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Yb(OTf)3-Catalyzed 1,3-Dipolar Cycloaddition of Nitrone with Alkene; Switch in Diastereoselectivity by Solvent and Bidentate Auxiliary

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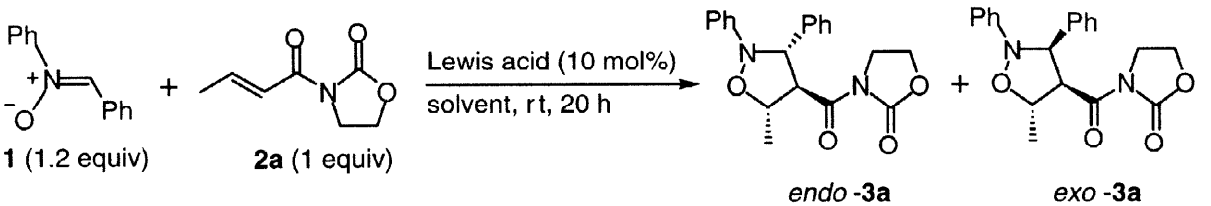
Abstract: Yb(OTf)3 (ytterbium trifluoromethanesulfonate)-catalyzed diastereoselective 1,3-dipolar cycloaddition of a nitrone with α,β-unsaturated carbonyl compounds was studied. While *endo*-cycloadduct was obtained from the reaction of *C, N*-diphenylnitrone with *N*-crotonoyl-oxazolidinone or *N*-crotonyl-2-pyrrolidinone in toluene, *exo*-adduct was predominant in acetonitrile. The enones carrying imidazolidinone or succinimide ring reacted with the nitrone to give the *exo*-adducts primarily in both solvents.

Recent studies have shown that lanthanide trifluoromethanesulfonates are effective Lewis acid catalysts in Aldol reactions, Michael additions, allylation of carbonyl compounds, Diels-Alder reactions and Friedel-Crafts acylation reactions.[1] This is mainly due to the unique properties of the lanthanides which include specific coordination numbers, strong Lewis acidity, and a high affinity toward carbonyl oxygens.[2] The stereochemistry of the Diels-Alder reaction has been successfully controlled utilizing lanthanide triflates.[3] In addition, Kanemasa et al.[4] and others[5] have described the Lewis acid-catalyzed stereocontrol of 1,3-dipolar cycloaddition of nitrones to alkenes. Although a problem exists, in that 1,3-dipoles have tendency to form complexes with Lewis acid in the cycloaddition of nitrones with alkenes, this problem can be alleviated by an appropriate design of structures of diporalophiles or Lewis acid.[4,5] From these points of view, we report herein the Yb(OTf)3 catalyzed *endo*- or *exo*-selective 1,3-dipolar cycloaddition of nitrones with alkenes which contain moieties suitable for bidentate coordination. In the course of our studies,[6] lanthanide-catalyzed 1,3-dipolar cycloaddition of nitrones with alkenes has been reported by Kobayashi[7] and Jørgensen,[8] respectively. It should be noted that these studies treat only the *endo*-selective cycloaddition and, in the case herein, both *endo*- and *exo*-selectivity are freely switchable.



1 (1.2 equiv) **2a** (1 equiv) *endo* -**3a** *exo* -**3a**

The cycloaddition of *C, N*-diphenylnitrone (**1**) with 3-crotonyl-1,3-oxazolidin-2-one (**2a**) using several lanthanide triflates as Lewis acid catalysts and toluene as a solvent to give cycloadducts **3a** was examined. In the

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absence of a catalyst no conversion took place after 20 h at room temperature. Lanthanide alkoxides, Ln(OPr-*i*)$_3$ (Ln: La, Sm and Yb), were not effective for the reaction. Lanthanide triflates, Ln(OTf)$_3$, which may have stronger Lewis acidity compared with Ln(OPr-*i*)$_3$, were found to catalyze the reaction. Among these, Yb(OTf)$_3$ exhibited both notable catalytic ability for the cycloaddition and a high diastereoselectivity (*endo*/*exo* = 95/5). We also checked the effects of solvents on diastereoselectivity. Surprisingly, the reaction in acetonitrile exhibited *exo*-selectivity (*endo*/*exo* = 18/82).

