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Asymmetric Lewis acid-catalyzed 1,3-dipolar cycloadditions*

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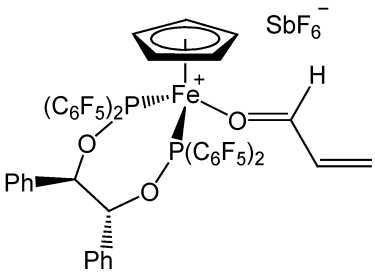
Abstract: Highly tuned, one-point binding chiral iron and ruthenium complexes selectively coordinate and activate α,β-unsaturated aldehydes and ketones toward asymmetric catalytic Diels–Alder cycloaddition reactions. Here we focus on the application of these transition-metal Lewis acids to asymmetric catalytic 1,3-dipolar cycloaddition reaction between enals and cyclic and acyclic nitrones as well as aryl nitrile oxides to give isoxazolidines and isoxazolines, respectively.

Keywords: Lewis acids; asymmetric reactions; 1,3-dipolar cycloadditions; nitrones; nitrile oxides.

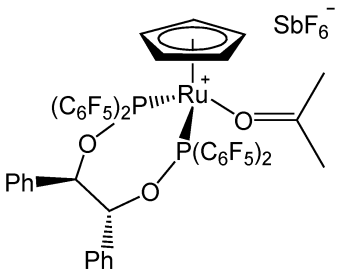
INTRODUCTION

Transition-metal-mediated and -catalyzed reactions continue to have a high impact on the venerable field of heterocyclic chemistry. Functionalized chiral *N*,*O*-heterocyclic compounds figure prominently due to the high versatility of these compounds either on their own or, after the reductive cleavage of the N–O bond, as acyclic chiral amino alcohol building blocks. Asymmetric catalytic cycloaddition reactions can afford an efficient access to highly enantiomerically enriched *N*,*O*-heterocycles [1].

We have developed structurally well-defined, single-point binding chiral transition-metal Lewis acid complexes of Fe(II) (**1**) and Ru(II) (**2**) that selectively bind and activate α,β-unsaturated aldehydes and ketones for asymmetric Diels–Alder reactions [2]. Structural and mechanistic studies provided insight into the mode of activation, the geometry of the coordinated and activated dienophile, the role of the counterion, and the factors governing *endo*/*exo*-selectivity of the cycloadditions.



(*R*,*R*)-**1**



(*R*,*R*)-**2**

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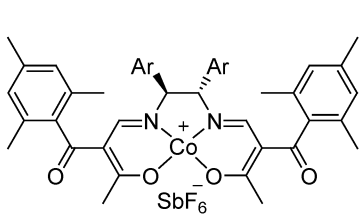
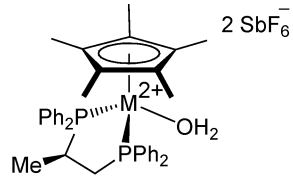
With its potential for the control of up to three contiguous stereogenic centers, the chiral Lewis acid-catalyzed 1,3-dipolar cycloaddition reaction between nitrones and alkenes is a direct and versatile route to these compounds. Catalytic asymmetric reactions between nitrones and α,β-unsaturated dicarbonyl compounds have been shown to be successfully catalyzed by two-point binding chiral Lewis acids [3]. For normal electron-demand cycloadditions, two-point binding of the dipolarophile appeared a necessity because one-point binding Lewis acids were shown to coordinate nitrones preferentially over simple α,β-unsaturated aldehydes. Thus, addition of a nitrose to a Lewis acid gives a 1:1 complex and this coordination is often irreversible. Any nitrone/enal cycloaddition would then be due to the non-catalyzed background reaction. This changed in 2002 when Kanemasa et al. showed that a sterically hindered Lewis acid prevents the bulky nitrone from coordinating at the metal and that α,β-unsaturated aldehydes can thus be activated and used in the 1,3-dipolar cycloaddition [4]. In the same year, we provided the first examples of one-point binding asymmetric catalytic 1,3-dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes [5], and Yamada et al., using β-ketoiminato Co(II) complexes, also published their first results shortly thereafter [6]. A subsequent full study showed the efficiency and versatility of these complexes as catalysts for the reaction of diarylnitrones and α,β-unsaturated aldehydes [7,8]. Carmona's dicationic, half-sandwich, Rh and Ir aqua complexes containing diphosphine or PN ligands also proved good catalysts for this transformation [9–12]. The same group recently provided the first examples of asymmetric catalytic cycloaddition reactions of nitrones with methacrylonitrile [13]. In situ prepared complexes of Ni, Zn, and Mg with DBFOX ligands also were found to be highly efficient and selective catalysts [14,15]. In elegant work, Maruoka et al. recently reported BINOL Ti-complexes to catalyze very efficiently the reaction of the less reactive *N*-benzyl and *N*-diphenylmethyl, aryl nitrones providing an access to isoxazoldines bearing readily cleavable groups at the nitrogen atom [16,17].

