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The Complete Characterization of a Rhodium Lewis Acid−Dipolarophile Complex as an Intermediate for the Enantioselective Catalytic 1,3-Dipolar Cycloaddition of *C,N*-Diphenylnitrone to Methacrolein

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The 1,3-dipolar cycloaddition reaction (1,3-DCR) of nitrones with alkenes represents one of the most useful and convenient methods for preparing isoxazolidines (Scheme 1) that are potential precursors for biologically important compounds such as alkaloids, amino acids, β-lactams, and amino sugars.[1] The greatest challenge for the 1,3-DCR of nitrones with alkenes is to control the enantioselectivity of the addition. For this purpose, the use of chiral Lewis acid transition-metal auxiliaries is one of the most promising approaches. Coordination of the organic substrates to the metal facilitates the addition. Additionally, this may render the reaction catalytic and can allow for an efficient control of the enantioselectivity.[2]

In the case of electron-deficient alkenes (normal electron demand reaction[3]), the reaction is favored by coordination of the alkene-withdrawing substituent to the metal. In general, coordination of the nitrone oxygen to a Lewis acid is more feasible than a monodentate coordination of a carbonyl function.[4] Therefore, while 1,3-dicarbonyl compounds, enabling a more favored bidentate coordination, turned out to be the model system of choice for most studies on Lewis-acid catalyzed 1,3-DCR of nitrones,[2−4] examples of one-point binding catalysts for the activation of alkenes are very limited.[5]

Here, we present the first example of a rhodium-based catalytic system successfully applied to the scarcely explored case of 1,3-DCR of nitrones to methacrolein. The catalytic process occurs with a reversal of regioselectivity,[6] perfect *endo* selectivity, and up to 92% ee. Additionally, the complete characterization of the involved intermediate allows us to interpret the observed selectivities.

A few years ago, some of us demonstrated that methacrolein coordinates to ruthenium in a half-sandwich complex.[7] This compound and the related rhodium derivative (S_{Rh},R_C)-[(η^5-C_5Me_5)-Rh(*R*-Prophos)(H_2O)](SbF_6)$_2$ [*R*-Prophos = (*R*)-(+)-1,2-bis(diphenylphosphino)propane, **1·SbF$_6$**][8] were shown to be active catalysts for the Diels−Alder reaction between methacrolein and cyclopentadiene. As the rhodium compound gave better enantioselectivity, we concentrated our efforts on rhodium diphosphine compounds in search of active systems for the 1,3-DCR of nitrones with methacrolein.

When *C,N*-diphenylnitrone **2** is allowed to react with methacrolein (**3**) (Scheme 1, Table 1), at room temperature in CH_2Cl_2 for 15 h in the absence of a catalyst, the **5** adduct is obtained in 63% yield (entry 1). At −25 °C, the reaction is inhibited, but in the presence of a catalytic amount of the achiral compound [(η^5-C_5Me_5)Rh(dppe)(H_2O)](SbF_6)$_2$ [dppe = 1,2-bisdiphenylphosphinoethane, (**6**)],[9] a 70:30 mixture of **4** and **5** adducts was obtained, with a conversion of 96%, after 10 h in CH_2Cl_2 (entry 2).

Scheme 1. 1,3-DCR between *C,N*-Diphenylnitrone and Methacrolein

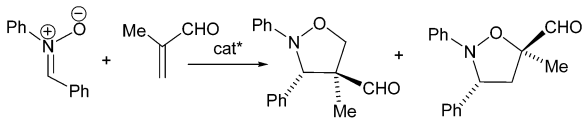

Table 1. Enantioselective 1,3-Dipolar Cycloadditions between Methacrolein and *C,N*-Diphenylnitrone[a]

