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Lewis Acid-Catalyzed Nitrone Cycloadditions to Bidentate and Tridentate α,β-Unsaturated Ketones. High Rate Acceleration, Absolutely *endo*-Selective and Regioselective Reactions

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Abstract: *α,β-Unsaturated ketone dipolarophiles having bidentate or tridentate ligand structures, such as (E)-1-benzyloxy- and (E)-1-(2-phenylthioethoxy)-3-penten-2-one, are activated by a Lewis acid catalyst in 1,3-dipolar cycloadditions of nitrones. Dichlorodiisopropoxytitanium and chlorotriisopropoxytitanium are especially effective. Lewis acid-mediated enhancement of stereo- and regioselectivity have been attained for the first time in intermolecular nitrone cycloadditions. Formation of dipolarophile/Lewis acid complexes is responsible for the remarkable Lewis acid catalysis.*

Like nitrile oxides, nitrones are among the most useful 1,3-dipoles ever used in organic synthesis.[1] Thus, their cycloadditions, followed by some functional group transformations including a reductive cleavage of the nitrogen-oxygen bond of cycloadducts, have found wide synthetic applications in elaboration of complex structures of natural products.[2] Since nitrones are not so highly reactive dipoles compared with nitrile oxides and their intermolecular cycloadditions are lack of stereoselctivity, most of synthetic applications reported have consisted of intramolecular versions of nitrone cycloadditions.[1,2]

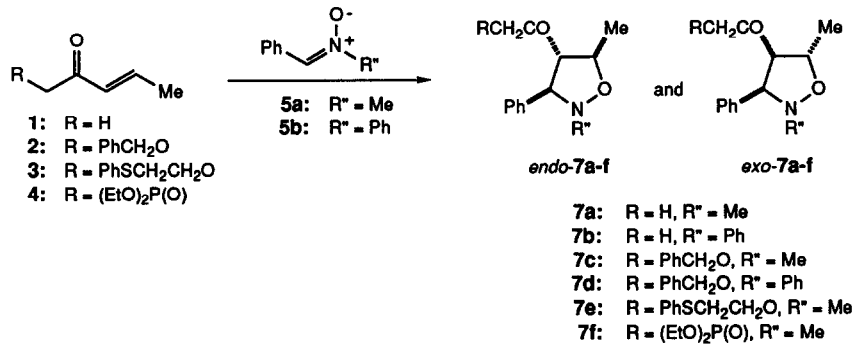
Based on numerous reports on successful Lewis acid-catalyzed stereocontrol of Diels-Alder reactions,[3] similar Lewis acid catalysis is expected in dipolar cycloadditions. However, no successful reactions are so far known.[4] A serious problem is that 1,3-dipoles act as much stronger bases than dienes. Then dipoles have a tendency to form inactive dipole/Lewis acid complexes (hereafter referred to as "dipole complex"). To overcome this difficulty we designed new electron-deficient olefinic dipolarophiles that have a chelate ligand structure. Our expectation is that the incorporation of a Lewis acid may be equilibrating between dipole and dipolarophile, and that acceleration of cycloaddition will occur only in the dipolarophile/Lewis acid complex (hereafter referred to as "dipolarophile complex").[5]

In the present communication, we describe the first example of reaction control of intermolecular nitrone cycloadditions by the aid of a Lewis acid catalyst. Significant rate acceleration, high stereo-, and regiocontrol can be attained by a proper choice of dipolarophiles and catalysts.

Cycloadditions of nitrones, such as benzylidenemethylamine *N*-oxide (**5a**) and -phenylamine *N*-oxide (**5b**), to a 1-propenyl ketone such as (*E*)-3-penten-2-one (**1**) are impracticably slow below 80 °C (Scheme 1 and Table 1, entries 1, 3). Although these reactions, when performed at 80 °C, are absolutely regioselective to produce 4-acetylisoxazolidines **7a,b**, stereoselectivities are quite low (*endo:exo* = 40:60 for **7a**; 73:27 for **7b**). Similarly high regioselectivities and low stereoselectivities result in nitrone cycloadditions to bidentate

and tridentate enones such as (*E*)-1-benzyloxy-3-penten-2-one (**2**), (*E*)-1-(2-phenylthioethoxy)-3-penten-2-one (**3**), and diethyl (*E*)-2-oxo-3-pentenylphosphonate (**4**) (entries 5, 10, 12, 15).[6]

