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Iron and Ruthenium Lewis Acid Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions between Nitrones and Enals

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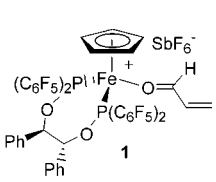
Enantiomerically pure isoxazolidines are direct precursors of chiral 1,3-amino alcohols which are effective synthons for the assembly of biologically active compounds such as β-lactams, β-amino acids, and alkaloids.[1] With its potential for the control of up to three contiguous stereogenic centers, the chiral Lewis acid catalyzed 1,3-dipolar cycloaddition reaction between nitrones and alkenes is a direct and versatile route to these compounds. Both nitrone activation and the activation of α,β-unsaturated carbonyl compounds have been developed successfully.[2] The former is essential in inverse electron-demand reactions while the latter is required for normal electron-demand cycloadditions with two-point binding substrates.[3] The simpler α,β-unsaturated aldehydes would be very attractive substrates but they have been shown to be poor performers. With a one-point binding Lewis acid, coordination of the nitrone is favored over coordination of the aldehyde and this results in an effective blocking of the catalyzed reaction pathway.[4] We wish to report here that this problem can be solved via the judicious choice of the chiral Lewis acid and we here present the first asymmetric Lewis acid catalyzed 1,3-dipolar cycloaddition reactions between nitrones and α,β-unsaturated aldehydes.[5] We note that this transformation has recently been achieved via an elegant, efficient, and highly enantioselective organocatalyzed route.[6]

The readily prepared, mild Fe and Ru Lewis acids **1**−**3** effectively catalyze the asymmetric Diels−Alder reaction of dienes with enals.[7] Structural and mechanistic studies have provided a detailed picture of enal coordination and chiral environment in these reactions. We reasoned that the highly tuned aldehyde-selective chiral Lewis acid site might be able to discriminate between enals and nitrones and either favor coordination of the first or bind nitrones in a readily reversible manner.



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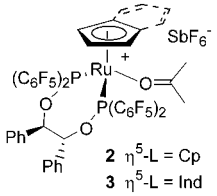
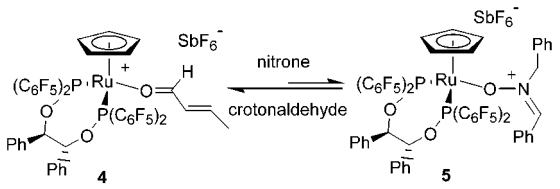


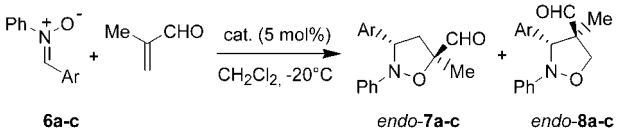
2 η^5-L = Cp
3 η^5-L = Ind

To test this hypothesis we first carried out qualitative ^{31}P NMR experiments of competitive nitrone−aldehyde Lewis acid coordination. The ^{31}P NMR spectrum of the crotonaldehyde complex **4**, formed upon addition of 2 equiv of the aldehyde to complex **2** (1 equiv) in CD_2Cl_2 consisted of an AB quartet at 126.3 ppm ($\Delta\nu_{AB}$ = 707 Hz, J_{AB} = 70 Hz). Upon addition of 10 equiv of *N*-benzylidenebenzylamine *N*-oxide a new AB quartet grew in (125.9 ppm, $\Delta\nu_{AB}$ = 332 Hz, J_{AB} = 69 Hz) and was tentatively assigned to the nitrone complex **5**. Signal integration indicated a ratio of crotonaldehyde complex **4** to nitrone complex **5** of 7:3. This ratio could be shifted further in favor of complex **4** by adding more crotonaldehyde. The above observations attest to the preference of aldehyde over nitrone coordination by the Ru complex and to the reversibility of coordination of both substrates. They were rendered possible because of the low reactivity of this nitrone toward the Lewis acid coordinated crotonaldehyde. As only traces of cycloaddition products were observed with these reaction partners, we turned our attention toward more reactive nitrones.