Table 1. Lanthanide Lewis Acid-Catalyzed 1,3-Dipolar Cycloaddition of **1** and **2a**[a)]

entry	Lewis acid	solvent	yield (%)[b)]	*endo* : *exo*
1	La(OTf)$_3$	PhMe	23	53 : 47
2	Sm(OTf)$_3$	PhMe	88	76 : 24
3	Eu(OTf)$_3$	PhMe	78	67 : 33
4	Yb(OTf)$_3$	PhMe	87 [c)]	95 : 5
5	Yb(OTf)$_3$	MeCN	63	18 : 82

a) Conditions: The catalyst Ln(OTf)$_3$ (0.1 mmol) was stirred with alkene **2a** (1 mmol) in a dry solvent for 0.5 h and subsequently nitrone **1** (1.2 mmol) was added. b) NMR yield. c) Isolated yield.

In order to better understand how the structure of auxiliary on the alkenoyl moiety influences the stereochemistry of 1,3-dipolar cycloaddition, alkenes **2b**-**2g** were examined in this Yb(OTf)$_3$-catalyzed reaction (Table 2). When alkene **2b** was reacted with nitrone **1** to investigate whether the auxiliary requires a ring system or not, reactivity and selectivity were quite low (38%, *endo*/*exo* = 54/46). Both alkene **2c**, having a monodentate coordination unit, and alkene **2g**, which contains a sulfur atom in the coordination site, did not react with **1**. When *N*-crotonyl-2-pyrrolidinone (**2d**) was employed in the cycloaddition,[9] the diastereoselectivity in toluene or acetonitrile showed the same tendency as was observed for **2a**. In addition, the introduction of an *N*-methylimidazolidinone or a succinimide unit as an auxiliary on the alkenoyl moiety gave interesting results. While the cycloaddition between **1** and **2e** in toluene proceeded *exo*-selectively,[10] the opposite diastereoselectivity was observed for the reaction of **1** with **2a** or **2e** whose auxiliary is oxazolidinone or 2-pyrrolidinone. The reaction of **1** with **2e** in acetonitrile showed better reactivity and *exo*-selectivity. The cycloaddition of alkene **2f** with **1** has been revealed to proceed with *exo*-selectivity by using TiCl$_2$(*i*-PrO)$_2$ as the catalyst in toluene or dichloromethane.[11] When **2f** was employed in the present reaction, the *exo*-cycloadduct was obtained with a high degree of selectivity in acetonitrile. It was found that the *exo*-selectivity of the reaction of **1** with **2f** decreased with the increase in the bulkiness of the alkyl substituent of nitrile solvents. Since the cycloadducts obtained in this reaction decomposed during their chromatography, they were immediately converted into amide derivatives (Q in cycloadducts **3f** = NH$_2$) by addition of aqueous hydrazine to the crude reaction mixture.[11] No regioisomer was detected in all the cycloadditions of **1** with **2a**,**b**, **d**-**f**. The reason for the change in diastereoselectivity by an appropriate choice of solvents and auxiliaries is not clear at present. However, acetonitrile might coordinate to the complex of a dipolarophile and the ytterbium as additional ligands to change steric circumstances, which causes reversal of diastereoselectivity of the cycloaddition of **1**.

In summary, we demonstrate here that Yb(OTf)$_3$ is an efficient catalyst for the 1,3-dipolar cycloaddition reaction of nitrones with alkenes. Although this is consistent with the results reported by two other groups, the diastereoselectivity was found to be controllable by an appropriate choice of solvents and auxiliaries on the

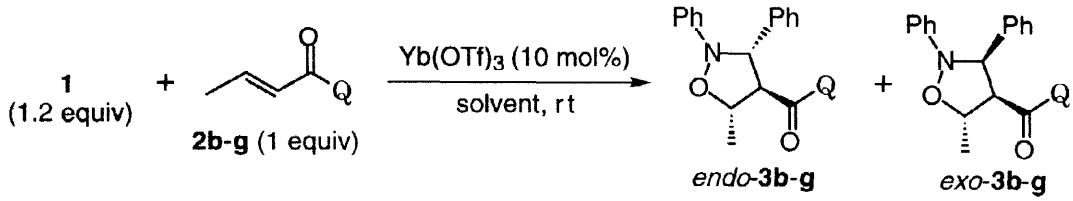
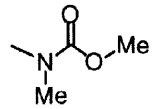
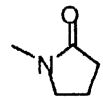
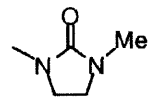
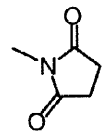
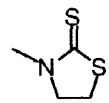


