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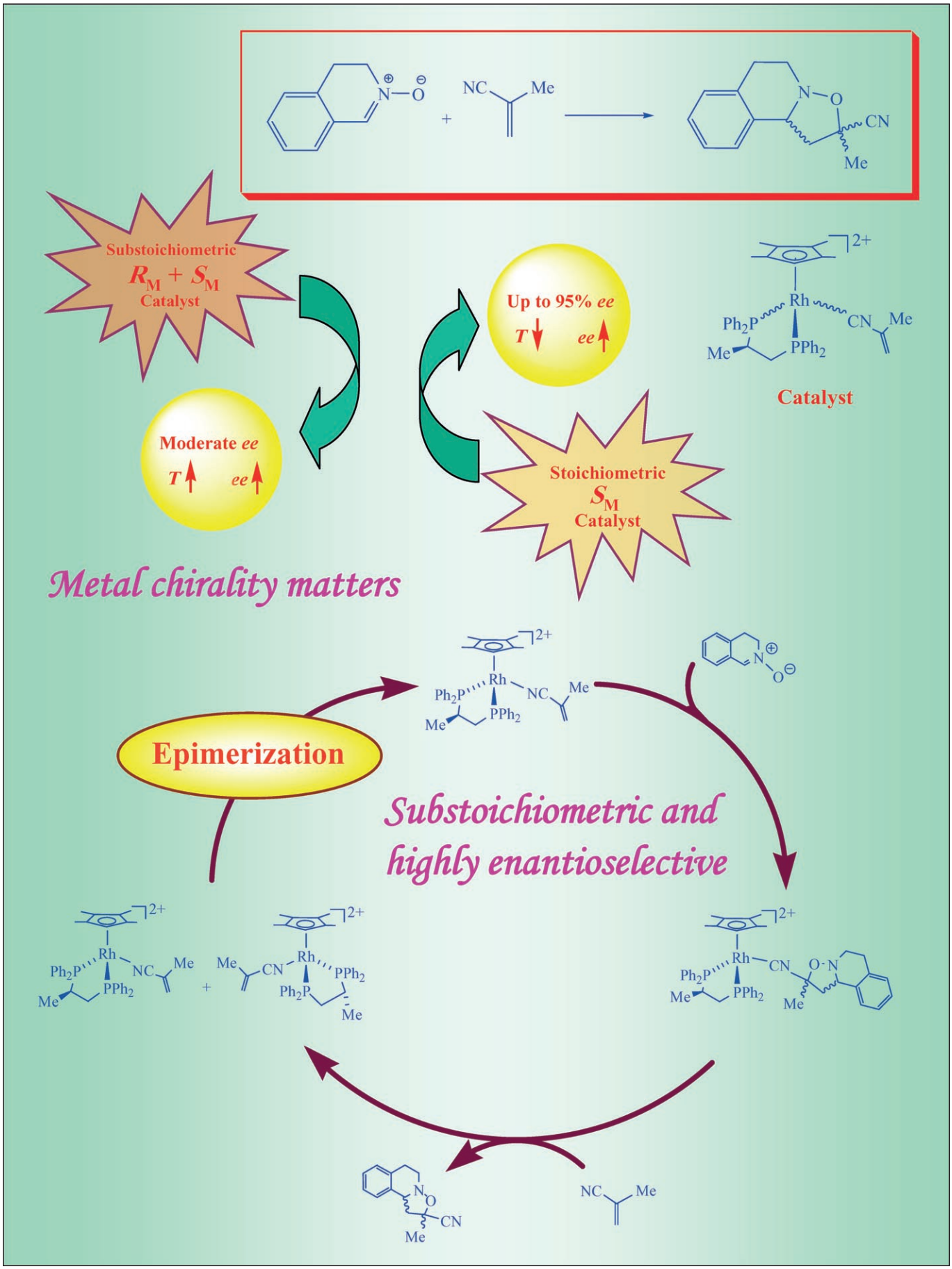


Half-Sandwich Rhodium (and Iridium) Complexes as Enantioselective Catalysts for the 1,3-Dipolar Cycloaddition of 3,4-Dihydroisoquinoline *N*-Oxide to Methacrylonitrile

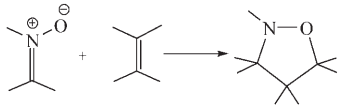
Daniel Carmona,* M. Pilar Lamata, Fernando Viguri, Ricardo Rodríguez, Fernando J. Lahoz, and Luis A. Oro[a]

Abstract: Cationic half-sandwich complexes containing the [(η^5-C_5Me_5)M-(Diphos*)] moiety (M = Rh, Ir; Diphos* = chiral diphosphine ligand) catalyze the cycloaddition of the nitrone 3,4-dihydroisoquinoline *N*-oxide (**A**) to methacrylonitrile (**B**) with excellent *regio* and *endo* selectivity and low-to-moderate enantioselectivity. The most active and selective catalyst, (S_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos)}(NC(Me)C=CH_2)]$(SbF_6)_2$, has been isolated and fully characterized including the determination of the molecular structure by X-ray diffraction. The *R*-at-metal epimers of the complexes [(η^5-C_5Me_5)M{(*R*)-Prophos)}(NC(Me)C=CH_2)]$(SbF_6)_2$ (M = Rh, Ir) isomerize to the corresponding *S*-at-metal diastereomers. The stoichiometric cycloaddition of **A** with **B** is catalyzed by diastereopure (S_M,R_C)-[(η^5-C_5Me_5)M{(*R*)-Prophos)}(NC(Me)C=CH_2)]$(SbF_6)_2$ with perfect *regio* and *endo* selectivity and very good (up to 95%) *ee*. The catalyst can be recycled up to nine times without significant loss of either activity or selectivity.

Keywords: asymmetric catalysis · cycloaddition · iridium · methacrylonitrile · nitrones · rhodium

Introduction

Cycloaddition reactions are arguably among the most powerful synthetic strategies for the preparation of functionalized cyclic structures.[1] Because suitable catalysts lower the barrier to addition reactions and improve the selectivity of the process, tremendous effort has been devoted to the development of catalytic enantioselective versions of this type of reaction. To this end, the use of chiral Lewis acids based on metal complexes as homogeneous catalysts remains as one of the dominant approaches.[2] In particular, 1,3-dipolar cycloadditions have been extensively used to prepare optically active five-membered heterocyclic ring systems and, among them, the enantioselective 1,3-dipolar cycloaddition reaction (DCR) of an alkene with a nitrone leads to the construction of up to three contiguous asymmetric carbon centers. The resulting five-membered isoxazolidine derivatives (Scheme 1) may be converted into amino alcohols, precursors to biologically important amino acids, alkaloids, or β-lactams.[3]



Scheme 1. 1,3-DCR between nitrones and alkenes.

Normal electron-demand 1,3-dipolar cycloaddition reactions of alkenes with nitrones involve the interaction between the alkene LUMO and the HOMO of the nitrone. Therefore, electron-deficient alkenes activated through coordination to a metal via an electron-withdrawing group constitute the ideal species to achieve this type of transformation.[4] However, in some instances, nitrone competes with the alkene for metal coordination eventually preventing the process from occurring.[5] To overcome this difficulty, two different approaches have been applied. The first one consists of making use of alkenes that enable a bidentate coordination to the metal such as 3-alkenoyl-2-oxazolidinones.

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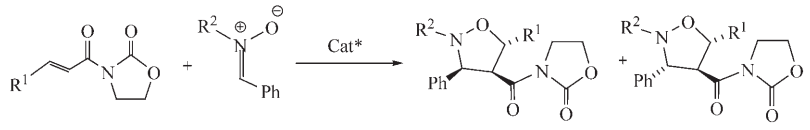
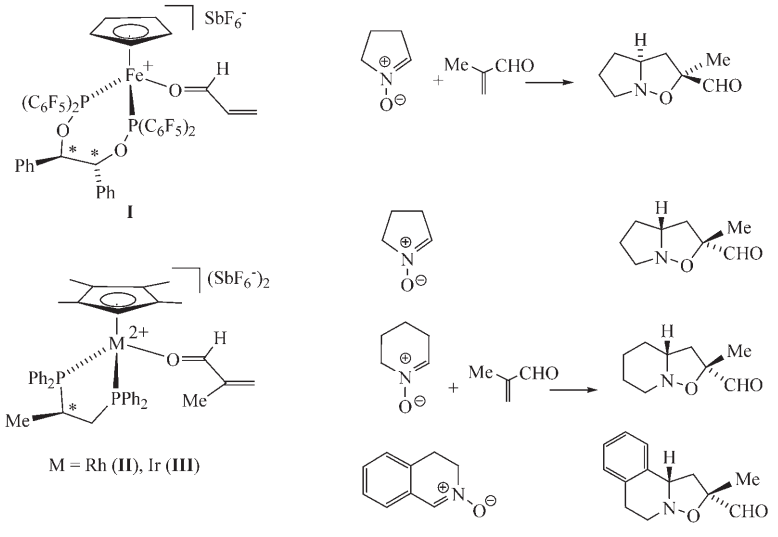
In fact, the first example of a transition-metal-catalyzed asymmetric DCR between alkenes and nitrones, reported in 1994 by Gothelf and Jørgensen, exploits this feature: chiral titanium compounds generated in situ from $[Ti(OiPr)_2Cl_2]$ and chiral diols catalyzed the addition of 3-alkenoyl-2-oxazolidinones to benzylideneamine *N*-oxides (Scheme 2).[6]



Scheme 2. DCR of 3-alkenoyl-2-oxazolidinones with nitrones.