Zinc(II) chloride and dichlorodiisopropoxytitanium were found to accelerate the cycloadditions of nitrones **5** to monodentate enone **1**. Stereoselectivities were either not effected (entry 4) or a little improved in favor of *exo*-isomer (entry 2). On the other hand, an 87:23 mixture of *endo*-**7c** and *exo*-**7c** was obtained in the zinc(II) chloride-mediated reaction of bidentate enone **2** with **5a** at room temperature in dichloromethane (entry 6).[7] Chlorotriisopropoxy- and dichlorodiisopropoxytitanium showed more effective rate acceleration as well as higher *endo*-selectivities (entries 7-9). Thus, reaction of **2** with **5a** proceeded at 0 °C to provide *endo*-**7c** as single diastereomer when catalyzed by dichlorodiisopropoxytitanium (entry 9); similarly, *endo*-**7d** was obtained from **2** with **5b** (entry 10).[8]



Scheme 1.

Table 1. Nitrone Cycloadditions to Mono-, Bi-, and Tridentate Enone Dipolarophiles **1-4**

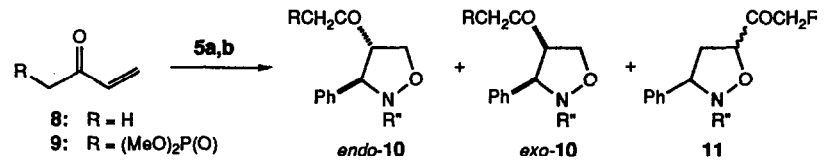
Entry	Olefin + Nitrone[a]	Catalyst[a]	Solvent[b]	Temp./°C	Time/h	Product	Yield/%	*endo:exo*
1	**1** + **5a**	-	BZN	80	20	**7a**	30	40:60
2	**1** + **5a**	$ZnCl_2$	DCM	rt	6 d	**7a**	39	20:80
3	**1** + **5b**	-	TLN	80	10	**7b**	70	73:27
4	**1** + **5b**	$Ti(OPr\text{-}i)_2Cl_2$	DCM	rt	18	**7b**	49	77:23
5	**2** + **5a**	-	BZN	80	8	**7c**	76	40:60
6	**2** + **5a**	$ZnCl_2$	DCM	rt	52	**7c**	77	87:23
7	**2** + **5a**	$Ti(OPr\text{-}i)_3Cl$	DCM	rt	14	**7c**	45	90:10
8	**2** + **5a**	$Ti(OPr\text{-}i)_2Cl_2$	DCM	rt	5	**7c**	35	94:6
9	**2** + **5a**	$Ti(OPr\text{-}i)_2Cl_2$	DCM	0	32	**7c**	50	>99:1
10	**2** + **5b**	-	TLN	80	15	**7d**	89	67:33
11	**2** + **5b**	$Ti(OPr\text{-}i)_2Cl_2$	DCM	0	17	**7d**	74	>99:1
12	**3** + **5a**	-	BZN	80	9	**7e**	64	35:65
13	**3** + **5a**	$Ti(OPr\text{-}i)_2Cl_2$	DCM	rt	9	**7e**	65	94:6
14	**3** + **5a**	ZnI_2	DCM	rt	6 d	**7e**	40	23:77
15	**4** + **5a**	-	TLN	110	21	**7f**	73	83:17
16	**4** + **5a**	$Ti(OPr\text{-}i)_3Cl$	DCM	rt	21	**7f**	45	83:17

[a]Each one equivalent of olefin, nitrone, and catalyst was used in all cases. [b]BZN: benzene; DCM: dichloromethane; TLN: toluene. [c]Yield of isolated mixture of isomers. [d]Based on ^1H NMR of the crude reaction mixture.

