ORGANIC LETTERS

2009
Vol. 11, No. 23
5366−5369

# Nitrile Ylides: Diastereoselective Cycloadditions using Chiral Oxzolidinones Without Lewis Acid

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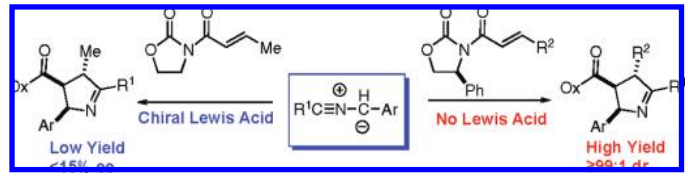
**Received August 10, 2009**

## ABSTRACT




**Lewis acid complexation is generally required for chiral-auxiliary-controlled stereoselectivity, and chiral Lewis acid catalysis is frequently optimal for introducing asymmetry. In this work, we show that nitrile ylide cycloadditions to electron-poor acceptors attached to chiral auxiliaries proceed in high yield and stereoselectivity in the absence of Lewis acids. In contrast, chiral Lewis acids are inferior in these cycloadditions.**

Small ring heterocycles are of great interest in medicinal chemistry.[1] Over the years, a variety of stereoselective methods have been developed for the preparation of nitrogen heterocycles.[2] A premiere method among these has been dipolar cycloadditions (Figure 1).[3] The control of relative and absolute stereochemistry in dipolar cycloadditions has been achieved using chiral auxiliaries, chiral Lewis acids, and more recently by the use of organocatalysts.[4] Among the large number of known dipoles, nitrones have received the most attention in enantioselective dipolar cycloadditions due to their stability and ease of synthesis.[5] Other stable dipoles have also been investigated, and we have recently shown that diazoesters undergo chiral Lewis acid-catalyzed cycloadditions to electron deficient acceptors to provide

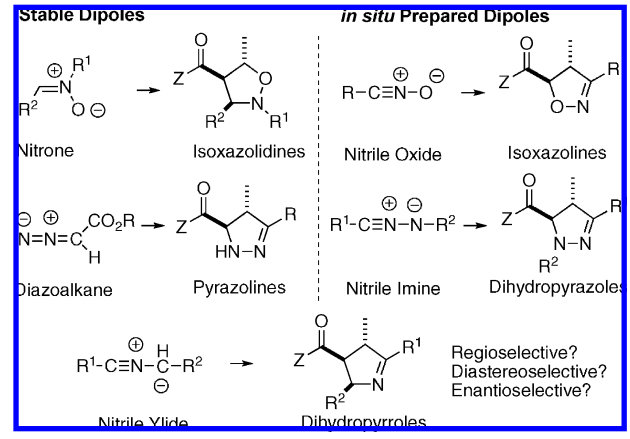



**Figure 1.** Dipolar cycloadditions with unsaturated acceptors.

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(2) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000.

(3) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003.

(4) For recent reviews of asymmetric 1,3-dipolar cycloadditions, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (c) Kanemasa, S. *Synlett* **2002**, *9*, 1371. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (e) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267.

(5) (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (b) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349. (c) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (d) Palomo, C.; Oiarbide, M.; Arceo, E.; Garcia, J. M.; Lopez, R.; Gonzalez, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187. (e) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431.

10.1021/ol9018584 CCC: $40.75 
**Published on Web 10/30/2009**

2-pyrazolines in high enantioselectivity.[6] Cycloadditions with the more reactive dipoles requiring in situ generation are much more challenging, since the bases used to generate the dipoles often interfere with the Lewis acids.[7] We have recently developed conditions involving in situ generated nitrile oxides[8] and nitrile imines[9] that undergo highly regio- and enantioselective cycloadditions using chiral Lewis acid catalysis.

Although initially described over 40 years ago by Huisgen and co-workers,[10] nitrile ylides, one of the more reactive dipoles, remain as one of the least explored dipoles.[11] In this work, we describe the first examples of highly stereoselective cycloadditions with nitrile ylides that proceed in good to excellent yields. Furthermore, we show that chiral auxiliaries in the absence of Lewis acids are the best source for the introduction of chirality in nitrile ylide cycloadditions to α,β-unsaturated enoates and that chiral Lewis acids are ineffective.