Subsequently, most research in the field was concentrated on bidentate substrates of the 3-alkenoyl-2-oxazolidinone type.[3b,4]

The second approach has been applied to monodentate alkenes, mostly α,β-unsaturated aldehydes with the intent of keeping the nitrone concentration low by adding it slowly to the reaction media.[7] Thus, excellent yield and high enantioselectivity was obtained in the reaction between methacrolein and 1-pyrrolidine *N*-oxide catalyzed by the Binop-F iron complex **I**, when the nitrone was added slowly (Scheme 3).[7a] Analogously, quantitative yields and enantio-

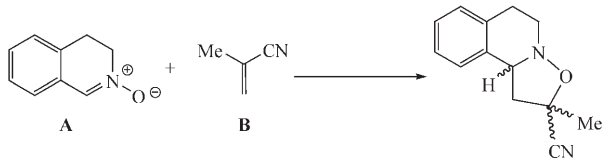


Scheme 3. DCR of methacrolein with nitrones.

meric excesses of about 90% were achieved in the reaction between methacrolein and 1-pyrrolidine *N*-oxide, 2,3,4,5,-tetrahydropyridine *N*-oxide or 3,4-dihydroisoquinoline *N*-oxide catalyzed by the complexes (S_M,R_C)-$[(\eta^5\text{-}C_5Me_5)M\{(R)\text{-Prophos}\}(methacrolein)](SbF_6)_2$ (M = Rh (**II**), or Ir (**III**)) when the addition of the corresponding nitrone was performed over 10–15 h (Scheme 3).[7b]

However, neither approach is of general application: bidentate coordination can be a harsh requirement for alkenes and slow addition of the nitrone does not work properly for any nitrone/alkene combination.

We envisaged the possibility of circumventing the problem of the competitive coordination of the nitrone in a different manner: to favor the coordination of the alkene to the metal in a monodentate fashion by using a good coordinating functionality such as a cyano group. The present paper reports on our efforts in this approach. We focus on the addition of the nitrone 3,4-dihydroisoquinoline *N*-oxide (**A**) to methacrylonitrile (**B**) (Scheme 4). After an initial



Scheme 4. 1,3-Dipolar cycloaddition reaction studied.

screening among a few chiral diphosphines, the $[(\eta^5\text{-}C_5Me_5)Rh\{(R)\text{-Prophos}\}]$ system was chosen as the most promising one. The influence of the temperature, solvent, and the rate of nitrone addition were studied.

To understand the results obtained, the characterization of the two epimers at the metal, that is, (S_M,R_C)- and (R_M,R_C)-$[(\eta^5\text{-}C_5Me_5)M\{(R)\text{-Prophos}\}(methacrylonitrile)](SbF_6)_2$ (M = Rh, Ir), including the determination of the molecular structure of the S_{Rh},R_C isomer by X-ray diffraction methods, as well as the epimerization of the *R* epimers to the *S* epimers, are also reported.

Subsequently, the stoichiometric reaction between nitrone **A** and dipolarophile **B** catalyzed by diastereopure (S_M,R_C)-$[(\eta^5\text{-}C_5Me_5)M\{(R)\text{-Prophos}\}(methacrylonitrile)]^{2+}$ was studied. The influence of the temperature and solvent on the conversion and selectivity was analyzed for the rhodium case. The rhodium catalyst was reutilized up to nine times with the activity and selectivity being essentially retained.

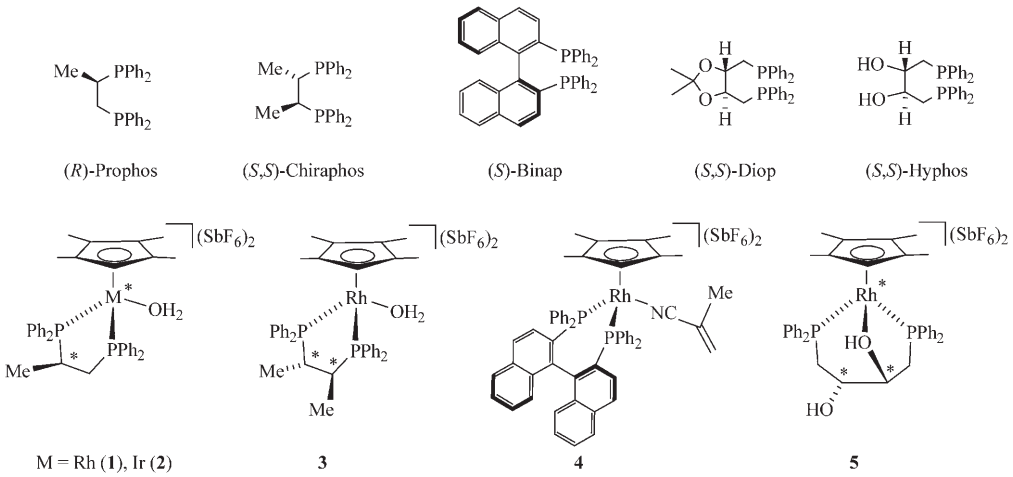
Results and Discussion

Preparation of the catalyst precursors: The aqua complexes (S_M,R_C)-[$(\eta^5$-$C_5Me_5)$M{(*R*)-Prophos}(H_2O)]$(SbF_6)_2$ (M = Rh (**1**), Ir (**2**)) were prepared as previously reported.[7b,8] The Chiraphos complex [$(\eta^5$-$C_5Me_5)$Rh{(*S*,*S*)-Chiraphos}(H_2O)]-$(SbF_6)_2$ (**3**) was prepared, in an isolated yield of 89%, by reacting the solvato complex[9] [$(\eta^5$-$C_5Me_5)$Rh$(acetone)_3]^{2+}$ with (*S*,*S*)-Chiraphos in acetone. The presence of trace amounts of water in the solvent is sufficient to afford pure complex **3**.[10] Attempts to isolate the homologous aqua complex with the diphosphine (*S*)-Binap, following a similar preparative route, were unsuccessful. However, the related methacrylonitrile complex [$(\eta^5$-$C_5Me_5)$Rh{(*S*)-Binap}(NC-(Me)C=CH_2)]$(SbF_6)_2$ (**4**) was prepared in 89% yield by successive addition of methacrylonitrile and (*S*)-Binap to a solution of [$(\eta^5$-$C_5Me_5)$Rh$(acetone)_3]^{2+}$ in acetone. On the other hand, the chiral diphosphine diol (*S*,*S*)-Hyphos containing complex **5** was isolated from the reaction of [$(\eta^5$-$C_5Me_5)$Rh$(acetone)_3]^{2+}$ with (*S*,*S*)-Diop in acetone (Scheme 5).

Complexes **3**–**5** were characterized by analytical and spectroscopic means. In particular, at room temperature, the ^{1}H NMR spectrum of the Chiraphos complex **3** shows two broad peaks at $\delta = 2.30$ and 1.35 ppm attributed to the two CH and two CH_3 of the -HC*(Me)-(Me)C*H- Chiraphos moiety, respectively. Accordingly, the ^{31}P NMR spectrum consists of a very broad signal centered at about $\delta = 67$ ppm. However, at −50 °C, two CH peaks at $\delta = 2.80$ and 2.51 ppm, as well as two methyl signals at $\delta = 1.40$ and 1.11 ppm, were recorded and the ^{31}P NMR spectrum shows two well-resolved double doublets at $\delta = 72.0$ (^1J(Rh,P^1) = 127.2 Hz, J(P^2,P^1) = 45.2 Hz) and $\delta = 59.6$ ppm (^1J(Rh,P^2) = 130.9 Hz). These variable-temperature spectra can be explained by assuming a rapid exchange, on the NMR timescale, between the relative orientations of water molecules and the C_5Me_5 ligands. Additionally, two IR bands centered at 3480 and 1700 cm^{-1} are attributed to the presence of a water molecule.

The NMR spectra of the Binap complex **4**, apart from the typical peaks for the coordinated Binap and C_5Me_5 ligands, show the presence of the coordinated nitrile. Thus, the ^{1}H NMR spectrum shows two singlet peaks at $\delta = 4.37$ and 5.65 ppm corresponding to the $=CH_2$ protons that correlate with a ^{13}C resonance at $\delta = 139.3$ ppm. The resonance of the nitrile methyl protons is overlapped by the C_5Me_5 signal that appears at $\delta = 1.33$ ppm as a pseudo-triplet due to the coupling to two phosphorus nuclei. One doublet at $\delta = 129.0$ ppm (^2J(Rh,C) = 5.75 Hz) and one singlet at $\delta = 114.9$ ppm in the ^{13}C NMR spectrum are assigned to the remaining NC and NC−*C* carbons, respectively. At room temperature, the ^{31}P NMR spectrum consists of two sharp double doublets centered at $\delta = 37.9$ (^1J(Rh,P^1) = 127.4 Hz, J(P^2,P^1) = 54.9 Hz) and 24.3 ppm (^1J(Rh,P^2) = 128.2 Hz). An IR band at 2253 cm^{-1} is attributed to the C≡N bond.