entry	catalyst	*T* (°C)	*t* (h)	yield (%)[b,c]	**4**[c]	**5**[c]	ee (%)[d]
1	none	room temp	15	63		100	
2	**6**	−25	10	96	70	30	
3	**1·SbF$_6$**	−25	15	100	63	37	90/75
4	**1·SbF$_6$**	+5	15	100	51	49	84/68
5	**1·SbF$_6$**	0	15	100	53	47	85/68
6	**1·SbF$_6$**	−15	15	100	59	41	88/72
7	**1·SbF$_6$**	−45	72	100	66	34	92/79
8	**1·PF$_6$**	−25	15	84	64	36	89/63
9	**1·BF$_4$**	−25	15	69	65	35	89/68
10	**1·CF$_3$SO$_3$**	−25	15	45	65	35	90/71
11[e]	**1·SbF$_6$**	−25	15	41	63	37	90/70
12[f]	**1·SbF$_6$**	−25	15	100	63	37	90/75
13	**1·SbF$_6$**	−25	15	90	63	37	90/74
14	**1·SbF$_6$**	−25	15	90	63	37	90/75
15	**1·SbF$_6$**	−25	15	80	63	37	90/70
16	**1·SbF$_6$**	−25	20	75	63	37	90/71

[a] Reaction conditions: catalyst 0.03 mmol (5.0 mol %), methacrolein 0.84 mmol, 50 mg of 4 Å molecular sieves, and nitrone 0.6 mmol in 5 mL of CH_2Cl_2. [b] Based on nitrone. [c] Determined by ^{1}H NMR. [d] Determined by integration of the ^{1}H NMR signals of the diastereomeric (*S*)-methylbenzyl imine derivatives. [e] Catalyst loading 1 mol %. [f] Catalyst loading 10 mol %.

Encouraged by this result, we attempted an enantioselective version using **1·SbF$_6$** as catalyst. In the presence of **1·SbF$_6$**, the reaction of methacrolein and nitrone **2**, after 15 h at −25 °C, afforded the corresponding **3**,**4**- and **3**,**5**-*endo* isoxazolidines in 90 and 75% ee, respectively (entry 3).[10] Temperature variation from +5 to −45 °C slightly affected both the product distribution and the enantioselectivity, the later smoothly increasing as temperature decreases (entries 3−7). The use of more coordinating anions,[9] such as PF_6^-, BF_4^-, or $CF_3SO_3^-$, decreased the yield. However, neither the **4**/**5** ratio nor the ee were significantly affected (entries 3, 8−10). These counterion effects could be explained in terms of competition of the anion and the substrate for the Lewis acid site.[11] In this line, conversion was also strongly affected by the solvent, especially by good coordinating solvents, such as acetone or nitromethane, which preclude catalysis. When the reaction was performed with only 1 mol % of catalyst, a conversion of 41% was measured after 15 h

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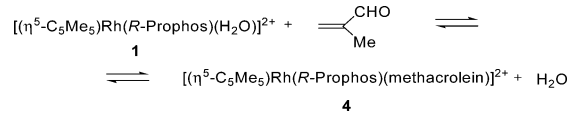
Scheme 2. Equilibrium between **1** and **7**



of treatment without significant changes in the ee values (entry 11). Increasing the catalyst loading did not improve the enantioselectivity (entry 12). Notably, despite it being a homogeneous system, the catalyst can be easily recovered and reused. Consecutive catalyst runs of up to four more times were possible, producing very similar results (entries 13−16).

^{31}P NMR studies revealed that water is partially displaced from **1** by methacrolein. At room temperature, in CD_2Cl_2, a mixture of complex **1·SbF$_6$** and 28 equiv of methacrolein consists of 68% of **1** and 32% of **7** (Scheme 2). The equilibrium is completely shifted to the right in the presence of 4 Å MS. In fact, pure complex **7·SbF$_6$** can be isolated from this solution, and single crystals, suitable for X-ray diffraction analysis, were obtained from CH_2Cl_2/*n*-hexane solutions (for spectroscopic and X-ray data, see the Supporting Information).