4 **5**

Confirming our starting hypothesis, the reaction of methacrolein with *C*,*N*-diaryl nitrones **6a**−**c** in the presence of catalysts **1**−**2** yielded the isoxazolidines *endo*-**7a**−**c** and *endo*-**8a**−**c** in moderate to high enantio- and regioselectivities and complete *endo*/*exo* selectivity. The pronounced *endo* preference of the reaction made the highly *exo*-selective indenyl catalyst **3** unsuitable for this reaction,[7a] giving only poor yields of mixtures of *endo*/*exo* **7**/**8** adducts.[8] The low solubility of nitrones **6b**−**c** resulted in much longer reaction times. This turned out to be problematic with the less stable Fe catalyst **1** and led us to explore a different set of nitrones.



6a-c *endo*-**7a-c** *endo*-**8a-c**

a : Ar = Ph
b : Ar = *p*-NO_2-Ph
c : Ar = *p*-CF_3-Ph

Absolute configuration not assigned

Table 1. Asymmetric 1,3-Dipolar Cycloadditions between Methacrolein and Nitrones **6a**−**c**

entry	catalyst	nitrone	yield (%)	*endo*-**7**/*endo*-**8**	ee **7**/**8** (%)
1[a]	(*R*,*R*)-**1**	**6a**	85	80/20	87/91
2	(*R*,*R*)-**2**	**6a**	92	60/40	76/94
3[b]	(*R*,*R*)-**2**	**6b**	80	100/0	66/−
4	(*R*,*R*)-**2**	**6c**	79	90/10	74/−

[a] Reaction performed in the presence of 2,6-lutidine (5 mol %, scavenger of acid impurities). [b] Reaction performed at 0 °C.

First experiments with pyrrolidine *N*-oxide **9** and methacrolein confirmed the high reactivity of this nitrone (Table 2, entry 1).[9]

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Presumably because of the background reaction the ee of the reaction with an equimolar mixture of methacrolein and nitrone **9** in the presence of (*R*,*R*)-**1** was a low 26% (entry 2). The improved yield and the fact that **10** was formed as a nonracemic mixture indicated, however, that the nitrone **9** was not blocking the Lewis acid catalyst site. Varying the nitrone:methacrolein ratio showed the expected variation in product enantioselectivity (entries 3−4). In all reactions, isoxazolidine **10** was formed as a single regio- and diastereoisomer. Recognizing the need to keep the nitrone concentration low in order to suppress the background reaction, a 0.8 M solution of **9** in CH_2Cl_2 was added slowly to the catalyst/enal reaction mixture. This afforded product **10** in excellent yield and high enantiomeric purity when the Fe catalyst (*R*,*R*)-**1** was used (entry 5). It also allowed a reduction of the catalyst loading. The Ru catalyst (*R*,*R*)-**2** is a slightly weaker Lewis acid than **1**.[7b] It also has a larger catalyst site and the two factors account for the inferior performance of **2** compared to **1** in this reaction (entries 6−7).

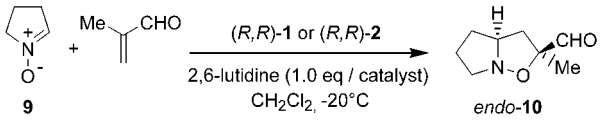


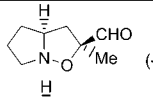
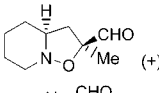
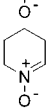
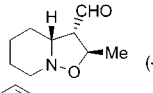
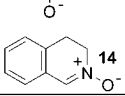
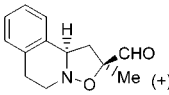
Table 2. Fe- and Ru-Lewis Acid Catalyzed 1,3-Dipolar Cycloadditions between Methacrolein and Nitrone **9**

entry	catalyst (mol %)	*n*[a]	yield (%)	ee (%)
1		1.2	45[b]	
2	(*R*,*R*)-**1** (10)	1.2	84	26
3	(*R*,*R*)-**1** (10)	0.2	87	12
4	(*R*,*R*)-**1** (10)	5.0	85	54
5[c]	(*R*,*R*)-**1** (5)	1.2	92	96
6[c]	(*R*,*R*)-**2** (5)	1.2	61	44
7[d]	(*R*,*R*)-**2** (5)	1.2	88	67