Bidimensional ^{1}H–^{1}H, ^{13}C–^{1}H, and ^{31}P–^{1}H NMR data of complex **5** are compatible with a P-CH_2-CH-CH-CH_2-P structural skeleton for the diphosphine ligand and exclude the presence of the $OOC(CH_3)_2$ Diop moiety. At room temperature, the ^{31}P NMR spectrum of complex **5** consists of two sharp double doublets centered at $\delta = 52.0$ and 13.9 ppm with the expected ^{103}Rh–^{31}P (134.75 and 132.8 Hz, respectively) and ^{31}P–^{31}P (47.6 Hz) coupling constants. The ^{1}H NMR spectrum shows two distinct OH peaks at $\delta = 8.25$ and 3.36 ppm. The latter appears as a double doublet with couplings of 3.8 and 2.4 Hz. These spectra remain essentially unchanged from +30 to −50 °C. A broad ν(OH) IR band centered at 3557 cm^{-1} denotes the presence of hydroxy groups. All these data are consistent with the presence of the (S_C,S_C)-1,4-bis(diphenylphosphino)butane-2,3-diol [(*S*,*S*)-Hyphos] ligand displaying a κ^3-*P*,*P*,*O* coordination mode (Scheme 5). Most probably, after coordination of the original (*S*,*S*)-Diop ligand, hydrolysis of its dioxolane ring occurs with formation of the [(*S*,*S*)-Hyphos] ligand. Subsequent coordination of one of the resulting hydroxy groups affords

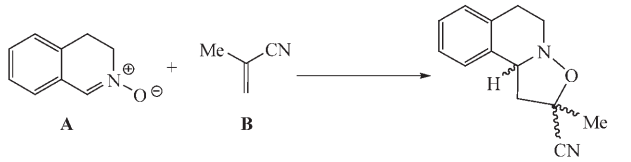


Scheme 5. Chiral diphosphines and precatalysts employed.

complex **5**. It has been previously reported that the antipode (*R*,*R*)-Hyphos ligand is also κ^3-*P*,*P*,*O* coordinated in the rhodium complex [Rh(nbd){(*S*,*S*)-Hyphos}]BF_4 (nbd = norbornadiene).[11]

Catalytic studies: Complexes **1**–**5** were tested as catalysts for the DCR between the nitrone 3,4-dihydroisoquinoline *N*-oxide and methacrylonitrile (Scheme 4). Table 1 lists a selection of the results together with the reaction conditions employed. The collected results are the average of at least two comparable reaction runs. Conversion and stereochemistry were determined by NMR spectroscopy. High conversions are obtained and, as expected for Lewis acid-catalyzed DCR of nitrones with one-point binding alkenes, *endo* preference is shown.[5] The cyclic nitrone employed affords 3,5-cycloadducts regioselectively in all cases.[7,12] Pure 3*S**,5*R***-endo* cycloadducts can be obtained by column chromatography. Enantioselectivity was determined by using HPLC.

Table 1. 1,3-Dipolar cycloadditions.[a]



Entry	Precatalyst	*t*[h]	Yield[%][b]	3,5-*endo*[%]	*ee*[%][c]
1	**1**	16	82	98	52
2	**2**	54	91	93	1
3	**3**	65	54	98	5
4	**4**[d]	65	100	97	6
5	**5**[d]	65	95	96	2

[a] Reaction conditions: Precatalyst 0.03 mmol (10.0 mol%), methacrylonitrile 2.1 mmol, and nitrone 0.3 mmol, in CH_2Cl_2 (4 mL). Runs were carried out at RT. [b] Based on nitrone. [c] Determined by HPLC. [d] 5.0 mol% of precatalyst loading.

Catalysts based on diphosphines with C_2 symmetry are very poorly enantioselective (entries 3–5, Table 1). A fair enantioselectivity was achieved with the Rh-Prophos catalyst (entry 1, Table 1). Surprisingly, this catalyst is much more enantioselective than the iridium analogue (entry 2, Table 1). In this respect, it is interesting to point out that both systems efficiently catalyze the DCR between enals and nitrones with *ee* values of around 90%, the Ir-Prophos system being a little more reactive and selective than its rhodium counterpart.[7b,13]

We focused our work on the Rh-Prophos system because the best results were obtained with this system. Temperature and reaction solvents generally influence the selectivity and catalytic activity in Lewis acid catalysis. Table 2 collects a selection of the results obtained for the DCR between the nitrone **A** and the α,β-unsaturated nitrile **B** catalyzed by the Rh-Prophos system at the indicated temperatures. The excellent *regio* and *endo* selectivities are essentially maintained, but a gradual increase of the enantiomeric excess from 36 to 64% was observed as temperature increased from −25 to +30°C. This is a surprising result because an opposite trend is generally encountered in catalytic DCR of nitrones with alkenes.[7b,14]

Table 2. Temperature effect.[a]

Entry	*T*[°C]	*t*[h]	Yield[%]	3,5-*endo*[%]	*ee*[%]
1	30	16	88	95	64
2	RT	16	82	98	52
3	0	48	36	99	40
4	−25	72	26	99	36

[a] For conditions see footnote of Table 1.

Next, the same reaction was carried out in a variety of solvents (Table 3). After a few hours at room temperature, good conversions were achieved in most assayed solvents, the less active medium being a H_2O/MeOH mixture (entry 6, Table 3). No significant differences can be ascribed to the coordination capability of the solvents, indicating that, most probably, solvent does not compete with the nitrile for metal coordination. Excellent *regio* and *endo* selectivities were uniformly reached. Enantiomeric excesses ranging from 29 to 73% were achieved, THF proving to be the solvent of choice.

Table 3. Solvents effect.[a]

Entry	Solvent	*t*[h]	Yield[%]	3,5-*endo*[%]	*ee*[%]
1	CH_2Cl_2	16	82	98	52
2	acetone	16	88	98	52
3	MeOH	16	16	99	57
4	EtAc	16	66	97	29
5	THF	16	90	98	73
6	H_2O/MeOH[b]	58	23	99	41

[a] For conditions see footnote of Table 1. Corresponding solvent (4 mL) was used. [b] 75:25 v/v.

Finally, it was observed that if the nitrone was slowly added to the reaction medium enantioselectivity significantly increased, as the sole noteworthy change (Table 4). In this respect, it is interesting to point out that coordination of the nitrone to the (C_5Me_5)Rh(Prophos) moiety was not observed in the presence of methacrylonitrile. Thus, the competitive coordination of the nitrone can be discarded as the

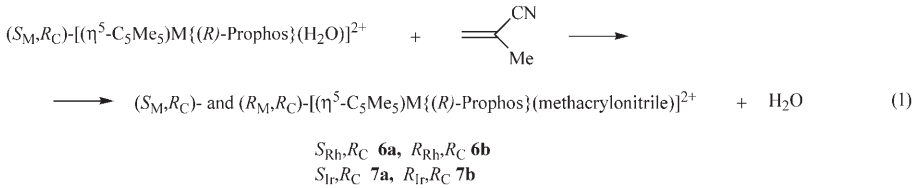
Table 4. Influence of the addition time of the nitrone.[a]

Entry	Addition time[h][b]	*t*[h][c]	Yield[%]	3,5-*endo*[%]	*ee*[%]
1	[d]	16	82	98	52
2	12	36	98	98	54
3	30	32	95	95	64
4	68	72	92	98	65

[a] For conditions see footnote of Table 1. Solvent: CH_2Cl_2. [b] The nitrone solution was added over the indicated period of time. [c] Total reaction time including the addition time period. [d] The nitrone solution was added in one portion at the beginning of the reaction.

main cause for the increase of the *ee* when the nitrone is slowly added.

(S_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(H_2O)](SbF_6)$_2$/methacrylonitrile system: Some of the above-mentioned results are unexpected and difficult to explain. In particular, the increase of the enantioselectivity, when temperature (Table 2) or nitrone addition time (Table 4) increase, does not have an obvious interpretation. To try and shed light on the catalytic system, we have studied the solution behavior of mixtures of the aqua complex (S_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(H_2O)](SbF_6)$_2$ with methacrylonitrile by NMR spectroscopy. When, at −70 °C, 1.5 equivalents of methacrylonitrile were added to a solution of (S_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(H_2O)]$^{2+}$ in CD_2Cl_2, NMR measurements show the immediate disappearance of the starting complex and the simultaneous formation of the new complexes (S_{Rh},R_C)- and (R_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(methacrylonitrile)]$^{2+}$ containing methacrylonitrile (**6a**, **6b**) in a molar ratio of approximately 38:62 [Eq. (1)].



The most abundant isomer was the *R*-at-rhodium epimer. Two pairs of double doublets, showing RhP and PP couplings in the ^{31}P NMR spectrum, and two pairs of singlets in the 5–6 ppm region, assigned to the methylene protons of the nitrile ligand, in the ^{1}H NMR spectrum, are diagnostic of the formation of the new complexes. At −70 °C, the isomeric composition of the solution mixture remains unchanged for hours; however, at −25 °C, **6b** slowly epimerizes to **6a** and after 45 min at 10 °C complex **6a** represents more than 99 % of the mixture. Kinetics measurements for the epimerization process of **6b** to **6a**, in CH_2Cl_2, at 10 °C, revealed that the epimerization obeys a first-order rate law with a derived rate constant of $(1.73\pm0.04)\times10^{-3}\ s^{-1}$.

At −25 °C, a 45:55 molar ratio mixture of **6a**/**6b**, as SbF_6 salts, was isolated and, after epimerization, pure **6a** could also be isolated. The ^{31}P NMR spectrum of compound **6a** consists of two double doublets centered at $\delta=75.0$ (^1J(Rh,P^1) = 121.4 Hz, J(P^2,P^1) = 35.7 Hz) and 45.9 ppm (^1J(Rh,P^2) = 125.8 Hz). A quartet at $\delta=5.92$ ppm (^4J(H,H) = 1.8 Hz) and a broad singlet at $\delta=5.32$ ppm, in the ^{1}H NMR spectrum assigned to $-CH_2$ protons, that correlate with a peak at $\delta=139.95$ ppm in the ^{13}C NMR spectrum, together with a ν(CN) IR band at 2257 cm^{-1} account for the presence of coordinated nitrile. The molecular structure of compound **6a** was determined by X-ray diffraction (see below).

