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Lanthanide-Catalyzed *Endo*- and Enantioselective 1,3-Dipolar Cycloaddition Reactions of Nitrones with Alkenes

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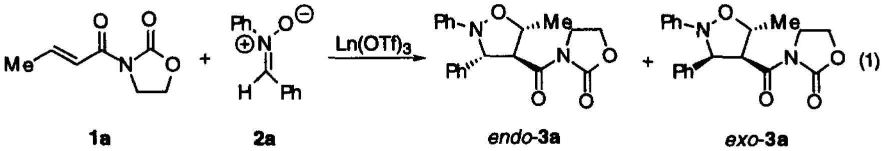
Abstract: The 1,3-dipolar cycloaddition reaction of alkenes with nitrones was catalyzed by $Yb(OTf)_3$ or $Sc(OTf)_3$ giving isoxazolidines in high yields and selectivities. The catalyst $Yb(OTf)_3$ induce a high *endo*-selectivity in the reaction of up to 94% de, whereas $Sc(OTf)_3$ show the highest rate accelerations. Both the conversion and *endo*-selectivity of the $Yb(OTf)_3$ and $Sc(OTf)_3$ catalyzed reactions proved to be dependent on the amount and type of molecular sieves added. The application of different chiral ligands in 1,3-dipolar cycloaddition reactions of a series of alkenes with nitrones catalyzed by $Yb(OTf)_3$ or $Sc(OTf)_3$ has been studied and it was found that high *endo*-selectivities and an ee's of up to 73% could be obtained by the use of $Yb(OTf)_3$ and 2,6-bis[4(S)-isopropyl-2-oxazolidin-2-yl]pyridine (PyBOX) as the chiral ligand. © 1997 Elsevier Science Ltd.

Asymmetric 1,3-dipolar cycloadditions between alkenes and nitrones leading to optically active isoxazolidines is an important reaction in organic chemistry and during the two last decades numerous enantioselective total syntheses using these isoxazolidines as key intermediates have been described.[1] In 1994 the first attempts to apply asymmetric catalysis for the 1,3-dipolar cycloaddition were published by Seerden *et al.*,[2] our laboratories,[3] and more recently also from others.[4] Compared to the asymmetric metal-catalyzed carbo- and hetero-Diels-Alder reaction, the development of the analogous 1,3-dipolar cycloaddition reaction, is several years behind.[5] One of the recent developments in asymmetric metal-catalyzed Diels-Alder reactions was published by Kobayashi *et al.*[6] They found that complexes between lanthanide triflates, (+)-binaphthol and a tertiary amine, induces enantioselectivity in the Diels-Alder reaction.[6]

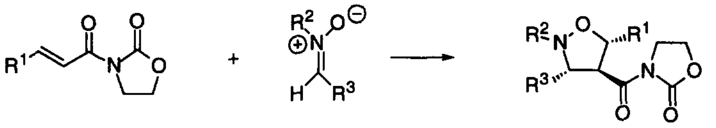
As a part of our development of new metal-catalyzed asymmetric 1,3-dipolar cycloadditions of nitrones with alkenes,[3] we have found that $Yb(OTf)_3$ and $Sc(OTf)_3$ are effective and selective catalysts for this reaction. The advantages with these new catalytic systems are that they are much easier to handle and much less sensitive to moist air. The reaction between alkene **1a** and nitrone **2a** was performed on a 0.1 mmolar scale in the presence of 10 mol% of the catalyst and 50 mg molecular sieves (MS) 4Å (eq 1). In the absence of a catalyst no conversion is observed. However, in the presence of 10 mol% of $Yb(OTf)_3{\cdot}(H_2O)$ a conversion of 77% was observed after 24 h and the isoxazolidines *endo*-**3a** and *exo*-**3a** were obtained in a ratio of 13:1.



The scandium catalyst proved to induce even higher reaction rates; by the application of 2 mol% of $Sc(OTf)_3$ as the catalyst a conversion of 71% was observed after 24 h, but the *endo:exo* ratio of 4:1 was lower compared to the $Yb(OTf)_3{\cdot}(H_2O)$-catalyzed reaction. Both for the racemic and enantioselective 1,3-dipolar cycloadditions the hydrate $Yb(OTf)_3{\cdot}(H_2O)$ gave better conversions than $Yb(OTf)_3$.[6d]

Both the conversion and the *endo/exo*-selectivity proved to be dependent on the amount of MS added. For the reactions of **1a** with **2a** on a 0.1 mmolar scale in 2 mL CH_2Cl_2 in the presence of 10 mol% $Yb(OTf)_3{\cdot}(H_2O)$ the highest *endo*-selectivities were observed in the presence of 40-100 mg activated powdered MS 4Å. In the absence of MS an *endo:exo* ratio of 1:1 was obtained. The highest reaction rates were observed in the presence of 0-50 mg powdered MS 4Å. Similar trends were also observed for the $Sc(OTf)_3$ catalyzed reactions. Other types of activated MS, such as powdered MS 3Å, MS 5Å and MS 10Å were tested, but, both the reaction rates, and *endo*-selectivities decreased compared to the use of powdered MS 4Å.