[a] Enal/nitrone ratio. [b] Isolated yield after 20 h. [c] Dropwise addition of **9** over 18 h. [d] Dropwise addition of **9** over 36 h.

The superior level of asymmetric induction and the higher activity of the Fe catalyst prompted us to select this catalyst for the additional examples detailed in Table 3. The (*R*,*R*)-catalysts afforded products (−)-*endo*-(3*S*,5*S*)-**10** and (−)-*endo*-(3*R*,4*S*,5*R*)-**13** (see Supporting Information). The X-ray structure of the catalyst **2**−methacrolein complex shows the enal to adopt an *s-trans* conformation.[7c] Absolute stereochemistry of the isoxazolidines **10** and **13** is consistent with an *endo* approach of the nitrone to the C_α-*Si*-face of the coordinated enal in the (*R*,*R*)-catalyst site (Figure 1). The minor enantiomer arises from cycloaddition to the C_α-*Re*-face of the enal either from the same side as above with the enal in the *s-cis* conformation or from the opposite side with the enal in the *s-trans* conformation. Furthermore, models show that cycloaddition through an *endo* approach of the nitrone minimizes steric interactions between the nitrone ring, the enal methyl group, and a C_6F_5 ring of the catalyst. Product **13** is formed in lower enantiomeric purity. It can be argued that addition to the *s-cis* enal C_α-*Re*-face becomes more important here because the reversed regiochemistry of the reaction results in a more hindered *endo* approach of the nitrone to the C_α-*Si*-face in the enal *s-trans* conformation.

Table 3. (*R*,*R*)-Fe-Lewis Acid Catalyzed Enantioselective 1,3-Dipolar Cycloadditions (5 mol %)

entry	nitrone	enal	yield (%)	product	ee (%)
1	 **9**		92	 (-)-**10**	96
2	 **11**		71	 (+)-**12**	>96
3	 **11**		75	 (-)-**13**	75
4	 **14**		71	 (+)-**15**	94

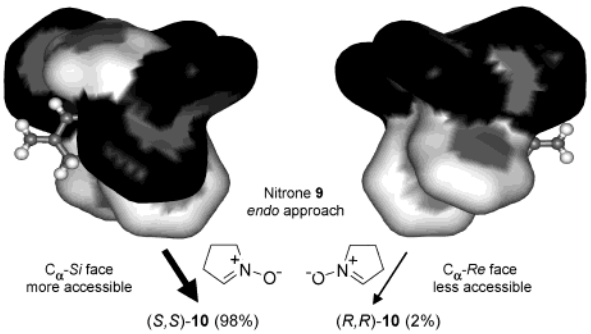


Figure 1. Endo addition of **9** to the alkene C_α-*Si*-face or C_α-*Re*-face in $[CpFe((R,R)\text{-BIPHOP-F})(\text{methacrolein})]^+$ (enal in *s-trans* conformation).

In conclusion, we have shown that single coordination site transition metal Lewis acids can efficiently promote enantioselective 1,3-dipolar cycloadditions of nitrones with α,β-unsaturated enals and represent a rapid access to substrates of high synthetic potential.

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Supporting Information Available: Experimental procedures and physical data of products **7**, **8**, **10**, **12**, **13**, **15**, and **16** (product of reductive amination of (−)-(3*S*,5*S*)-**10** with (1*R*,2*S*)-norephedrine) and crystallographic data, bond lengths, bond angles, dihedral angles, and hydrogen bonds (PDF); X-ray crystallographic file (CIF) for (−)-**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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