For comparative purposes, the iridium analogue [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(methacrylonitrile)](SbF_6)$_2$ (**7**) was also prepared according to Equation (1). The two epimers at the metal, $S_{Ir}R_C$ and $R_{Ir}R_C$ (**7a** and **7b**, respectively), were obtained in a 67:33 **7a**/**7b** molar ratio. Notably, the diastereomeric composition of the mixture remained unchanged during a week, in CD_2Cl_2, at room temperature. However, pure **7a** could be obtained by heating the mixture at 50 °C in acetone.

Molecular structure of compound 6a: A molecular representation of the complex cation **6a** is depicted in Figure 1 and selected geometrical parameters are listed in Table 5. The rhodium atom exhibits a pseudo-tetrahedral coordination environment and is coordinated to a η^5-C_5Me_5 ring, to the two phosphorus atoms of the (*R*)-Prophos ligand, and to the nitrogen atom of the methacrylonitrile. The metal atom, configured as a chiral center, presents an *S* isomer absolute configuration.[15] The Rh-P(1)-C(36)-C(35)-P(2) metallacycle shows, as is usual, a λ conformation[16] with an ^3E puckering descriptor (Cremer and Pople parameters $Q=0.472(8)$ Å and $\varphi=73.5(6)°$).[17] As commonly observed in other related half-sandwich complexes,[18] the sterically demanding Cp* ligand, together with the methyl group attached to the chiral carbon, occupy equatorial positions in this five-membered metallacycle ring, whereas the nitrile group is situated in an axial position.

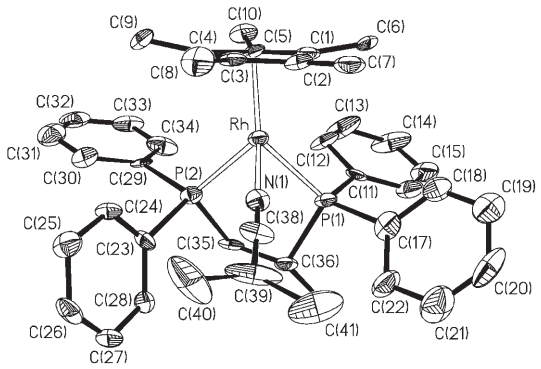


Figure 1. Molecular structure of the cation of complex **6a**.

Table 5. Selected bond lengths [Å] and angles [°] for compound **6a**.[a]

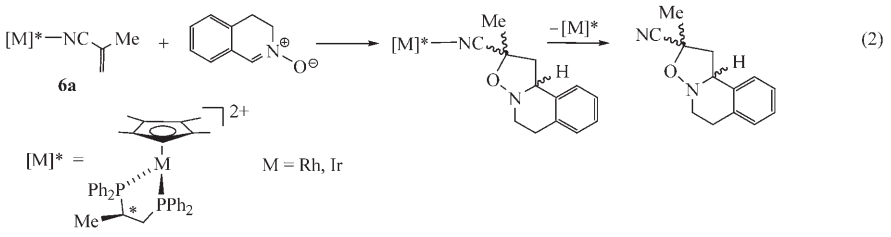
Rh−P(1)	2.331(3)	Rh−C(1)	2.228(11)
Rh−P(2)	2.329(3)	Rh−C(2)	2.196(12)
Rh−N(1)	2.067(7)	Rh−C(3)	2.247(11)
Rh−G[a]	1.858(5)	Rh−C(4)	2.247(10)
		Rh−C(5)	2.187(7)
N(1)−C(38)	1.151(10)	C(39)−C(40)	1.40(2)
C(38)−C(39)	1.418(12)	C(39)−C(41)	1.426(19)
P(1)-Rh-P(2)	84.17(8)	Rh-N(1)-C(38)	173.5(6)
P(1)-Rh-N(1)	86.6(2)	N(1)-C(38)-C(39)	177.3(14)
P(1)-Rh-G[a]	131.66(18)	C(38)-C(39)-C(40)	117.8(14)
P(2)-Rh-N(1)	90.5(2)	C(38)-C(39)-C(41)	116.9(14)
P(2)-Rh-G[a]	130.54(18)	C(40)-C(39)-C(41)	125.2(11)
N(1)-Rh-G[a]	119.6(2)		

[a] G represents the centroid of the pentamethylcyclopentadienyl ring.

The Rh–P and Rh–G(Cp* centroid) bond lengths in **6a** do not significantly differ from the values reported in related analogous rhodium(III) half-sandwich complexes of the type $[(\eta^5\text{-}C_5Me_5)Rh\{(R)\text{-Prophos}\}L]^{2+}$ containing different oxygen-donor ligands (L = H_2O, methacrolein, tetrahydropyridine *N*-oxide, or *trans*-2-methyl-2-butenal (Rh–P 2.323–2.334(2), Rh–G 1.853–1.867(2) Å).[7b,13] However the Rh–N bond length, 2.067(7) Å is statistically shorter than the Rh–O bond lengths observed in these complexes (2.111–2.198(7) Å) indicating, in a first approximation, a stronger bonding interaction with the metal atom. This seems to be also the case in isoelectronic Ru^{II} complexes such as $[(\eta^5\text{-}C_5Me_5)Ru(dppe)(NCPh)]^+$ (Rh–N 2.027(5) Å),[19] $[(\eta^6\text{-}C_6H_6)Ru(dppe)(NCMe)]^{2+}$ (Rh–N 2.040(2) Å),[20] or $[(\eta^5\text{-indenyl})Ru(dppe)(NCMe)]^+$ (Rh–N 2.0488(14) Å).[21]

Bearing in mind the linearity of the Rh-N(1)-C(38)-C(39) fragment (see Table 5), the relative disposition of the methacrylonitrile ligand within the metal coordination sphere could be characterized by the torsion angle C_5Me_5-(centroid)-Rh···C(39)-C(40) that relates the plane around C(39) (alkene plane of the nitrile) to that of the sterically demanding C_5Me_5 ligand; a value of 74.5° has been observed in **6a** that is similar, although of different sign, to that reported in the related methacrolein or nitrone compounds $[(S_M,R_C)\text{-}[(\eta^5\text{-}C_5Me_5)Rh\{(R)\text{-Prophos}\}(L)]^{2+}$ where the plane of this coordinated olefinic molecule is close to a parallel disposition to the C_5Me_5 plane (−64.6(6)° for methacrolein, and −65.7(6)° for the nitrone).[7b] In these molecules, this nearly parallel disposition has been associated to the presence of a CH/π interaction that contributes to the restriction in the rotation of the alkene ligand and, consequently to the stabilization of a preferred conformation for this unsaturated substrate. Unfortunately, the limited quality of crystallographic data (high thermal parameters for nitrile carbon atoms and low precision for their respective hydrogen atoms) prevents a deeper discussion for **6a** of this particular aspect.

Stoichiometric reactions: At this point we envisaged that the catalytic results obtained in the DCR between nitrone **A** and methacrylonitrile **B** catalyzed by the Rh-Prophos system would be strongly influenced by the formation of the two epimers, **6a** and **6b**, and by the epimerization process that takes place between them. We realized that, under the catalytic conditions employed, both isomers of complex **6** were formed and, assuming that both are active in catalysis, enantioselectivity could be decreased if they induce differently. If so, enantioselectivity could be increased by using only one epimer of **6** as catalyst. Thus, we carried out the stoichiometric reaction between isolated complex **6a** and 3,4-dihydroisoquinoline *N*-oxide. After the appropriate reaction time, an excess of nBu_4NBr was added to dissociate the isoxazolidine formed, which was recovered in quantitative yield [Eq. (2)].



(2)

Table 6 collects the *ee* values obtained by working at different temperatures and in different solvents. The 3,5-*endo* adduct was selectively obtained in high enantioselectivity in all cases. Two facts merit comment. Employing pure **6a** instead of **6a**/**6b** mixtures, i) at room temperature, the *ee* increased from 52 to 77% in CH_2Cl_2 (entry 1, Table 6) and from 73 to 84% in THF (entry 6, Table 6) and, ii) as it can be seen in Table 6, enantioselectivity increases as temperature decreases.

Table 6. Stoichiometric reactions.

