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Metal−Nitroalkene and *aci*-Nitro Intermediates in Catalytic Enantioselective Friedel−Crafts Reactions of Indoles with *trans*-β-Nitrostyrenes

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Supporting Information

ABSTRACT: The half-sandwich aqua complex (S_{Rh},R_C)-$[(\eta^5$-$C_5Me_5)Rh\{(R)$-Prophos$\}(H_2O)][SbF_6]_2$ (Prophos = propane-1,2-diylbis(diphenylphosphane)) efficiently catalyzes the asymmetric reaction between *N*-methyl-2-methylindole and *trans*-β-nitrostyrenes (up to 94% ee). The metal−nitroalkene complex involved has been characterized by X-ray crystallography, and the *aci*-nitro intermediate complex has been spectroscopically detected. A plausible catalytic cycle is proposed.

The catalytic asymmetric Friedel−Crafts (FC) alkylation of aromatic substrates with electron-deficient alkenes is a key reaction in synthetic organic chemistry that enables the formation of new C−C bonds.[1] In the past few years, the addition of indoles to nitroolefins has attracted considerable attention, due to the synthetic versatility of the nitro group, which allows further derivatization leading to the synthesis of pharmacologically active molecules.[2] A variety of chiral catalysts, including organocatalysts such as bis-sulfonamides,[2k] thioureas,[2j,3] and phosphoric acids[2f,h,4] as well as Zn,[2e,5] Cu,[2d,g,6] and, to a lesser extent, Ni,[2a] Al,[2i] Pd,[7] and Pt[8] salts (mostly containing nitrogen donor ligands as chiral sources) have been successfully applied to this reaction.

For metal-based catalytic systems, activation of nitroolefins through bidentate coordination to the metal[2a,5g,6d] and bifunctional mechanisms, which involve the simultaneous interaction of both the nitroolefin and the indole with the catalyst,[5a,e,f,6a,b] have been suggested. On the other hand, Arai and co-workers have hypothesized the formation of a nitronate intermediate in the Cu-catalyzed tandem Friedel−Crafts/Henry reaction of nitroalkenes, indoles, and aldehydes[9] as well as in the Friedel−Crafts/protonation of indoles and nitroacrylates.[10] However, to our knowledge, there is no experimental proof for intermediates involved in these reactions.

Herein, we disclose an unexpected catalytic pathway for the FC reaction between *trans*-β-nitrostyrenes and indoles catalyzed by the aqua complex[11] (S_{Rh},R_C)-$[(\eta^5$-$C_5Me_5)Rh\{(R)$-Prophos$\}(H_2O)][SbF_6]_2$ (**1**; Prophos = propane-1,2-diylbis(diphenylphosphane)) (Figure 1), which involves the formation of uncommon metal−nitroalkene, metal−*aci*-nitro, and free *aci*-nitro intermediates.[12]

At the outset of this work, we examined the catalytic activity of **1** for the reaction of *trans*-β-nitrostyrene with a variety of indoles. In general, enantioselectivities were poor except for the reaction with *N*-methyl-2-methylindole, in which an ee value of 94% was achieved (see the Supporting Information).

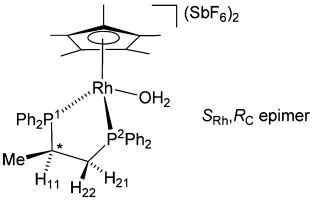

Figure 1. Catalyst precursor **1**.

A series of *trans*-β-nitrostyrenes was subsequently investigated in the reaction with *N*-methyl-2-methylindole catalyzed by the rhodium complex **1** (Table 1). In the cases of 3- and 4-substituted aromatic nitroalkenes, high conversions were also obtained (entries 3, 4, 6−9, 11, and 13). Probably due to steric hindrance, 2-substitution strongly lowered both the yield and ee (entries 5, 10, and 12). Enantioselection also decreased for nitroalkenes bearing substituents on the 3- and 4-positions but to a moderate extent for electron-donating substituents and more markedly for electron-withdrawing substituents.

