52
9	$Zn(OTf)_2$	**9**	90 (7)	86/14	47	
10	$Mg(OTf)_2$	**9**	82 (15)	57/43	27	
11	$Fe(NTf_2)_2$	**9**	44 (53)	45/55	−17	−12
12	$Sc(OTf)_3$	**9**	98	2/98		2

[a] For details of the reaction conditions, see Supporting Information. [b] 30 mol % Lewis acid. [c] Diastereomer ratio determined by ^1H NMR (500 MHz). [d] Isolated yield for the product after chromatography. The amount of starting material recovered is after column chromatography. [e] Determined by chiral HPLC. [f] MS 4 A was added.

10.1021/ja039087p CCC: $27.50

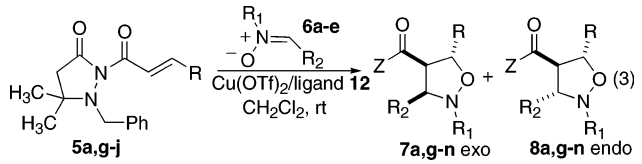
Table 2. Evaluation of Relay Templates



ent	R	R_1	no.	yield[a]	exo/endo[b]	exo (ee)[c]
1	CH_3	CH_3	**5b**	96	92/8	78
2	phenyl	CH_3	**5a**	96	90/10	75
3	1-naphthyl	CH_3	**5c**	93	89/11	86
4[d]	1-naphthyl	CH_3	**5c**	94	87/13	91
5	phenyl	cyclohexyl	**5d**	93	95/5	79
6	phenyl	benzyl	**5e**	94	91/9	93
7	1-naphthyl	cyclohexyl	**5f**	97	90/10	85

[a] Isolated yield. [b] Diastereomer ratio determined by ^{1}H NMR (400 or 500 MHz). [c] Determined by chiral HPLC. [d] Reaction at 3 °C.

Table 3. Reactions with Various Dipolarophiles and Nitrones



ent	subs. (R)	R_1	R_2	yield[a] (SM)	exo/ endo[b]	ee exo (endo)[c]
1	H **5g**	CH_3	Ph **6a**	85	66/34	99 (12)
2	CH_3 **5a**	CH_3	Ph **6a**	94	96/4	98
3	Et **5h**	CH_3	Ph **6a**	88 (10)	94/6	99
4[d,e]	Ph **5i**	CH_3	Ph **6a**	23 (76)	84/16	75
5[f]	CO_2Et **5j**	CH_3	Ph **6a**	44 (37)	67/33	85 (45)
6	CH_3 **5a**	Bn	Ph **6b**	92	93/7	99
7	CH_3 **5a**	Bn	4-ClPh **6c**	52 (41)	85/15	98
8[g]	CH_3 **5a**	Bn	4-MeOPh **6d**	45	95/5	98
9	CH_3 **5a**	Ph	Ph **6e**	85 (13)	52/48	99 (90)

[a] Isolated yield. [b] Diastereomer ratio determined by ^{1}H NMR (400 or 500 MHz). [c] Determined by chiral HPLC. [d] Ligand **9** was used in place of **12**. [e] MS 4 A was added. [f] 50 mol % catalyst was used. [g] O_2 balloon was used.

entries 2, 5, and 6). On the other hand, when both N1- and C5-substituents are large, the exo adduct enantioselectivity does not change (compare entry 3 with 7). These results suggest that there is a fine balance between the N1 and C5 substituents in providing optimal levels of selectivity. When the pyrazolidinone ring was replaced by a simple oxazolidinone, the reaction proceeded in high yield (98%) and exo selectivity (98:2), but with modest enantioselectivity (40% ee). This result suggests that the chiral relay templates amplify enantioselectivity but are not the source of exo selectivity.

We have carried out a small breadth and scope study by varying the enoyl substrate (entries 1−5) as well as the nitrone (entries 6−10), and these results are tabulated in Table 3 (eq 3). We chose ligand **12** which had provided high selectivity in Table 1. The parent acrylate **5g** gave the exo isomer in good yield and selectivity (entry 1). As illustrated earlier, the crotonate (**5a**) gave high selectivity (entry 2). The β-ethyl (**5h**) and cinnamate (**5i**) substrates were less reactive, but the ee's for the major exo adducts were high (entries 3 and 4). The fumarate (**5j**) was less efficient and somewhat less selective (entry 5). In terms of nitrone structure, compound **6a** was very reactive and also gave the highest exo:endo selectivity (entry 2). A benzyl group on the nitrogen as in **6b** was well tolerated and

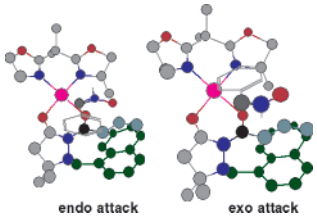


Figure 1. Stereochemical model.

gave high diastereo- and enantioselectivity (entry 6). Both electron-deficient (**6c**) and electron-rich (**6d**) nitrones gave addition products in modest yields, although enantioselectivity remained high in both cases (entries 7 and 8). Reaction with *N*-phenyl substituted nitrone **6e** was very efficient and highly enantioselective, but the exo/endo selectivity was low (entry 9).

Our results suggest that the key to exo selectivity is the use of a Lewis acid that forms square planar complexes (Figure 1 for substrate **5c**, nitrone **6a**, and ligand **9**, and copper triflate).[11] The exo attack is not sterically encumbered in this complex. As was demonstrated in our previous work,[5a] the pyrazolidinone relay template in a square planar arrangement works in concert with the ligand to amplify enantioselectivity.

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

Supporting Information Available: Characterization data for compounds **5**−**12** and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Karlssson, S.; Hogberg, H.-E. *Org. Prep. Proced. Int.* **2001**, *33*, 103. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (c) Kanemasa, S. *Synlett* **2002**, 1371. (d) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, 1.

(2) (a) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (b) Karlsson, S.; Hogberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923. (c) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (d) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (e) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227. (f) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001.

(3) For a discussion, see: Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346.

(4) For reactions proceeding with good exo diastereoselectivity or enantioselectivity, see: (a) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (b) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (c) Crosignani, S.; Desimoni, G.; Fiata, G.; Filippone, S.; Mortoni, A.; Righeti, P. P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007. (d) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017. (e) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483.

(5) Achiral templates with fluxional groups in synthesis, see: (a) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444. (b) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem.-Eur. J.* **2003**, *9*, 28. (c) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181.

(6) See Supporting Information for details on the synthesis of the starting materials, nitrones, stereochemistry analysis, and experimental conditions.

(7) The identities of the exo and endo adducts were established by converting them to known compounds. See Supporting Information for details.

(8) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *35*, 325.

(9) (a) References 2a, 4a, and 4c. (b) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213.

(10) These results suggest that there may be competing pathways when MS are added. The high enantioselectivity for the exo adduct with or without MS suggests that it may be formed without the involvement of the sieves.

(11) This conclusion is consistent with the high exo selectivity with copper as a Lewis acid (square planar complex) rather than magnesium or iron Lewis acids (typically tetrahedral or octahedral geometry).

JA039087P