At −90 °C, in the catalytic conditions, the NMR spectra revealed the presence of **7** and free nitrone both remaining unchanged for hours. At −50 °C, while the ^{31}P NMR spectrum did not change, the ^{1}H NMR spectrum showed the presence of the **4** and **5** cycloaddition adducts (ca. 2% conversion, based on the nitrone, after 1 h at −50 °C). At −25 °C, the sole significant spectral change was the progressive increasing of the adducts signals. These measurements strongly indicate that, in the catalytic conditions, (i) coordinated methacrolein is not displaced by nitrone **2**, (ii) most probably, the reaction occurs through attack of the nitrone to the activated enal, and (iii) the rate-determining step is the nitrone attack to the methacrolein complex **7**. It is worth mentioning that, from −90 °C to room temperature, only one epimer at the metal has been detected.

The X-ray analysis of compound **7·SbF$_6$** showed that the rhodium atom has an absolute *S* configuration. The methacrolein molecule adopts an *s-trans* conformation, and it maintains its planar structure upon coordination. In the only two previously reported examples of related chiral Lewis acid−methacrolein complexes,[7,11b] the methacrolein lies in a plane roughly perpendicular to the ring (*p*-$MeC_6H_4{}^i$Pr or Cp) plane. Interestingly, in compound **7**, the methacrolein plane forms an angle of only 27.36(27)° with the C_5 ring plane. Additionally, the CHO proton points to the *pro-S* phenyl group of the $Ph_2PC(CH_3)H$ fragment being only 2.7 and 3.0 Å apart from their *ipso* and *ortho* carbons, respectively. In this disposition, the *Re-face* of the methacrolein is shielded by the C_5Me_5 methyls.

The NMR data at −25 °C are consistent with the retention of the stereochemistry in solution. In particular, the strong shielding of the CHO methacrolein proton upon coordination (about 2.5 ppm) strongly indicates that it is pointing to a phenyl group, in such a way that it is shielded by the anisotropic ring current.[12] Selective ROESY experiments are also in good agreement with this stereochemistry.

The structural characterization of this intermediate permits us to propose the absolute configuration of the adducts and to interpret the observed *endo* preference. The nitrone attack would preferably occur through the methacrolein *Si-face*, and an *exo* approach of the nitrone would be disfavored due to repulsive interactions between the nitrogen substituent and the methyl *R*-Prophos group. Therefore, the configuration of the two major isomers obtained will be 3*S*,4*S* for **4** and 3*S*,5*S* for **5**.

To summarize, we present here a rhodium-based system in which the formation of the dipolarophile/catalyst complex is favored with respect to nitrone coordination. Therefore, it represents a rare example of efficient activation of electron-deficient monofunctionalized alkenes toward the 1,3-dipolar cycloaddition reaction of nitrones. In addition, this activation leads to 3,4-isoxazolidines as major regioisomers with enantioselectivities up to 92%. The characterization of the enal coordinated intermediate **7** sheds significant light on the nature of the catalytic outcome. Notably, the catalyst can be recovered and reused at least up to four times without significant loss of either activity or selectivity. Further studies to establish the scope of the catalytic reaction and to explore the activity of related half-sandwich platinum group metal complexes are in progress.

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Supporting Information Available: Selected spectroscopic data for complexes **1·PF$_6$**, **1·BF$_4$**, **1·CF$_3$SO$_3$**, **6**, and **7** (PDF), and details of the crystal structure analysis of **7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Compounds **1·PF$_6$**, **1·BF$_4$**, **1·CF$_3$SO$_3$**, and **6** were prepared following the same method reported for **1·SbF$_6$** in ref 8. For selected spectroscopic data, see the Supporting Information.
(10) Complex **1·SbF$_6$** catalyzes the hydrolysis of nitrone **2**. To avoid this side reaction, it was pretreated with methacrolein, in the presence of 4 Å MS, in CH_2Cl_2 during 30 min, before the addition of the nitrone.
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