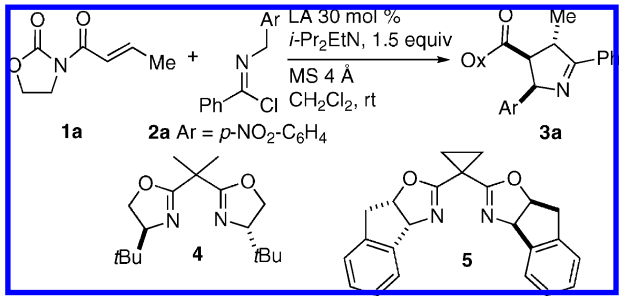
With our recent success in the development of enantioselective dipolar cycloadditions mediated by chiral Lewis acids, we began our work on determining an optimal protocol to carry out cycloadditions with nitrile ylides. Toward this end, we chose the well-known compound **2a** and oxazolidinone crotonate **1a** as our starting materials. It has been established in the literature that compound **2a** generates a nitrile ylide on treatment with an organic base.[12] At the outset, we were concerned with the high reactivity of the nitrile ylides. First, will they be compatible with Lewis acids? Second, will they be so reactive that addition to unactivated substrates (background reaction) competes with addition to Lewis-acid activated substrates?

To answer these questions, we carried out cycloadditions of the nitrile ylide generated from **2a** to the crotonate **1a** using Lewis acids (30 mol %) differing in strength (Table 1). Reaction with the highly Lewis acidic hafnium, scandium, and samarium triflates gave little or none of the desired adduct (entries 1−3).[13,14] Reactions using moderately Lewis acidic copper and zinc triflates gave no product (data not shown). Cycloaddition did occur in the presence of weakly acidic magnesium triflate, silver triflate and nickel bromide (entries 4−6). The cycloaddition product was formed as a single compound. The observed regiochemistry in the cycloadditions is consistent with that obtained with α,β-unsaturated esters and amides.[11,15] Cycloadditions in the presence of chiral Lewis acids were low-yielding and unselective (entries 7 and 8).[16] In each of the low yielding reactions, decomposition of the ylide was observed, presumably Lewis-acid induced.

By contrast, when the reaction was carried out in the absence of any Lewis acid (entry 9), the reaction gave the cycloadduct as a single isomer in 91% yield, the highest observed in the series. These results show that the background reactivity in the absence of Lewis acid is sufficiently high. Lewis acid activation is not only unnecessary for the desired cycloaddition, but is instead harmful in that it facilitates undesired decomposition of the nitrile ylide. Relatively weak Lewis acids probably are not effective. Lewis-acid incompatibility may be a limitation with other highly reactive dipoles as well.

The ineffectiveness of the chiral Lewis acids for enantioselective nitrile ylide cycloadditions led us to explore reactions with acceptors appended with a chiral auxiliary (Table 2). For initial screening, a chiral oxazolidinone derived from phenyl glycine was used. Chelating Lewis acids are normally used for reactions involving chiral oxazolidinone auxiliaries, such that the carbonyl group is locked in the syn s-cis arrangement.[17] There are only a few scattered reports of moderate to good selectivity in transformations using chiral oxazolidinone auxiliaries in the absence of Lewis acid

**Table 1.** Chiral Lewis Acid Mediated Nitrile Ylide Cycloadditions




| entry[a] | Lewis acid | ligand | yield, % entry[b] | ee, %[c] |
|---|---|---|---|---|
| 1 | $Hf(OTf)_4$ | – | nr | |
| 2 | $Sc(OTf)_3$ | – | 15 | |
| 3 | $Sm(OTf)_3$ | – | 32 | |
| 4 | $Mg(OTf)_2$ | – | 68 | – |
| 5 | AgOTf | – | 54 | – |
| 6 | $NiBr_2$ | – | 88 | – |
| 7 | $Mg(OTf)_2$ | **4** | 64 | 14 |
| 8 | $Mg(OTf)_2$ | **5** | 37 | 17 |
| 9 | None | – | 91 | – |

[a] For detailed reaction conditions, see Supporting Information. [b] Isolated yields after purification by column chromatography. [c] ee values were determined by chiral HPLC.