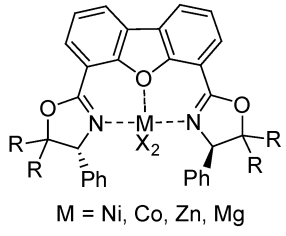


Yamada *et al.*



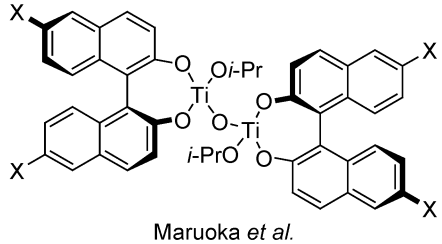
M = Rh, Ir

Carmona *et al.*



M = Ni, Co, Zn, Mg

Kanemasa *et al.*



Maruoka *et al.*

Preceding the asymmetric transition-metal-catalyzed dipolar nitrone cycloadditions, and stimulating this research in the first place, are the organocatalyzed reactions reported by McMillan et al. in 2000 [18]. This field also has seen much recent progress [19–23].

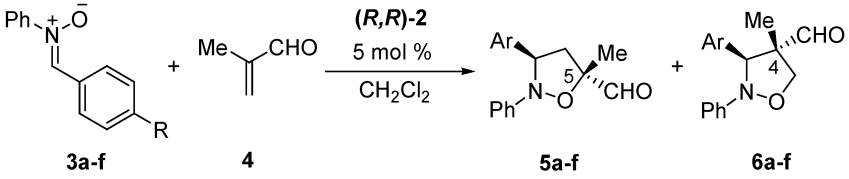
In this short article, we review our recent results in asymmetric Lewis acid-catalyzed 1,3-dipolar cycloaddition reactions of enals with acyclic nitrones [24] and the extension of these reactions to nitrile oxides [25].

DIARYL NITRONES

As mentioned above, the Lewis acid-catalyzed cycloaddition reaction between enals and nitrones was long thought impossible to realize since nitrones are better ligands than aldehydes and they therefore prevent enal activation by Lewis acids and poison the catalyst. We found that judicious choice of metal ligand environment and Lewis acidity can overcome this preference. Both (*R*,*R*)-**1** and (*R*,*R*)-**2** are efficient catalysts for the asymmetric cycloaddition reaction of enals with a variety of cyclic nitrones. The cycloadducts were obtained in excellent yields and high enantiomeric purity when the reaction was performed in the presence of 5 mol % of (*R*,*R*)-**1** [5].

Acyclic nitrones are generally more difficult substrates due to the possibility of forming two regioisomeric products. Initial results with diphenylnitrone confirmed the ability of (*R*,*R*)-**1** and (*R*,*R*)-**2** to efficiently catalyze the reaction with methacrolein [5]. Only the *endo*-products were obtained, but regioselectivity was poor (3:2 mixture). While the catalyst of choice for the cyclic nitrones was the Fe complex (*R*,*R*)-**1**, the Ru analog (*R*,*R*)-**2** proved better in the case of the diaryl nitrones.

Despite giving good results in terms of selectivities, at –20 °C the cycloaddition was slow and suffered further due to the low solubility of the diphenylnitrone at this temperature (Table 1, entry 1). Raising the temperature to –10 °C and concentrating the reaction mixture led to nearly quantitative yields and a shortening of the reaction time (entry 2). Moreover, selectivities were perfectly preserved, showing thus that the background reaction, even though present at –10 °C, can be completely suppressed by the very active Ru catalyst (*R*,*R*)-**2**. The complex can be efficiently recovered and reused after the reaction [24].



3a-f **4** **5a-f** **6a-f**

Table 1 Ru-Lewis acid-catalyzed asymmetric 1,3-dipolar cycloadditions of methacrolein with diaryl nitrones.

Entry	Nitrone	*T* (°C)	Time (h)	Isolated yield (%)	**5a/6a**[a]	ee (%) **5a/6a**[b]
1	**3a**, R = H	–20	32	84	60/40	75/94
2	**3a**, R = H	–10	14	>98	67/33	75/94
3	**3b**, R = NO_2	–10	74	16	95/5	71/–
4	**3c**, R = CF_3	–10	64	>98	91/9	74/88
5	**3d**, R = Cl	–10	64	89	73/27	77/89
6	**3e**, R = Me	–10	22	>98	41/59	74/95
7	**3f**, R = OMe	–10	22	>98	21/79	75/92

[a]Determined by NMR analysis.
[b]Determined by chiral HPLC analysis of the cycloadduct after reduction to the primary alcohol.