Stereochemistries of *endo*- and *exo*-**7a-d** were clearly assigned on the basis of ^1H and ^{13}C NMR spectra. Protons of 4-substituent RCH_2CO of *exo*-**7** are more effectively shielded by 3-phenyl group since they

are cis each other; both C-3 and C-4 of *exo*-**7** appear in higher chemical shifts due to a compression effect. Two diastereomers of **7d**, *endo*-**7d** and *exo*-**7d**, offered the typical case.[8]

Tridentate enone **3** was also effectively catalyzed by dichlorodiisopropoxytitanium to show the *endo:exo* ratio of 94:6 at room temperature (entry 13). On the other hand, no preference for *endo*-selectivity resulted in the zinc(II) iodide-accelerated nitrone cycloaddition to **3**, but rather, the *exo*-selectivity was more favored (entries 12, 14). Such preference of *exo*-selectivity was observed in the reaction with **1** (entry 2), while the zinc(II) chloride-catalyzed reaction to **2** was highly *endo*-selective (entry 6). No satisfactory explanation is so far available. Enone **4** having a phosphoryl moiety was activated by chlorotriisopropoxytitanium, but no any increase of *endo*-selectivity was observed (entries 15, 16).



Scheme 2.

Regioselectivity is not always high in nitrone cycloadditions to terminal olefins.[1,2] For example, reaction of **5a** with dimethyl 2-oxo-3-butenylphosphonate (**9**) under reflux in toluene affords a 34:66 mixture of regioisomers **10b** (*endo* only) and **11b** (*endo:exo* = 1:1). When catalyzed by chlorotriisopropoxytitanium, the *endo*-isomer of 4-acetyl regioisomer *endo*-**10a** was yielded as a single product (rt, 24 h in dichloromethane, 41% yield). Similarly, only *endo*-**10c** was produced in the chlorotriisopropoxytitanium-catalyzed reaction between **5b** and **9** (rt, 21 h in dichloromethane, 46% yield). However, the regioselectivity was not improved in the reaction between **5a** and **8** even under catalyzed conditions, indicating the insufficient coordination of Lewis acid to monodentate enone **8**.

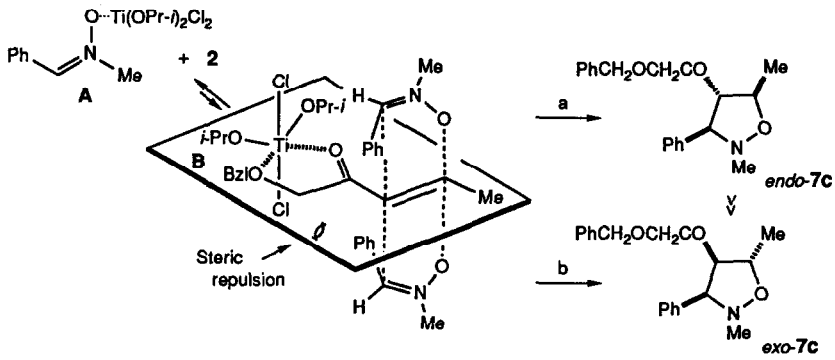


Figure 1. Titanium-mediated *endo*-selective nitrone cycloadditions.

A Lewis acid catalyst can be incorporated both in nitrone **5a** and bidentate enone **2**. It is clear that the catalyst is mostly incorporated in the dipole complex **A** rather than the dipolarophile complex **B** (Fig. 1).[9]

Although inactive complex **A** does not undergo cycloadditions, more reactive complex **B**, albeit as minor contributor, participates in cycloadditions. The enhanced regioselectivity would be due to the increase of electron deficiency at the β-carbon of enone complex **B**; the highly *endo*-selective reaction through route "a" leading to *endo*-**7c** is a result of the serious steric repulsion developing in the *exo*-selective counterpart (route "b").[10]