To gain some insight into the mechanism of this catalytic process, the reaction between the catalyst precursor (S_{Rh},R_C)-$[(\eta^5$-$C_5Me_5)Rh\{(R)$-Prophos$\}(H_2O)][SbF_6]_2$ (**1**) and the substrates *N*-methyl-2-methylindole and *trans*-β-nitrostyrene was studied. Addition of the indole to solutions of **1** did not produce significant changes in the NMR spectra of the metal derivative. However, the addition of 1 equiv of nitroalkene at 193 K to CD_2Cl_2 solutions of **1** in the presence of 4 Å molecular sieves yielded the clean formation of the nitroalkene complex **2a** (Figure 2). The reaction proceeded diastereose-

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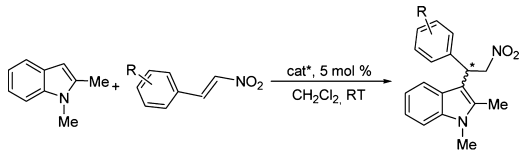
Table 1. Asymmetric FC Reaction of *N*-Methyl-2-methylindole with *trans*-β-Nitrostyrenes[a]



entry	R	*t* (min)	conversn (%)[b,c]	ee (%)[d]
1	H	10	99 (93)	94
2	2-OMe	30	41 (37)	84
3	3-OMe	15	>99 (94)	92
4	4-OMe	5	>99 (93)	74
5	2-OBn	150	32 (25)	9
6	3-OBn	5	>99 (91)	79
7	4-OBn	10	99 (94)	81
8	4-Me	5	99 (94)	71
9	4-OH	5	94 (90)	65
10	2-Cl	30	50 (46)	27
11	4-Cl	10	99 (91)	53
12	2-Br	150	54 (51)	38
13	4-Br	10	>99 (90)	66
14	2,3-$(OMe)_2$	180	29 (25)	74

[a]Reaction conditions: catalyst 0.03 mmol (5.0 mol %), indole 0.60 mmol, *trans*-β-nitrostyrene 0.90 mmol, 100 mg of molecular sieves in 4 mL of CH_2Cl_2. [b]Based on indole. Determined by NMR. [c]Yield of isolated product given in parentheses. [d]Determined by HPLC.

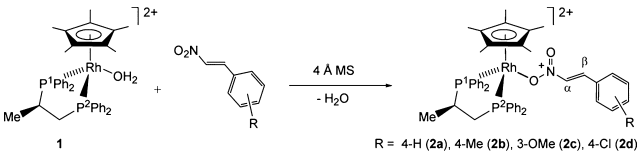


Figure 2. Metal−nitroalkene complexes **2**.

lectively with no apparent intermediates, and notably, it affords only one of the two possible epimers at the metal, as indicated by the detection of only one set of NMR signals from 193 to 293 K.

Related rhodium complexes containing *trans*-β-nitrostyrenes with different substituents on the nitroalkene aromatic ring (**2b−d**) have been prepared in a similar manner. The most striking feature of their NMR spectra was the strong shielding observed for the H_β proton (Figure 2) of the coordinated nitroalkene (about 1 ppm), with concomitant deshielding of the C_β carbon (about 8 ppm), with respect to the free molecule. The activation of the C_β toward nucleophilic attack becomes apparent. On the other hand, the NOE relationship between the H_β proton of the nitroalkenes and the aliphatic protons H_{11}, H_{21}, and H_{22} of the Prophos ligand (see Figure 1) indicated an *S* configuration at the metal in all of the studied complexes.

The crystal structure of the *trans*-4-chloro-β-nitrostyrene rhodium derivative **2d** has been determined by X-ray crystallography[13] (Figure 3). The most interesting feature of the structure is the establishment of intramolecular CH/π interactions involving the H_β proton (H(39) in Figure 3b) and the *pro*-*R* phenyl ring of the $P(2)Ph_2$ group.[14] These interactions place the H_β proton of this ligand inside of the electronic diamagnetic ring current of the phenyl ring of the $P(2)Ph_2$ group (Figure 3b). and most probably, they are also operating in solution, giving rise to the strong shielding observed for this proton in the ^1H NMR spectrum.