Entry	Solvent	*T*[°C]	*ee*[%]
1	CH_2Cl_2	RT	77
2	–	0	90
3	–	−25	94
4	–	−35	94
5	–	−50	95
6	THF	RT	84
7	–	0	91
8	–	−25	94
9	–	−50	95
10	acetone	−25	91.5
11	MeOH	−25	87.5

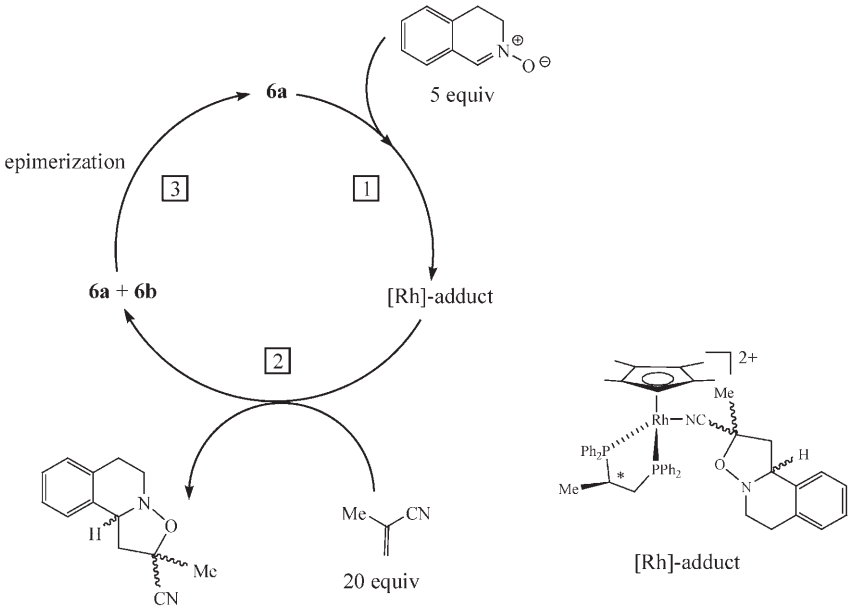
Similarly, pure iridium isomer **7a** reacts with 3,4-dihydroisoquinoline *N*-oxide in CH_2Cl_2, at room temperature, rendering regio- and diastereoselectively the 3,5-*endo* cycloadduct with an *ee* of 74%. This *ee* value is comparable to that obtained with the rhodium catalyst under the same conditions (entry 1, Table 6).

We also carried out the stoichiometric cycloaddition reaction with a **6a**/**6b** mixture as catalyst. Thus, when nitrone **A** was added to a 45:55 **6a**/**6b** molar ratio mixture in CH_2Cl_2, the 3,5-*endo* cycloadduct was obtained with an *ee* of 34.5 and 31% at −35 and −50 °C, respectively,[22] the most abundant enantiomer obtained being the same as that obtained when pure **6a** was employed. These results clearly indicated that *R*-at-metal epimers (**6b**, **7b**) also catalyze the cycloaddition reaction and they have either to be less enantioselective than the corresponding *S*-at-metal isomers **6a** and **7a**, or to preferentially render the antipode adduct.[23]

The observed increase in enantioselectivity on increasing the temperature (Table 2) or nitrone addition time (Table 4)

can be correlated to the relative increment of **6a**, at the expense of **6b**, under these conditions. Conversely, the poor performance of the iridium system in substoichiometric conditions, as compared to its rhodium counterpart (Table 1, entries 1 and 2), could be due to the reluctance of the iridium isomer **7b** to epimerize (see above). All these data supported a strong influence of the configuration at the metal on the stereochemistry of the catalytic outcome.

Recycling experiments: The data collected in Table 6 prove that pure **6a** is a highly enantioselective catalyst for the cycloaddition reaction we are studying. As methacrylonitrile reacts with the metallic fragment (η^5-C_5Me_5)Rh{(*R*)-Prophos} producing **6a**/**6b** mixtures, a catalytic substoichiometric reaction affords the adduct in up to 73% *ee* (see Table 3). Therefore, only stoichiometric amounts of the product can be prepared with high enantioselectivity (>90% *ee*). To increase the ratio of adduct/catalyst without loss of *ee*, we planned to carry out recycling experiments in repetitive batch mode. Scheme 6 shows the three steps of the procedure we have developed. In the first step, five equivalents of nitrone were added to diastereopure **6a**. After the required reaction time, the excess of nitrone was extracted in Et_2O/CH_2Cl_2 to avoid the simultaneous presence of nitrone, nitrile, and catalyst in the reaction medium. The adduct was dissociated from its rhodium complex by adding 20 equivalents of nitrile in the second step. Simultaneously, a **6a**/**6b** mixture was formed. The adduct and the excess of nitrile were extracted in Et_2O/CH_2Cl_2 and from the resulting solution the adduct was recovered. In the third step, the **6a**/**6b** mixture was allowed to epimerize to **6a**, which restarts a further catalytic run.



Scheme 6. Recycling experiments.

Following this experimental protocol at least ten consecutive catalytic runs can be performed with very similar results. Figure 2 shows the yield and enantioselectivity achieved in the 3,5-*endo* cycloadduct after reaction at 0°C for 15 h. Whereas the conversion slowly decreases along the runs from 97 (run 1) to 84% (run 10), the enantioselectivity remains essentially constant at around 90% *ee*. In summary, the procedure shown in Scheme 6 renders the catalytic reaction between nitrone **A** and nitrile **B** substoichiometric with an effective catalyst loading of 10 mol%. In total, the 3,5-*endo* cycloadduct is isolated in 90.5% yield and 90.6% *ee*.

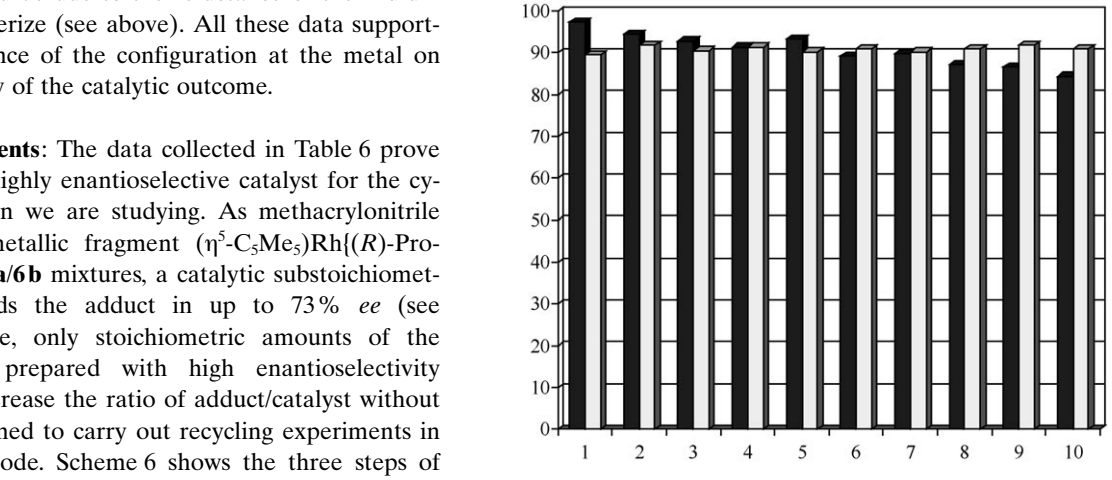


Figure 2. Recycling experiments. ■ = yield [%]; □ = *ee* [%].

Conclusion

The results reported herein reveal the important role that the characterization of the metallic intermediates involved in catalysis plays to optimize the performance of the catalytic system. Thus, the paper shows how, taking advantage of the knowledge of the relative abundance and stereochemistry of the metallic species present in the catalytic system, a moderate enantioselectivity can be improved to achieve an excellent level of selection. Furthermore, unexpected trends observed when temperature changes or when the speed of addition of reagents decreases can be appropriately addressed. Notably, a direct relationship between the configuration of the metal and the stereochemical outcome of the catalytic reaction can be es-

tablished. Finally, the highly enantioselective stoichiometric reaction can be carried out in a substoichiometric way.

Experimental Section

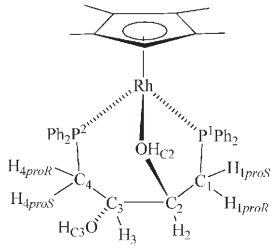
All solvents were dried over appropriate drying agents, distilled under argon, and degassed prior to use. All preparations were carried out under argon. Infrared spectra were obtained as KBr pellets with a Perkin–Elmer Spectrum One FTIR spectrophotometer. Carbon, hydrogen, and nitrogen analyses were performed by using a Perkin–Elmer 240 B microanalyzer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AV-300 (300.13 MHz), or Bruker AV-400 (400.16 MHz), or Bruker AV-500 (500.13 MHz) spectrometer. Chemical shifts are expressed in ppm upfield from $SiMe_4$. NOEDIFF and ^{1}H correlation spectra were obtained by using standard procedures. Analytical high-performance liquid chromatography (HPLC) was performed by using an Alliance Waters (Water 2996 PDA detector) instrument by using a Daicel Chiralpack AD-H (0.46 cm × 25 cm) chiral column. CD spectra were determined in solutions in dichloromethane in a 1-cm-path-length cell by using a Jasco-810 apparatus. Optical rotations were recorded on a Perkin–Elmer-241 polarimeter (10 cm cell, 589 nm).

Complexes (S_M,R_C)-[(η^5-C_5Me_5)M{(*R*)-Prophos}(H_2O)](SbF_6)$_2$ (M = Rh, Ir)[7b] and the nitrone 3,4-dihydroisoquinoline *N*-oxide[24] were prepared by using literature procedures. All other chemicals were obtained commercially.