Table 2. $Yb(OTf)_3$-Catalyzed 1,3-Dipolar Cycloaddition of **1** and **2b-f**

	Q	time (h)	solvent	yield (%)	*endo* : *exo*
2b		20	PhMe	38	54 : 46
2c		20	PhMe	0	———
2d		24	PhMe	70	91 : 9
		24	MeCN	65	21 : 79
2e		52	PhMe	27 [a]	17 : 83
		52	MeCN	71	7 : 93
2f		24	PhMe	31	15 : 85
		24	MeCN	46	<5 : >95
		24	EtCN	36 [b]	<5 : >95
		24	*i*-PrCN	54 [b]	11 : 89
		24	*t*-BuCN	22 [b]	32 : 68
2g		24	PhMe	0	———

a) **2e** was recovered in 22%. b) determined by ^{1}H-NMR.

alkenyl moiety of the dipolarophiles. The oxazolidinone or 2-pyrrolidinone auxiliary exhibited *endo*-selectivity with toluene as the solvent and the imidazolidinone or succinimide auxiliary gave rise to *exo*-selectivity with acetonitrile as the solvent. An investigation of enantioselective 1,3-dipolar cycloadditions is now underway.

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9 Selected spectroscopic data for *endo*-**3d**: oil; IR (neat) 1734, 1683 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.3 Hz, 3H), 1.99 (tt, *J* = 7.3, 7.9 Hz, 2H), 2.52 (t, *J* = 7.9 Hz, 2H), 3.80 (t, *J* = 7.3 Hz, 2H), 4.45 (dq, *J* = 6.3, 7.6 Hz, 1H), 4.84 (dd, *J* = 6.9, 7.6 Hz, 1H), 5.17 (d, *J* = 6.9 Hz, 1H), 6.89-7.48 (m, 10H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 16.9, 17.7, 33.6, 46.1, 63.7, 74.4, 79.5, 114.5, 121.5, 126.6, 127.7, 128.7, 128.8, 141.2, 151.7, 171.4, 174.9; EI-MS *m/z* 350 (M^+, 8). *exo*-**3d**: oil; IR (neat) 1728, 1683 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.44 (d, *J* = 6.0 Hz, 3H), 1.49-1.57 (m, 1H), 1.72-1.87 (m, 1H), 2.22-2.51 (m, 2H), 2.28-2.91 (m, 1H), 3.47-3.57 (m, 1H), 4.40 (dd, *J* = 9.5, 10.6 Hz, 1H), 4.91 (d, *J* = 10.6 Hz, 1H), 5.09 (dq, *J* = 6.0, 9.5 Hz, 1H), 6.89-7.43 (m, 10H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 16.9, 17.2, 33.6, 45.2, 61.3, 71.7, 74.5, 116.1, 122.2, 128.2, 128.27, 128.34, 128.5, 138.7, 149.9, 169.7, 175.0; EI-MS *m/z* 350 (M^+, 12).

10 Spectroscopic data for *endo*-**3e**: oil; IR (neat) 1725, 1665 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.3 Hz, 3H), 2.82 (s, 3H), 3.35-3.45 (m, 2H), 3.76-3.91 (m, 2H), 4.41 (dq, *J* = 6.3, 7.9 Hz, 1H), 5.02 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.23 (d, *J* = 7.9 Hz, 1H), 6.88-7.42 (m, 10H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 17.4, 30.7, 39.9, 42.7, 62.4, 74.6, 77.2, 79.9, 114.4, 121.4, 126.6, 127.5, 128.8, 141.5, 151.9, 153.7, 170.6; EI-MS *m/z* 365 (M^+, 5). *exo*-**3e**: Mp. 140-141 °C; IR (neat) 1722, 1672 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.44 (d, *J* = 5.9 Hz, 3H), 2.82 (s, 3H), 2.84-2.95 (m, 2H), 3.08-3.22 (m, 1H), 2.43-3.57 (m, 1H), 4.52 (dd, *J* = 10.8, 8.9 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 5.09 (dq, *J* = 8.9, 5.9 Hz, 1H), 6.87-7.46 (m, 10H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 17.3, 30.6, 39.1, 43.0, 59.9, 72.0, 74.5, 116.0, 122.0, 127.9, 128.0, 128.3, 128.4, 139.0, 150.0, 154.3, 168.9; EI-MS *m/z* 365 (M^+, 100).

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