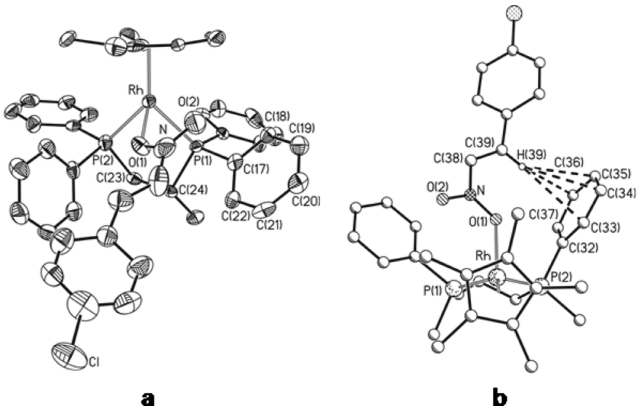


Figure 3. (a) Molecular structure of the cation of (S_{Rh},R_C)-[$(\eta^5$-$C_5Me_5)$Rh{(*R*)-Prophos}(4-chloro-β-nitrostyrene)][$SbF_6]_2$ (**2d**). Hydrogen atoms have been omitted for clarity. (b) Intramolecular CH/π interactions.

Furthermore, in this conformation the nitroalkene C(39)-*Si* face becomes hindered by the *pro*-*S* phenyl ring of the $P(1)Ph_2$ group (C(17)−C(22)) and, therefore, the indole attack would take place preferentially through the *Re* face, rendering *S*-configured Friedel−Crafts products.

After coordination of the nitroalkene, the next step of the catalytic cycle would be the reaction of the nitroalkene complex with the indole. To confirm this proposal, the reaction of preformed **2a** with *N*-methyl-2-methylindole was monitored by NMR spectroscopy (Figure 4). Selected regions of the ^1H and ^{31}P NMR spectra are also depicted in Figure 4.

Trace A in Figure 4 shows the spectra at 193 K of **2a** in these regions: residual dichloromethane in the proton NMR spectrum and the doublet of doublets assigned to the P^2 phosphorus nucleus of **2a** in the ^{31}P NMR spectrum. After the addition at 193 K of 5 equiv of the indole and 10 equiv of *trans*-β-nitrostyrene, the immediate disappearance of **2a** with concomitant formation of two diastereomers of the rhodium *aci*-nitro complex **3** in a ca. 70:30 molar ratio was observed (Figure 4, trace B). Complexes **3** were characterized by two pairs of coupled doublets centered at 6.22 (H_α) and 5.29 (H_β) ppm (major isomer) and at 6.10 (H_α) and 4.81 (H_β) ppm (minor) together with a strongly deshielded broad resonance at about 17.5 ppm attributed to the OH functionality (trace B). Correspondingly, the ^{31}P NMR spectrum shows two new doublets of doublets (one much less abundant) attributed to the P^2 nuclei of two isomers of **3**.[15] At 193 K, these NMR spectra did not change for hours. However, when the solution was heated to 223 K for 20 min and then the NMR spectra were recorded at 193 K,[16] the gradual consumption of the indole with the concomitant appearance of *aci*-nitro compound **4** (Figure 4) was readily observed: the H_β (5.58 ppm, ^3J = 8.1 Hz) and OH (13.56 ppm) signals of **4** grew at the expense of the C^3−H indole proton resonance at 6.25 ppm (traces B−E). Further heating to 223 K gave rise to the progressive and complete rearrangement of the *aci*-nitro compound **4** to the corresponding FC adduct **5**.[15] On the other hand, when all the indole was consumed, the remaining *trans*-β-nitrostyrene displaced coordinated *aci*-nitro, regenerating the nitroalkene complex **2a** (trace F).

Taking together all the above experimental data, the catalytic cycle depicted in Figure 5 can be proposed. The coordinated water molecule in **1** is displaced by *trans*-β-nitrostyrene, giving