[(η^5-C_5Me_5)Rh{(*S*,*S*)-Chiraphos}(H_2O)](SbF_6)$_2$ (3): To a suspension of [{(η^5-C_5Me_5)RhCl}$_2$(μ-Cl)$_2$] (100.0 mg, 0.162 mmol) in acetone (20 mL), $AgSbF_6$ (222.4 mg, 0.647 mmol) was added. The resulting suspension was stirred at room temperature for 15 h. The mixture was filtered over kieselguhr and the precipitate was washed with acetone (3 × 1 mL). The filtrate was concentrated to about 5 mL and cooled to −25 °C. Solid (*S*,*S*)-Chiraphos (138.2 mg, 0.324 mmol) was added. The solution was stirred at −25 °C for 15 min and 20 mL of hexanes was then added. The resulting orange oil was stirred at room temperature until it was converted to an orange solid, which was washed with hexanes three times and vacuum dried (331.6 mg, 89 %). ^{1}H NMR (400 MHz, CD_2Cl_2, −50 °C): δ = 8.0–7.0 (m, 20H; Ph), 3.56 (s br, 2H; H_2O), 2.80 (m, 1H; CH), 2.51 (m, 1H; CH), 1.40 (m, 3H; Me), 1.34 (s br, 15H; C_5Me_5), 1.11 ppm (m, 3H; Me); ^{13}C NMR (100.62 MHz, CD_2Cl_2, −50 °C): δ = 135.5–119.7 (Ph), 105.6 (s br, C_5Me_5), 39.3 (dd, J(P,C) = 32.3 Hz, J(Rh,C) = 16.8 Hz, CH), 34.2 (dd, J(P,C) = 32.9 Hz, J(Rh,C) = 14.6 Hz, CH), 14.1 (m, 2 × Me), 9.2 ppm (s, C_5Me_5); ^{31}P NMR (121.49 MHz, CD_2Cl_2, −50 °C): δ = 72.0 (dd, ^1J(Rh,P^1) = 127.2 Hz, J(P^2,P^1) = 45.2 Hz), 59.6 ppm (dd, ^1J(Rh,P^2) = 130.9 Hz); IR (KBr pellets): $\tilde{\nu}$ = 3480, 1700 (OH_2), 659 cm^{-1} (s) (SbF_6); elemental analysis calcd (%) for $C_{38}H_{45}F_{12}OP_2RhSb_2$: C 39.55, H 3.93; found: C 39.80, H 4.06.

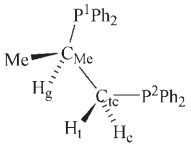
[(η^5-C_5Me_5)Rh{(*S*)-Binap}(NC(Me)C=CH_2)](SbF_6)$_2$ (4): To a suspension of [{(η^5-C_5Me_5)RhCl}$_2$(μ-Cl)$_2$] (100.0 mg, 0.162 mmol) in acetone (20 mL), $AgSbF_6$ (222.7 mg, 0.648 mmol) was added. The resulting suspension was stirred at room temperature for 15 h. The mixture was filtered through a cannula and the precipitate was washed with acetone (3 × 1 mL). To the filtrate methacrylonitrile (162.8 mL, 1.941 mmol) was added. The solution was stirred for 15 min, concentrated to about 5 mL, and cooled to −25 °C. Solid (*S*)-Binap (202.5 mg, 0.324 mmol) was added. The solution was stirred at −25 °C for 60 min and then for an additional period of 60 min at room temperature. After stirring, hexanes (20 mL) were added. The resulting yellow oil was stirred at room temperature until it was converted to a yellow solid, which was washed with hexanes three times and vacuum-dried (401.1 mg, 89 %). ^{1}H NMR (500 MHz, CD_2Cl_2, RT): δ = 7.0–8.1 (m), 6.72 (d, J = 8.8 Hz), 6.07 (d, J = 8.8 Hz) (36H; Binap); 5.65 (s), 4.37 (s) (2H; =CH_2), 1.33 ppm (pt, J = 3.65 Hz, 15H; C_5Me_5); ^{13}C NMR (125.77 MHz, CD_2Cl_2, RT): δ = 144–120 (aromatic carbons), 139.3 (s, =CH_2), 129.0 (d, ^2J(Rh,C) = 5.75 Hz, CN), 114.9 (s, *C*CN), 109.9 (dt, ^1J(Rh,C) = 5.8 Hz, ^2J(P,C) = 1.9 Hz, C_5Me_5), 18.6 (s, Me), 9.70 ppm (s, C_5Me_5); ^{31}P NMR (202.45 MHz, CD_2Cl_2, RT): δ = 37.9 (dd, ^1J(Rh,P^1) = 127.4 Hz, J(P^2,P^1) = 54.9 Hz), 24.3 ppm (dd, ^1J(Rh,P^2) = 128.2 Hz); IR (KBr pellets): $\tilde{\nu}$ = 2253 (m) (C≡N), 659 cm^{-1} (vs) (SbF_6); elemental analysis calcd (%) for $C_{58}H_{52}F_{12}NP_2RhSb_2$: C 49.78, H 3.75, N 1.00; found: C 49.53, H 3.93, N 0.97.

[(η^5-C_5Me_5)Rh{(*S*)-Hyphos}](SbF_6)$_2$ (5): To a suspension of [{(η^5-C_5Me_5)RhCl}$_2$(μ-Cl)$_2$] (100.0 mg, 0.162 mmol) in acetone (20 mL), $AgSbF_6$ (223.0 mg, 0.649 mmol) was added. The resulting suspension was stirred at room temperature for 15 h. The mixture was filtered through a cannula and the precipitate washed with acetone (3 × 1 mL). The filtrate was concentrated to about 5 mL and cooled down to −25 °C. Solid (*S*,*S*)-Diop (161.3 mg, 0.324 mmol) was added. The solution was stirred at −25 °C for 60 min and then for an additional period of 60 min at RT. After stirring, hexanes (20 mL) were added. The resulting orange oil was stirred at room temperature until it was converted to an orange solid, which was washed with hexanes three times and vacuum-dried (364.2 mg, 96 %). ^{1}H NMR (400 MHz, CD_2Cl_2, RT): δ = 8.25 (s br, 1H; OH_{C3}), 7.8–6.8 (m, 20H; Ph), 4.87 (dd, J = 25.25, 8.05 Hz, 1H; H_3), 3.83 (m, 1H; H_2), 3.56 (dd, J = 16.3, 11.9 Hz, 1H; H_{4proS}), 3.36 (dd, J = 3.8, 2.4 Hz, 1H; OH_{C2}), 3.07 (m, 1H; H_{4proR}), 2.50 (pt, J = 16.5, 1H; H_{1proS}), 2.15 (pt, J = 12.4, 1H; H_{1proR}), 1.43 ppm (pt, J = 3.7 Hz 15H; C_5Me_5); ^{13}C NMR (100.62 MHz, CD_2Cl_2, RT): δ = 133–122 (aromatic carbons), 106.6 (dpt, ^1J(Rh,C) = 6.1 Hz, ^2J(P,C) = 3.8 Hz, C_5Me_5), 76.3 (C_3), 62.2 (d, ^2J(Rh,C) = 6.1 Hz, C_2), 30.55 (d, J = 29.9 Hz, C_4), 30.4 (d, J = 23.8 Hz, C_1), 9.6 ppm (s, C_5Me_5); ^{31}P NMR (161.96 MHz, CD_2Cl_2, RT): δ = 52.0 (dd, ^1J(Rh,P^2) = 132.8 Hz, J(P^1,P^2) = 47.6 Hz), 13.9 ppm (dd, ^1J(Rh,P^1) = 134.75 Hz); IR (KBr pellets): $\tilde{\nu}$ = 3557 (br) (OH), 658 cm^{-1} (vs) (SbF_6); elemental analysis calcd (%) for $C_{38}H_{43}F_{12}O_2P_2RhSb_2$: C 39.07, H 3.71; found: C 38.84, H 3.53.



Catalytic procedure: The corresponding metallic complex **1**–**5** (0.03 mmol, 10.0 mol %) was dissolved in CH_2Cl_2 (3 mL) at room temperature. Methacrylonitrile (176.1 μL, 2.1 mmol) and 3,4-dihydroisoquinoline *N*-oxide (44.15 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) were added. After the mixture had been stirred at room temperature for the appropriate reaction time, hexane (20 mL) was added. The resulting suspension was filtered over Celite and the filtrate was evaporated to dryness. Regio and diastereoselectivity were determined for the crude mixture by ^{1}H NMR analysis in $CDCl_3$. The enantiomeric ratio was determined by HPLC analysis by using a Chiralpack AD-H column (85:15 hexane/2-propanol, 0.5 mL min^{-1}); major isomer t_r = 19.8 min and minor isomer t_r = 34.3 min.

[(η^5-C_5Me_5)M{(*R*)-Prophos}(NC(Me)C=CH_2)](SbF_6)$_2$ (M=Rh (6), Ir (7)): At −25 °C, under argon, to a solution of [(η^5-C_5Me_5)Rh{(*R*)-Prophos}(H_2O)](SbF_6)$_2$ (150.0 mg, 0.132 mmol) in CH_2Cl_2 (5 mL), methacrylonitrile (22.1 μL, 0.263 mmol) was added. The solution was stirred for 5 min. The addition of dry hexane (20 mL) to the yellow solution afforded a yellow solid, which was washed with hexanes and vacuum-dried (144.2 mg, 92 %). Composition: 45:55 Molar ratio **6a**/**6b**. The iridium analogue was prepared similarly. Yield 90 %. Composition: 67:33 molar ratio, **7a**/**7b**.



For the spectroscopic data of **6a** (S_{Rh},R_C isomer) see below.

6b (**R_{Rh},R_C isomer**): ^{1}H NMR (400 MHz, CD_2Cl_2, −25 °C): δ = 5.80 (s br, 1H; =CH*H*), 5.17 (s br, 1H; =C*H*H), 3.49, 3.24 (2 × m, 3H; H_c, H_t, H_g), 1.46 (s br, 15H; C_5Me_5), 1.40 (s br, 3H; nitrile Me), 1.11 ppm (dd, J = 15.0, 6.9 Hz, 3H; Me); ^{31}P NMR (161.96 MHz, CD_2Cl_2, −70 °C): δ = 79.0 (dd, ^1J(Rh,P^1) = 125.3, J(P,P) = 23.3 Hz, P^1), 64.8 ppm (dd, ^1J(Rh,P^2) = 124.3 Hz, P^2).