(6) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553. Also see: Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.

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(12) A variety of organic bases and solvents were evaluated. Diisopropylethylamine was the base of choice and methylene chloride was the optimal solvent.

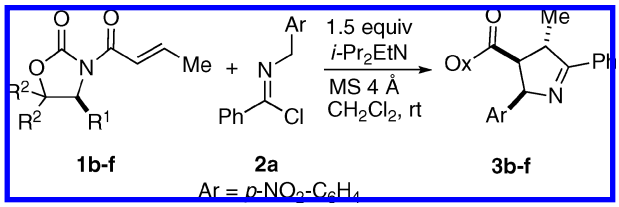
(13) Molecular sieves (4 Å) were used to maintain the integrity of the nitrile ylide. Nitrile ylides react with water to give the corresponding amide. In addition, water can react with Lewis acids in the presence of amines to make inactive metal hydroxides.

(14) Lewis acids have been shown to be incompatible with azomethine ylides, see: Ma, Z.; Wang, S.; Cooper, A C. S.; Fung, K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883.

(15) De March, P.; El Arrad, M.; Figueredo, M.; Font, J. *Tetrahedron* **1998**, *54*, 11613.

(16) A variety of chiral Lewis acids were explored in the cycloadditions. Results form these experiments gave low yields and or selectivity.

**Table 2.** Chiral Auxiliaries in Nitrile Ylide Cycloadditions



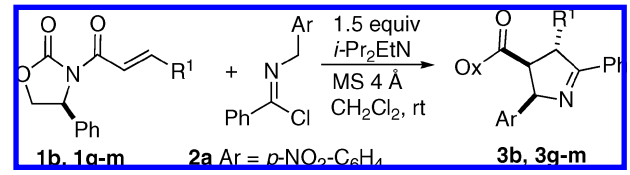

| entry[a] | $R^1$ | $R^2$ | Lewis acid[b] | prod | yield,%[c] | dr[d] |
|---|---|---|---|---|---|---|
| 1 | Ph (**1b**) | H | $Cu(OTf)_2$ | **3b** | trace | – |
| 2 | Ph (**1b**) | H | $Mg(OTf)_2$ | **3b** | 53 | ≥98:2 |
| 3 | Ph (**1b**) | H | $Sc(OTf)_3$ | **3b** | 19 | ≥98:2 |
| 4 | Ph (**1b**) | H | $NiBr_2$ | **3b** | 78 | ≥98:2 |
| 5 | Ph (**1b**) | H | – | **3b** | 87 | ≥98:2 |
| 6 | Bn (**1c**) | H | – | **3c** | 81 | 91:9 |
| 7 | Bn (**1d**) | Me | – | **3d** | 72 | 55:45 |
| 8 | *i*-Pr (**1e**) | H | – | **3e** | 83 | ≥98:2 |
| 9 | $Ph_2CH$ (**1f**) | H | – | **3f** | 80 | ≥98:2 |

[a] For reaction conditions, see Supporting Information. [b] Lewis acid (30 mol %) was used. [c] Yields are for isolated materials after column chromatography. [d] Diastereomeric ratios were determined by both NMR and by hplc following reduction of the acyl oxazolidinone.

additives.[18] Reaction of the crotonate derived from 4-phenyloxazolidinone and the nitrile ylide derived from **2a** was thus evaluated using different Lewis acids (entries 1−4). As was true in with the achiral oxazolidinone **1a**, yields were better with the weaker magnesium triflate and nickel bromide Lewis acids (entries 2 and 4). We then carried out a cycloaddition of **1b** and **2a** in the absence of a Lewis acid (entry 5). As expected based on the achiral series, the reaction gave an improved yield. Surprisingly the selectivity was outstanding, providing the product as a single regio- and diastereoisomer. The sense of stereoinduction was the same as that obtained for experiments with Lewis acid additives, again suggesting that cycloadditions that proceeded in the presence of weak Lewis acids did not actually involve Lewis acid-coordinated reactants. The auxiliary was cleaved by treatment with sodium borohydride to provide a primary alcohol. Enantiomeric excess analysis by chiral HPLC indicated that the cycloaddition product was formed in ≥99% purity. In the absence of Lewis acid acyl oxazolidinones react with the two carbonyls anti to each other (see X-ray results below); our results indicate that excellent face shielding is possible from the anti arrangement. The selectivity in Table 2 reflects the highest observed diastereoselectivity for reactions involving chiral oxazolidines in the absence of chelating Lewis acids. Other chiral oxazolidinone auxiliaries were also investigated in the cycloadditions (entries 6−9).[19] Of these only the 'Superquat' auxiliary derived from phenyl alanine failed to give high selectivity (entry 7).[20]