This easy approach to *endo*-isoxazolidines by the use of $Yb(OTf)_3{\cdot}(H_2O)$ or $Sc(OTf)_3$ as catalysts for the 1,3-dipolar cycloaddition has been extended to reactions of the alkenes **1a,b** with the nitrones **2a-c** (eq 2). The reactions catalyzed by $Yb(OTf)_3{\cdot}(H_2O)$ generally proceeded to give the respective isoxazolidines in high yields and *endo*-selectivities (Table 1, entries 1-5), with the exception of the reaction of **1b** with **2c** where no conversion was observed. The catalyst $Sc(OTf)_3$ is also effective in the reactions of alkenes **1a,b** with nitrone **2a** (entries 6,7).



(2)

endo-**3**

1a: R^1 = Me
1b: R^1 = Pr

2a: R^2 = R^3 = Ph
2b: R^2 = Pr, R^3 = Ph
2c: R^2 = Bn, R^3 = Ph
2d: R^2 = Ph, R^3 = *p*-MePh

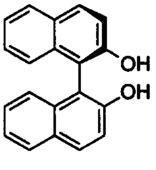
3a: R^1 = Me, R^2 = R^3 = Ph
3b: R^1 = Me, R^2 = Pr, R^3 = Ph
3c: R^1 = Me, R^2 = Bn, R^3 = Ph
3d: R^1 = Me, R^2 = Ph, R^3 = *p*-MePh
3e: R^1 = Pr, R^2 = R^3 = Ph
3f: R^1 = Pr, R^2 = Pr, R^3 = Ph
3g: R^1 = Pr, R^2 = Bn, R^3 = Ph
3h: R^1 = Pr, R^2 = Ph, R^3 = *p*-MePh

Table 1 *Endo*-selective 1,3-dipolar cycloadditions of **1a,b** with **2a-c** catalyzed by $Yb(OTf)_3$ (10 mol%) or $Sc(OTf)_3$ (5 mol%).

Entry[a]	Alkene	Nitrone	Catalyst	Reaction time	Product	Yield[b] (%)	*endo/exo*[c] (%)
1	**1a**	**2a**	$Yb(OTf)_3$	48 h	**3a**	95	97:3
2	**1a**	**2b**	$Yb(OTf)_3$	48 h	**3b**	78	94:6
3	**1a**	**2c**	$Yb(OTf)_3$	48 h	**3c**	74	97:3
4	**1b**	**2a**	$Yb(OTf)_3$	4 days	**3e**	94	92:8
5	**1b**	**2b**	$Yb(OTf)_3$	4 days	**3f**	94	96:4
6	**1a**	**2a**	$Sc(OTf)_3$	5 h	**3a**	88	93:7
7	**1b**	**2a**	$Sc(OTf)_3$	24 h	**3e**	73	82:18

a) Reaction conditions: The catalyst $Yb(OTf)_3{\cdot}H_2O$ (0.1 mmol) or $Sc(OTf)_3$ (0.05 mmol) was stirred with powdered MS 4Å (500 mg) in dry CH_2Cl_2 (10 ml) for 0.5h and subsequently the alkene **1a,b** (1.0 mmol) and the nitrone **2a-c** (1.25 mmol) were added. b) Isolated products obtained by filtration and PTLC (1.5% MeOH in CH_2Cl_2).
c) Determined by ^1H NMR spectrocopy.

By the application of (+)-binaphthol **4** and Yb(OTf)$_3$·(H$_2$O) as the chiral catalyst, the 1,3-dipolar cycloaddition between **1a** and **2a** proceeds with *endo*-selectivity, but unfortunately, the resulting isoxazolidine *endo*-**3a** was racemic. Kobayashi *et al.* reported that by the concomitant addition of a sterically crowded tertiary amine the enantioselectivity of the Yb(OTf)$_3$-**4** catalyzed Diels-Alder reaction was significantly improved.[6d] In the 1,3-dipolar cycloaddition of **1a** with **2a** the catalyst consisting of ethyldiisopropylamine (20 mol%) Yb(OTf)$_3$·(H$_2$O) (10 mol%) and **4** (12 mol%) led to a very slow reaction in which a mixture of racemic *endo*-**3a** and *exo*-**3a** was formed in an 1:1 ratio.