For the 1,3-dipolar cycloaddition reaction, both steric and electronic properties are known to influence regioselectivity. In order to assess the latter, a series of diarylnitrones substituted in the *para*-position of the C-aryl moiety were probed as substrates in the reaction with methacrolein (entries 3–7). 5 mol % of the Ru catalyst (*R*,*R*)-**2** and the optimized conditions at –10 °C were sufficient to give the desired cycloadducts in almost quantitative yield, complete *endo*-selectivity, and high enantiomeric purity. The ee, determined by HPLC analysis after conversion to the primary alcohols, was consistently

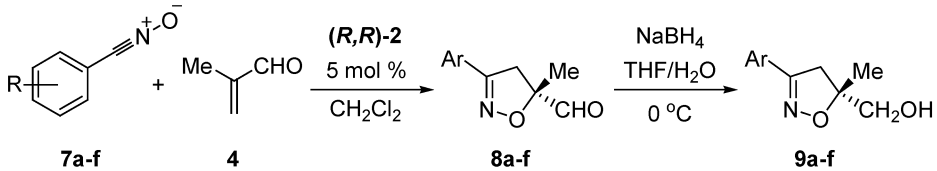
higher for the 4-substituted isoxazolidines than for the 5-substituted isomers. The low yield obtained with the *p*-NO_2-substituted nitrone is interpreted as resulting from competitive coordination of the nitro group at the Ru center, thus interfering with the catalytic cycle (entry 3).

The variation of the regioisomeric ratio with the electronic character of the aryl substituent R is a particularly notable feature in this series. Thus, in the case of electron-withdrawing substituents the 5-substituted isoxazolidine are the predominant products. On the other hand, electron-donating substituents on the nitrone lead to the formation of the 4-substituted isoxazolidines as the major product [26].

ARYL NITRILE OXIDES

While nitrones have been widely used in catalytic asymmetric 1,3-dipolar cycloaddition reactions [1], this is not the case for nitrile oxides. Synthetically, the 2-isoxazolines are very attractive products, but development of the use of nitrile oxides in these reactions is hampered by their tendency to dimerize. Not surprisingly, literature reports on efficient catalytic, enantioselective 1,3-dipolar cycloaddition reactions of nitrile oxides with alkenes are scarce [27–30].

Our initial reactions were carried out using the relatively stable mesityl nitrile oxide. Slow addition of the nitrile oxide by means of a syringe pump to a stirred mixture of methacrolein and 5 mol % of *(R,R)*-**2** in CH_2Cl_2, at –15 °C, followed by reduction, led to the exclusive formation of 2-isoxazoline **9a** in 71 % yield and 62 % ee (Table 2, entry 1). In the following, the study was extended to other aryl nitrile as shown below [25]. In all cases, reactions afforded the 3,5-substituted isoxazolines as single regioisomers.



7a-f **4** **8a-f** **9a-f**

Table 2 Asymmetric catalyzed 1,3-dipolar cycloadditions between methacrolein and aryl nitrile oxides.

Entry	Nitrile oxide	*T* (°C)	Time (h)	Isolated yield (%)	ee (%)[a]
1	**7a**, 2,4,6-Me	–15	72	75	60
2	**7b**, 4-CF_3	–20	16	60	93
3	**7c**, 4-F	–20	24	38	77
4	**7d**, 3,5-CF_3	–20	16	40	82
5	**7e**, 4-OMe	–5	39	57	65
6	**7f**, 4-*i*Pr	–5	38	65	63

[a]Determined by chiral HPLC analysis.

Two main trends arise from the results shown above. For the aromatic nitrile oxides bearing electron-poor substituents, the best results were obtained at –20 °C (entries 2–4), while in the case of electron-rich substitution, results of reactions carried out at –5 °C were better (entries 5, 6). Electron-withdrawing aryl groups at the nitrile oxide gave products with higher ee (up to 93 %) than those with electron-releasing groups. As in the case of nitrones, the absolute configuration is in perfect agreement with an approach of the nitrile oxide on the accessible C_α-Si face of the methacrolein bound at the Ru in an *anti s-trans* conformation [5,24,25].

In summary, using 5 mol % of the [Ru(acetone)(*R*,*R*-BIPHOP-F)Cp][SbF_6] complex **2** and carefully optimized reaction conditions, the asymmetric 1,3-dipolar cycloaddition reaction between diaryl nitrones and methacrolein can be efficiently catalyzed. Moreover, the mild Lewis acid character of this Ru complex allows for a unique reversal of the regioisomeric ratio as a function of the electronic nature of the dipole. The same catalyst has been successfully used in the first asymmetric, single-point binding, catalytic 1,3-dipolar cycloaddition between aryl nitrile oxides and methacrolein. High asymmetric inductions can be achieved, although yields leave room for improvement.

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