For the spectroscopic data of **7a** (S_{Ir},R_C isomer) see below.

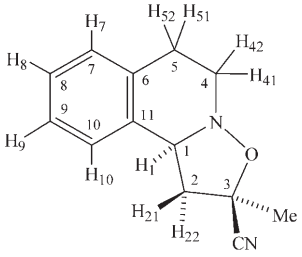
7b (R_{Ir},R_C isomer): ^{1}H NMR (500 MHz, CD_2Cl_2, 20 °C): δ = 5.79 (dq, J(H,H) = 1.7, 0.5 Hz, 1H; =CH*H*), 5.19 (sbr, 1H; =C*H*H), 3.48, 3.37, 3.25 (3×m, 3H; H_c, H_t, H_g), 1.56 (pt, ^3J(P,H) = 2.4 Hz, 15H; C_5Me_5), 1.41 (pt, J(H,H) = 1.7 Hz, 3H; nitrile Me), 1.25 ppm (dd, J = 15.4, 7.1 Hz, 3H; Me); ^{31}P NMR (202.45 MHz, CD_2Cl_2, 20 °C): δ = 42.1 (sbr, P^1), 29.7 ppm (sbr, P^2).

(S_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(NC(Me)C=CH_2)](SbF$_6$)$_2$ (6a): A 45:55 molar ratio mixture of **6a**/**6b** (100.0 mg) was dissolved in CH_2Cl_2 (10 mL). After stirring at room temperature for 1 h, the solution was concentrated to about 1 mL and then hexane (10 mL) was added. The resulting yellow solid (pure **6a**, S_{Rh},R_C isomer) was filtered off and vacuum-dried (97.0 mg, 97 %). ^{1}H NMR (400 MHz, CD_2Cl_2, 20 °C): δ = 7.9–7.3 (m, 20H; Ph), 5.92 (q, J(H,H) = 1.8 Hz, 1H; =C*H*H), 5.32 (sbr, 1H; =C*H*H), 3.43 (ptddd, J = 53.4, 16.7, 4.8, 2.2 Hz, 1H; H_c), 3.04 (m, 1H; H_g), 2.63 (ptpt, J = 15.4, 5.8, 1H; H_t), 1.54 (pt, ^3J(P,H) = 3.5 Hz, 15H; C_5Me_5), 1.53 (3H; nitrile Me, overlapped with the C_5Me_5 signal), 1.34 ppm (ddd, J = 13.5, 6.6, 0.7 Hz, 3H; Me); ^{13}C NMR (100.62 MHz, CD_2Cl_2, 20 °C): δ = 139.95 (s, =CH_2), 134–119 (Ph), 128.5 (d, J = 5.85 Hz, CN), 114.8 (s, *C*CN), 107.4 (dpt, ^1J(Rh,C) = 5.1, ^2J(P,C) = 2.2 Hz, C_5Me_5), 32.4 (dd, J(P,C) = 34.0, J(P,C) = 14.3 Hz, C_{tc}), 32.2 (dd, J(P,C) = 31.8, J_{PC} = 10.6 Hz, C_{Me}), 18.9 (s, nitrile Me), 15.1 (dd, ^2J(P,C) = 17.9, ^3J(P,C) = 5.5 Hz, Me), 9.2 ppm (s, C_5*Me$_5$*); ^{31}P NMR (161.96 MHz, CD_2Cl_2, 20 °C): δ = 75.0 (dd, ^1J(Rh,P^1) = 121.4, J(P,P) = 35.7 Hz, P^1), 45.9 ppm (dd, ^1J(Rh,P^2) = 125.8 Hz, P^2); IR (KBr pellets): $\tilde{\nu}$ = 2257 (m) (C≡N), 658 cm^{-1} (vs) (SbF$_6$); elemental analysis calcd (%) for $C_{41}H_{46}F_{12}NP_2RhSb_2$: C 41.41, H 3.90, N 1.18; found: C 41.31, H 3.59, N 0.98.

(S_{Ir},R_C)-[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(NC(Me)C=CH_2)](SbF$_6$)$_2$ (7a): A 67:33 molar ratio solid mixture of **7a**/**7b** (101.3 mg) was dissolved in acetone (10 mL). After stirring at 50 °C for 5 h, the solution was concentrated to about 1 mL and then hexane (10 mL) was added. The resulting yellow solid (pure **7a**, S_{Ir},R_C isomer) was filtered off and vacuum-dried (yield 96.5 mg, 95 %). ^{1}H NMR (500 MHz, CD_2Cl_2, 20 °C): δ = 7.9–7.2 (m, 20H; Ph), 5.86 (q, J(H,H) = 1.7 Hz, 1H; =C*H*H), 5.22 (sbr, 1H; =C*H*H), 3.43 (dddd, J = 48.9, 16.1, 11.5, 5.0 Hz, 1H; H_c), 3.01 (m, 1H; H_g), 2.63 (ptdd, J = 15.4, 6.85, 4.9, 1H; H_t), 1.60 (pt, ^3J(P,H) = 2.3 Hz, 15H; C_5Me_5), 1.48 (pt, J(H,H) = 1.3 Hz, 3H; nitrile Me), 1.37 ppm (ddd, J = 14.4, 6.6, 1.0 Hz, 3H; Me); ^{13}C NMR (125.77 MHz, CD_2Cl_2, 20 °C): δ = 140.75 (s, =CHH), 134–119 (Ph), 123.8 (s, CN), 114.55 (s, *C*CN), 101.9 (sbr, C_5Me_5), 33.1 (dd, J(P,C) = 39.8, J(P,C) = 11.9 Hz, C_{tc}), 32.4 (dd, J(P,C) = 37.3, 7.6 Hz, C_{Me}), 19.0 (s, nitrile Me), 14.3 (dd, ^2J(P,C) = 17.8, ^3J(P,C) = 4.2 Hz, Me), 8.5 ppm (s, C_5*Me$_5$*); ^{31}P NMR (202.45 MHz, CD_2Cl_2, 20 °C): δ = 41.05 (d, J(P,P) = 10.7 Hz, P^1), 15.7 ppm (d, P^2); IR (KBr pellets): $\tilde{\nu}$ = 2260 (m) (C≡N), 658 cm^{-1} (vs) (SbF$_6$); elemental analysis calcd (%) for $C_{41}H_{46}F_{12}IrNP_2Sb_2$: C 38.52, H 3.63, N 1.10; found: C 38.31, H 3.85, N 1.23.

Stoichiometric reactions: To 4 mL of an approximately 7.5×10^{-2} mol L^{-1} solution of (S_M,R_C)-[(η^5-C_5Me_5)M{(*R*)-Prophos}(NC(Me)C=CH_2)](SbF$_6$)$_2$ (M = Rh (**6a**), Ir (**7a**)) under the conditions (temperature and solvent) indicated in Table 6, five equivalents of the nitrone 3,4-dihydroisoquinoline *N*-oxide were added. The solution was stirred for 3 (room temperature), 15 (0 °C), 24 (−25 °C), or 48 h (−50 °C), respectively, at the corresponding temperature and then an excess (ca. 5 equiv) of nBu$_4$NBr in CH_2Cl_2 (1 mL) was added. The solution was concentrated under vacuum to dryness and the residue was extracted with diethyl ether/CH_2Cl_2 5:1 (3×5 mL). The resulting solution was evaporated to dryness and the colorless oil obtained was analyzed and characterized by using NMR and HPLC techniques. Quantitative yield.

2-cyano-2-methyl-1,5,6,10b-tetrahydro-isoxazolo[3,2-*a*]isoquinoline: The residue was purified by column chromatography over silica gel with hexane/AcOEt 80:20 v/v to provide 2-cyano-2-methyl-1,5,6,10b-tetrahydro-isoxazolo[3,2-*a*]isoquinoline as a white solid. Optical data (*ee* = 90 %): $[\alpha]_D^{23} = -145.5$ (c = 1.02 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) 7.3–7.1 (m, 4H; H_7-H_{10}), 4.71 (pt, 1H; H_1), 3.50, 3.43 (2×m, 2H; H_{51}, H_{52}), 2.99 (pt, 1H; H_{21}), 3.13, 2.91 (2×m, 2H; H_{41}, H_{42}), 2.77 (dd, J(H,H) = 12.7, 7.6 Hz, 1H; H_{22}), 1.76 ppm (s, 3H; Me); ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 133.4, 133.0, 128.6, 127.4, 127.1, 126.6 (C_6-C_{11}), 122.2 (CN), 74.1 (C_3), 63.5 (C_1), 48.7 (C_4), 48.6 (C_2), 28.9 (C_5), 26.8 ppm (Me); CD (CH_2Cl_2, 1.2×10^{-3} M, RT): λ ($\Delta\varepsilon$) = 263 (+0.17), 271 (+0.15).



Kinetic experiments: A 45:55 molar ratio mixture of **6a**/**6b** (19.8 mg) was dissolved in CD_2Cl_2 (0.6 mL) in a 5-mm NMR tube. The probe was kept at 10 °C and rate data were acquired (12 spectra/45 min). The concentrations of **6a** and **6b** were assayed by integration of the =C*H*H resonance at δ = 5.29 ppm (**6a**) and δ = 5.25 ppm (**6b**). Reaction rate was obtained from the least-squares fitting of the intensity decrease of the δ = 5.25 ppm (**6b**) ^{1}H NMR signal as a function of time.