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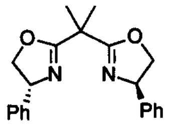

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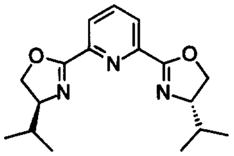

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Application of the chiral bisoxazoline **5**,[7] as the ligand for Yb(OTf)$_3$- and Sc(OTf)$_3$-catalyzed 1,3-dipolar cycloadditions of **1a** with **2a** also led to a racemic product. Better results were obtained using 2,6-bis[4-(*S*)-isopropyl-2-oxazolidin-2-yl]pyridine (PyBOX) **6**[8] as the chiral ligand.[8] The reaction between **1a** and **2a** catalyzed by Yb(OTf)$_3$·(H$_2$O)-**6** and 50 mg MS 4Å in CH$_2$Cl$_2$ takes place with high *endo*-selectivity to give *endo*-**3a** with 67% ee (Table 2, entry 1).

Table 2. Asymmetric 1,3-dipolar cycloadditions of alkenes **1a,b** with nitrones **1a-d** catalyzed by Yb(OTf)$_3$.(H$_2$O)-**6** (20 mol%).

Entry[a]	Alkene	Nitrone	Solvent	Reaction time	Product	Yield[b] (%)	*endo/exo*[c] (%)	ee(*endo*) (%)
1	**1a**	**2a**	CH$_2$Cl$_2$	20 h	**3a**	(37)	93:7	67
2	**1a**	**2a**	Et$_2$O	20 h	**3a**	(77)	94:6	61
3	**1a**	**2a**	THF	20 h	**3a**	(48)	67:33	55
4	**1a**	**2a**	dioxane	20 h	**3a**	(38)	95:5	67
5	**1a**	**2a**	MeNO$_2$	20 h	**3a**	(6)	63:7	-
6	**1a**	**2a**	toluene	20 h	**3a**	53 (82)	94:6	67
7	**1a**	**2c**	toluene	4 d	**3c**	52	97:3	8
8	**1a**	**2d**	toluene	5 d	**3d**	54	96:4	73
9	**1b**	**2a**	toluene	2 d	**3e**	69	92:8	69
10	**1b**	**2c**	toluene	7 d	**3g**	52	96:4	28
11	**1b**	**2d**	toluene	3 d	**3h**	58	97:3	67

a) Reaction conditions: The catalyst Yb(OTf)$_3$·H$_2$O (0.01 mmol) and **6** was stirred with powdered MS 4Å (50 mg) in dry CH$_2$Cl$_2$ (2 ml) for 0.5h and subsequently the alkene **1a,b** (0.1 mmol) and the nitrone **2a-d** (0.125 mmol) were added. b) Isolated products obtaned by filtration and PTLC (1.5% MeOH in CH$_2$Cl$_2$); conversions are given in parantheses. c) The *endo/exo* ratio was determined by ^{1}H NMR spectroscopy. d) The ee´s were determined by HPLC using a Daicel Chiralcel OD column (*i*-PrOH:Hexane)

Surprisingly, the analogous reaction of Sc(OTf)$_3$ instead of Yb(OTf)$_3$·(H$_2$O) was racemic. The reaction was, however, very slow and it was necessary to use 20 mol% of the catalyst to obtain a conversion 37% after 20 h at rt. The reaction proceeds faster in Et_2O or THF as the solvent, but the selectivities were lower, while in dioxane a result similar to that obtained in CH_2Cl_2 was found (entries 1-4). $MeNO_2$ turned out to be a poor solvent for the 1,3-dipolar cycloaddition (entry 5). The best result for the 1,3-dipolar cycloaddition of **1a** with **2a** was obtained using toluene as the solvent (entry 6). In this reaction both the conversion, *endo*-selectivity and the ee of 67% were satisfying. The catalyst $Yb(OTf)_3{\cdot}(H_2O)$-**6** was then applied in a series of reactions between alkenes **1a,b** and nitrones **2a,c,d** (entries 6-11). The nitrone **2b** gave low conversions and the results are not presented here. For the reactions given in entries 6-11, high *endo:exo* ratios of 92:8 to 97:3 were obtained and more remarkably enantioselectivities between 67-73% ee were observed, except for nitrone **2c**.

As a conclusive remark the application of $Yb(OTf)_3{\cdot}(H_2O)$ in combination with MS 4Å provides a simple and effective catalyst for *endo*-selective 1,3-dipolar cycloaddition reactions. Compared to the previously reported asymmetric metal-catalyzed 1,3-dipolar cycloadditions of alkenes with nitrones, involving Ti-TADDOLate,[3a,c-f,4a] Mg-bisoxazoline[3b] and Pd-BINAP[4b] catalysts, the approach described in this communication offers some advantages. The catalyst is readily prepared from stable compounds and the exclusion of air in not required. The lanthanide triflate-PyBOX catalyst has been applied in one previous report dealing with diastereoselective reactions[9] and only very few examples of the application of chiral nitrogen compounds as ligands for lanthanide catalysts are known.[8,9]

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