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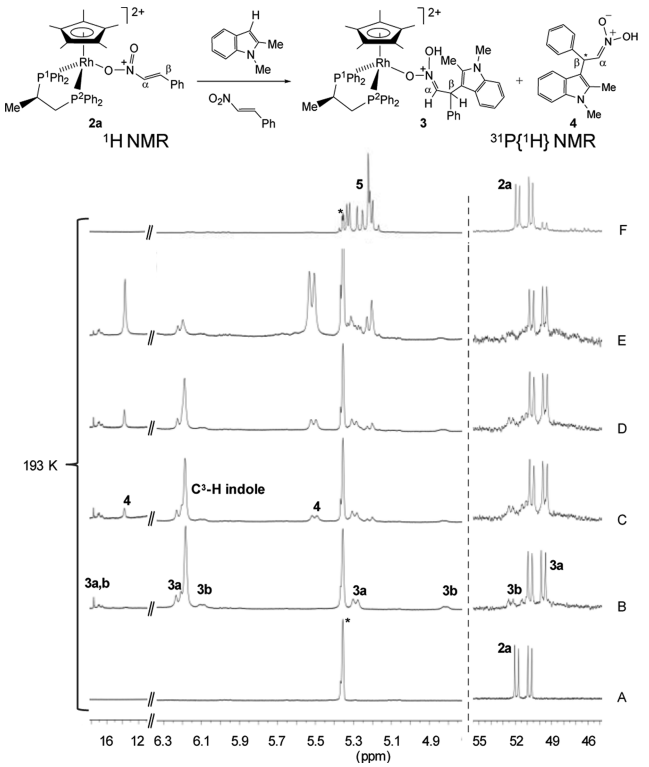

Figure 4. Selected regions of the ^{1}H and ^{31}P NMR spectra of a 1/10/5 catalyst/*trans*-β-nitrostyrene/indole molar ratio mixture at 193 K: (A) spectra of **2a**; (B) spectra after the addition of indole and *trans*-β-nitrostyrene; (C–E) spectra recorded at 193 K after successive heating at 223 K for 20 min; (F) spectra after total consumption of the indole. The asterisk denotes residual $CHDCl_2$.

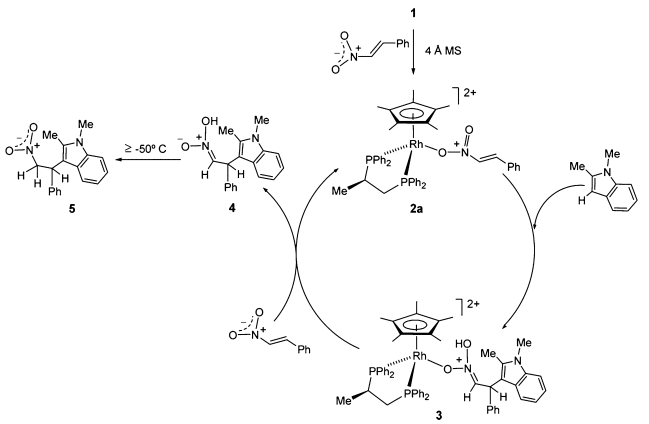

Figure 5. Proposed catalytic cycle.

the nitroalkene complex **2a**. Indole attack on the activated C_β of the coordinated nitroalkene, which renders *aci*-nitro complex **3**, is the enantioselectivity-determining step. Reaction of **3** with *trans*-β-nitrostyrene eliminates the *aci*-nitro ligand **4** and regenerates complex **2a** that restarts the cycle. Finally, free *aci*-nitro **4** spontaneously rearranges to the FC adduct **5**.

In summary, precatalyst **1** is well suited for FC reactions between *trans*-β-nitrostyrenes and indoles. ee values up to 94% can be achieved. Metal–nitroalkene, metal–*aci*-nitro and free *aci*-nitro intermediates, which have been detected and spectroscopically characterized, make up a plausible catalytic cycle that accounts for the catalytic outcome. For the metal–nitroalkene complexes only one epimer at metal has been detected. This fact, together with the establishment of CH/π interactions between the H_β proton of the coordinated nitroalkene and the *pro-R* phenyl ring of the P(2)Ph$_2$ group of the diphosphane, explains the high ee obtained. Detection of the *aci*-nitro ligated complex **3** opens the door to application of complexes of the type **1** in related catalytic processes involving nitroalkenes as electrophiles as well as to enantioselective catalytic tandem reactions pivoting around coordinated nitronates. Further studies along these lines are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and a CIF file giving experimental details, spectroscopic data, and X-ray crystallographic data, including full details of the structural analysis of complex **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Complete spectroscopic data for the *aci*-nitro complexes **3**, the free *aci*-nitro **4**, and the FC product **5** are included in the Supporting Information.
(16) At 213 K only broad unresolved NMR signals were recorded.