Having identified optimal reaction conditions for nitrile ylide cycloadditions, we then investigated the scope of the dipolarophile (Table 3). For these reactions we chose the 4-phenyl-oxazolidin-2-one as the chiral auxiliary and **2a** as the dipole. As was discussed earlier, reaction with the crotonate **1b** was efficient and highly selective (entry 1). The acrylate also underwent cycloaddition in good yield and high selectivity (entry 2). Enoates with $\beta$-alkyl (entry 3), aryl (entries 4 and 5), or heteroaryl (entry 6) substituents were competent substrates in the dipolar cycloadditions. The yields were good to excellent and the products were obtained as single regio- and stereoisomers. Reactions with the fumarate (entry 7) and the $\beta$-*p*-methoxybenyzloxy substituent (entry 8) also proceeded in good yields and selectivities. These experiments demonstrate that a variety of dipolarophiles undergo nitrile ylide cyloadditions in good yield and the products are formed as single isomers.

**Table 3.** Scope of the Acceptor in Nitrile Ylide Cycloadditions




| entry[a] | starting material, $R^1$ | product | yield[b] | dr[c] |
|---|---|---|---|---|
| 1 | Me (**1b**) | **3b** | 87 | ≥98:2 |
| 2 | H(**1g**) | **3g** | 74 | ≥98:2 |
| 3 | Et (**1h**) | **3h** | 91 | ≥98:2 |
| 4 | Ph (**1i**) | **3i** | 80 | ≥98:2 |
| 5 | 4-$BrC_6H_4$ (**1j**) | **3j** | 88 | ≥98:2 |
| 6 | 2-Furyl (**1k**) | **3k** | 68 | ≥98:2 |
| 7 | $CO_2t$-Bu (**1l**) | **3l** | 73 | ≥98:2 |
| 8 | OPMB (**1m**) | **3m** | 63 | ≥98:2 |

[a] For detailed reaction conditions, see Supporting Information. [b] Yields are for isolated materials after column chromatography. [c] Diastereomeric ratios were determined by both NMR and by hplc following reduction of the acyl oxazolidinone. The minor isomer was not detected.

After assessing the scope of the acceptor in nitrile ylide cycloadditions we then examined the effect of the dipole on efficiency and selectivity (Table 4), using compound **1b** as the acceptor. Nitrile ylides containing different aromatic and heteroaromatic substituents were examined in the cycloaddition reaction (entries 1−4). All of these reactions gave good yields of the cycloadduct and each product was formed as a single stereoisomer. An imidoyl chloride prepared from pivalyl aldehyde (**2e**) was also competent in the cycloaddition

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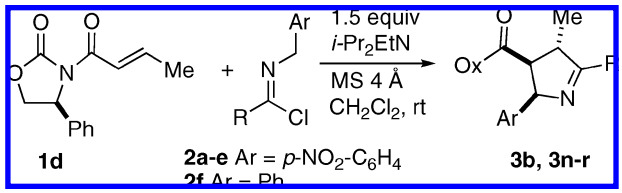
(18) (a) Okamura, H.; Morishige, K.; Iwagawa, T.; Nakatani M. *Tetrahedron Lett.* **1998**, *39*, 1211. (b) Garanti, L.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1285. (c) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1975. (d) Karlsson, S.; Han, F.; Högberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605. (e) Harrison-Marchand, A.; Collet, S.; Guingant, A.; Pradèrea, J.-P.; Toupet, L. *Tetrahedron* **2004**, *60*, 1827. (f) Krysiak, J.; Kato, T.; Gornitzka, H.; Baceiredo, A.; Mikolajczyk, M.; Bertrand, G. *J. Org. Chem.* **2001**, *66*, 8240.