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References and Note

1. a) Tufariello, J. J. "Nitrones," as Chapter 9 of Vol 2 of "1,3-Dipolar Cycloaddition Chemistry," ed by Padwa, A., John Wiley & Sons, New York (1984), pp 83-168. b) Confalone, P.; Huie, E. M. *Org. Reactions* **1988**, *36*, 1-173. c) Breuer, E.; Aurich, H. G.; Nielsen, A. "Nitrones, nitronates and nitroxides," ed by Patai, S.; Rappoport, Z., John Wiley & Sons, New York (1989), pp 139-312.
2. a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. "Natural Product Synthesis through Pericyclic Reactions," American Chemical Society, Washington (1983), pp. 89-117. b) Padwa, A.; Schoffstall, A. M. "Intramolecular 1,3-Dipolar Cycloaddition Chemistry," in "Advances in Cycloaddition," ed by Curran, D. P., Vol 2, JAI Press, Greenwich (1990), pp. 1-89.
3. a) Taschner, M. J. "Asymmetric Diels-Alder Reactions," in "Organic Synthesis - Theory and Applications," ed by Hudlicky, T., Vol 1, JAI Press, Greenwich (1989), pp. 1-101. b) Carruthers, W. "Cycloaddition Reactions in Organic Synthesis," Pergamon Press, Oxford (1990), pp. 1-208.
4. Metal-assisted dipolar cycloadditions: a) Barr, D. A.; Grigg, R.; Gunaratune, H. Q. N.; Kemp, J.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1988**, *44*, 557-570. b) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384-1391. c) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817-5820.
5. The dipole complex as a major contributor deactivates cycloadditions, while the minor dipolarophile complex activates. Control of this equilibrium in favor of the dipolarophile complex is a point.
6. Enones **2** and **3** were prepared by phosphorylmethylation of ethyl benzyloxyacetate and ethyl (2-phenylthioethyl)acetate, respectively, followed by Horner-Emmons olefination with acetaldehyde. Enone **4** was prepared by a sequence of aldol reaction of the dianion of diethyl 2-oxopropylphosphonate, *O*-mesylation, and elimination.
7. All isolable products reported herein were fully characterized on the basis of spectral data.
8. Only *endo*-**7d** was isolated by a silica gel column chromatography at the expence of weight loss, *exo*-**7d** being tentatively assigned on the basis of ^{1}H and ^{13}C NMR spectra of the mixture. *endo*-**7d**: Pale yellow liquid; IR (neat) 3070-2900, 1720, 1600, 1495, 1105, 760, and 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.42 (3H, d, $J_{Me\text{-}5}$ = 6.2 Hz, 5-Me), 3.50 (1H, dd, $J_{4\text{-}5}$ = 8.4 and $J_{4\text{-}3}$ = 7.3 Hz, H-4), 3.92, 3.99 (each 1H, dd, J_{gem} = 17.5 Hz, CH_2O), 4.41 (1H, dq, $J_{5\text{-}4}$ = 8.4 and $J_{5\text{-}Me}$ = 6.2 Hz, H-5), 4.44 (2H, s, $PhCH_2$), 5.01 (1H, d, $J_{3\text{-}4}$ = 7.3 Hz, H-3), 6.87-6.95, and 7.13-7.50 (15H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.70 (5-Me), 69.07 (C-4), 73.29, 73.69, 75.27, 77.59 (C-3, C-5, CH_2O, and $PhCH_2$), 114.35, 121.74, 126.35, 127.83, 128.00, 128.16, 128.53, 128.88, 129.01, 136.55, 141.39, 151.53 (each Ph), and 204.54 (CO); MS (rel intensity, %) *m/z* 388 (M^+ + 1, 29), 387 (M^+, base peak), 222 (20), 181 (23), 180 (27), 131 (35), 91 (82), and 77 (23). Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.15; H, 6.55; N, 3.48. *exo*-**7d**: ^{1}H NMR ($CDCl_3$) δ = 1.37 (3H, d, $J_{Me\text{-}5}$ = 6.0 Hz, 5-Me), 3.24, 3.65 (each 1H, dd, J_{gem} = 17.2 Hz, CH_2O), 3.71 (1H, t, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 9.6 Hz, H-4), 4.27 (2H, s, $PhCH_2$), 4.92 (1H, m, H-5), 4.94 (1H, d, $J_{3\text{-}4}$ = 9.6 Hz, H-3), 6.86-6.98, and 7.12-7.50 (15H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.77 (5-Me), 63.11 (C-4), 71.95 (C-3), 73.04, 74.30, 75.20 (C-5, CH_2O, and $PhCH_2$), 115.79, 122.18, 127.76, 127.99, 128.06, 128.28, 128.36, 128.55, 128.66, 136.89, 138.21, 150.22 (each Ph), and 205.64 (CO).
9. Treatment of $ZnCl_2$ (one equivalent) with a 1:1 mixture of **2** and **5a** only causes the lowfield shifts of protons of **5a**, indicating the catalyst is mostly incorporated in **5a**.
10. Based on the chemical shifts of *N*-methyl (δ = 3.89) and =CH (7.37) protons, nitrone **5a** exists in a *Z*-form in chloroform solution.[11]
11. Bjorgo, J.; Boyd, D. R.; Neil, D. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 254-259.

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