(19) Other auxiliaries were also investigated. For example, reaction of crotonate derived from camphor sultam and **2a** gave the cycloadduct in 77% yield and 56% de.

(20) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886.

**Table 4.** Scope of the Nitrile Ylide in Cycloadditions




| entry | nitrile ylide, R[a] | product | yield, %[b] | dr[c] |
|---|---|---|---|---|
| 1 | Ph (**2a**) | **3b** | 87 | ≥98:2 |
| 2 | 4-Br$C_6H_4$ (**2b**) | **3n** | 83 | ≥98:2 |
| 3 | 2-Furyl (**2c**) | **3o** | 84 | ≥98:2 |
| 4 | 2-Thiophenyl(**2d**) | **3p** | 84 | ≥98:2 |
| 5 | *t*-Bu (**2e**) | **3q** | 73 | ≥98:2 |
| 6[d] | Ph (**2f**) | **3r** | 64 | ≥98:2 |

[a] For reaction conditions, see Supporting Information. [b] Yields are for isolated materials after column chromatography. [c] Diastereomeric ratios were determined by both NMR and by hplc following reduction of the acyl oxazolidinone. The minor isomer was not detected. [d] Two equivalents of a phosphazene base ($P_1$-*t*-Bu) was used for the preparation of the ylide.

(entry 5). The *p*-nitrobenzyl group is not a requirement for the preparation of the ylide; upon treatment with a stronger phosphazene base *N*-benzyl imidoyl chloride **2f** gave the nitrile ylide, which underwent cycloaddition with good efficiency and high selectivity (entry 6). These experiments demonstrate that there is reasonable scope for the nitrile ylide in diastereoselective cycloadditions.

In the present work the nitrile ylide adds to the unsaturated acceptor in a highly regioselective manner. This is consistent with a dominant interaction between the HOMO of the dipole and the LUMO of the acceptor.[21] Furthermore, the cycloaddition to the chiral oxazolidinone leads to a single stereoisomer. As is evident from Tables 1 and 2, the reaction rates are good even without Lewis acids, and reactions with the highly reactive nitrile ylides do not require activation. The formation of the same stereoisomer in the presence and absence of a Lewis acid additive (Table 2) suggests that Lewis acids play no role in the stereochemical outcome of the reaction. We have obtained an X-ray crystal structure of the product **3r**, thus enabling us to assign absolute stereochemistry for the cycloadduct (Figure 2). The dihydropyrrole product had

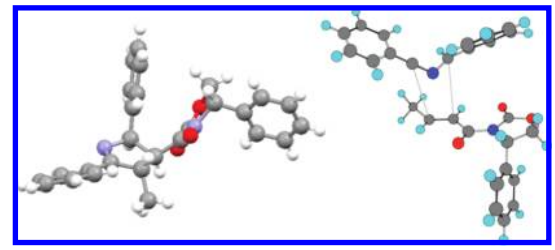


**Figure 2.** Model for explaining stereochemical outcome in nitrile ylide cycloaddition to chiral acyl oxazolidinones.

the (2*R*,3*S*,4*S*) configuration. The stereochemical outcome for the reaction is consistent with exo cycloaddition to an s-cis conformer of the oxazolidinone with the two carbonyls in an anti orientation (dipole−dipole repulsion). The high selectivity in the present work can be accounted for by selective approach of the dipole to the $C_\alpha$-*re* face of the dipolarophile, while approach to the $C_\alpha$-*si* face is disfavored by steric interactions between the dipole and the chiral substituent of the auxiliary. It is likely that the steric size at both ends of the dipole facilitates the high diastereoselectivity, particularly on the end approaching the α-carbon of the enoyl group which is nearer the blocking group of the auxiliary.

In conclusion, we have demonstrated for the first time that nitrile ylide cycloaddition to electron poor acceptors proceeds in high yield and selectivity. Our work demonstrates that outstanding stereocontrol is possible with acyl oxazolidinones in the absence of Lewis acids, a process not commonly appreciated.

**Acknowledgment.** We thank the National Science Foundation (NSF-CHE-0709061) for financial support of this work.

**Supporting Information Available:** Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9018584

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