Recycling experiments: To enantiopure (S_{Rh},R_C)-[(η^5-C_5Me_5)Rh{(*R*)-Prophos)}(NC(Me)C-CH_2)](SbF$_6$)$_2$ (**6a**) (100.0 mg, 0.084 mmol) in CH_2Cl_2 (4 mL), 3,4-dihydroisoquinoline *N*-oxide (61.9 mg, 0.420 mmol) was added. The resulting solution was stirred for 15 h, at 0 °C and was then vacuum-evaporated to dryness. The residue was washed with an Et_2O/CH_2Cl_2 9:1 v/v mixture (10×7 mL) to eliminate the excess of nitrone. To the remaining solid dissolved in CH_2Cl_2 (4 mL), methacrylonitrile (141.0 μL, 1.682 mmol) was added. After stirring for 4 h at 0 °C, the solution was concentrated under reduced pressure to dryness. The residue was extracted with an Et_2O/CH_2Cl_2 9:1 v/v mixture (10×7 mL) and the solution was concentrated under vacuum to dryness. Yield and enantiomeric purity of this solid was determined by the usual methods. The residue of the extraction, which consisted of **6a**/**6b** mixtures enriched in the first component, was dissolved in CH_2Cl_2 (4 mL) and the solution was stirred for 1 h at room temperature to complete epimerization to **6a**. Addition of 3,4-dihydroisoquinoline *N*-oxide (61.9 mg, 0.420 mmol) to this solution intitated the next catalytic run.

Determination of the molecular structure of compound 6a by X-ray diffraction: Preparation of a suitable sample required several attempts scanning over different crystallization conditions. In most cases the crystalline material obtained was of a very small size. Several samples were checked by using the diffractometer, but showed, in general, broad mosaicity and very weak intensities. Eventually a tiny (0.075×0.061×0.016 mm) weakly diffracting crystal grown by slow diffusion of *n*-hexane into a solution of **6a** in dichloromethane was selected for data collection. Preliminary indexing of reflections revealed the presence of a minor twinned crystal, but subsequent integration was carried out without considering its presence. Intensity data were collected at low temperature (100(2 K)) on a Bruker SMART CCD area detector diffractometer equipped with graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) by using narrow frames (0.3° in ω). Cell parameters were refined from the observed setting angles and detector positions of strong reflections (2297 reflns, $2\theta <$ 39.6°). Data were corrected for Lorentz and polarization effects, and multiscan absorption corrections were applied with the SADABS program.[25]

The structure was solved by the Patterson method and was completed by successive difference Fourier syntheses (SHELXS-86).[26] Refinement, by full-matrix least-squares on F^2 with SHELXL97,[26] was carried out including isotropic and subsequent anisotropic displacement parameters for all non-hydrogen atoms. At this stage, a dichloromethane partially disordered molecule was also observed in the crystal structure; one of the chloride atoms was refined in two complementary positions (0.684 versus 0.316(9) occupancies). In the late stages of refinement some atoms showed some inconsistencies in their displacement parameters and some feeble restraints were necessary (DELU and ISOR applied to C(1), C(11), C(35), and C(36)) to keep these parameters within reasonable values. All hydrogen atoms in the metal complex were included in the refinement in calculated positions and were refined with riding positional

and thermal parameters. All the highest electronic residuals (smaller than 1.37 e Å^{-3}) were observed in close proximity of the Sb or Rh atoms and have no chemical significance.

Crystal data for 6a: $C_{41}H_{46}F_{12}NP_2RhSb_2{\cdot}CH_2Cl_2$, $M_r = 1274.06$; yellow irregular block, $0.075 \times 0.061 \times 0.016$ mm^3; monoclinic, $P2_1$; $a = 13.1332(9)$, $b = 13.2461(9)$, $c = 14.0183(9)$ Å, $\beta = 100.8490(10)°$; $Z = 2$; $V = 2395.1(3)$ Å^3; $\rho_{calcd} = 1.767$ g cm^{-3}; $\mu = 1.717$ mm^{-1}, min and max transmission factors 0.794 and 0.976; $2\theta_{max} = 54.0°$; 22347 reflections collected, 10244 unique ($R_{int} = 0.0612$); number of data/restraints/parameters 10244/20/576; final GoF 1.063, $R_1 = 0.0667$ (8037 reflections, $I > 2\sigma(I)$), $wR_2 = 0.1246$ for all data. The absolute configuration was determined on the basis of previously known internal reference ((*R*)-Prophos) and was confirmed by using the Flack parameter ($x = -0.02(3)$.[27] CCDC-655302 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**.
[2] a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), *Vol I–III*, Springer, New York, **1999,** and Suppl. 1 and 2, Springer, New York, **2004**; b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim, **2000**; c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, **1994**.
[3] a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, Hoboken, New Jersey, **2003**, pp. 1–83; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 867–883; c) M. Frederickson, *Tetrahedron* **1997**, *53*, 403–425; d) J. J. Tufariello in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Pawda), Wiley, New York, **1984**, Chapter 9, pp. 83–167.
[4] K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, 1449–1458.
[5] J. Tanaka, S. Kanemasa, *Tetrahedron* **2001**, *57*, 899–905.
[6] K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1994**, *59*, 5687–5691.
[7] a) F. Viton, G. Bernardinelli, E. P. Kündig, *J. Am. Chem. Soc.* **2002**, *124*, 4968–4969; b) D. Carmona, M. P. Lamata, F. Viguri, R. Rodríguez, L. A. Oro, F. J. Lahoz, A. I. Balana, T. Tejero, P. Merino, *J. Am. Chem. Soc.* **2005**, *127*, 13386–13398.
[8] D. Carmona, C. Cativiela, R. García-Correas, F. J. Lahoz, M. P. Lamata, J. A. López, M. P. López-Ram de Víu, L. A. Oro, E. San José, F. Viguri, *Chem. Commun.* **1996**, 1247–1248.
[9] C. White, S. J. Thompson, P. M. Maitlis, *J. Chem. Soc. Dalton Trans.* **1977**, 1654–1661.
[10] See for example: a) D. Carmona, C. Vega, F. J. Lahoz, S. Elipe, L. A. Oro, M. P. Lamata, F. Viguri, R. García-Correas, C. Cativiela, M. P. López-Ram de Víu, *Organometallics* **1999**, *18*, 3364–3371; b) A. Davenport, D. L. Davies, J. Fawcett, S. A. Garratt, D. R. Russell, *J. Chem. Soc. Dalton Trans.* **2000**, 4432–4441; c) J. W. Faller, B. J. Grimmond, D. G. D'Alliessi, *J. Am. Chem. Soc.* **2001**, *123*, 2525–2529; d) Y. Takahashi, S. Hikichi, M. Akita, Y. Moro-oka, *Chem. Commun.* **1999**, 1491–1492; e) B. Therrien, T. R. Ward, *Angew. Chem.* **1999**, *111*, 418–421; *Angew. Chem. Int. Ed.* **1999**, *38*, 405–408.
[11] S. Borns, R. Kadyrov, D. Heller, W. Baumann, A. Spannenberg, R. Kempe, J. Holz, A. Börner, *Eur. J. Inorg. Chem.* **1998**, 1291–1295.
[12] SK. A. Ali, J. H. Khan, M. I. M. Wazeer, *Tetrahedron* **1988**, *44*, 5911–5920.
[13] a) D. Carmona, C. Cativiela, R. García-Correas, F. J. Lahoz, M. P. Lamata, J. A. López, M. P. López-Ram de Víu, L. A. Oro, E. San José, F. Viguri, *Chem. Commun.* **1996**, 1247–1248; b) D. Carmona, M. P. Lamata, F. Viguri, R. Rodríguez, T. Fischer, F. J. Lahoz, I. T. Dobrinovitch, L. A. Oro, *Adv. Synth. Catal.* **2007**, *349*, 1751–1758.
[14] a) D. Carmona, M. P. Lamata, F. Viguri, R. Rodríguez, L. A. Oro, A. I. Balana, F. J. Lahoz, T. Tejero, P. Merino, S. Franco, I. Montesa, *J. Am. Chem. Soc.* **2004**, *126*, 2716–2717; b) S. Kezuka, N. Ohtsuki, T. Mita, Y. Kogami, T. Ashizawa, T. Ikeno, T. Yamada, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2197–2207.
[15] The ligand priority sequence η^5-$C_5Me_5 > P(1) > P(2) > N$ has been used to assign the configuration to the rhodium atom: a) C. Lecomte, Y. Dusausoy, J. Protas, J. Tirouflet, A. Dormond, *J. Organomet. Chem.* **1974**, *73*, 67–76; b) K. Stanley, M. C. Baird, *J. Am. Chem. Soc.* **1975**, *97*, 6598–6599; c) T. E. Sloan, *Top. Stereochem.* **1981**, *12*, 1–36.
[16] *Nomenclature of Inorganic Chemistry* (Ed.: G. J. Leigh), Blackwell, Oxford, **1991**.
[17] D. Cremer, J. A. Pople, *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
[18] I. T. Dobrinovitch, PhD thesis, Universidad de Zaragoza (Spain), **2007**.
[19] R. L. Cordiner, D. Albessa-Jove, R. L. Roberts, J. D. Farmer, H. Pushmann, D. Corcoran, A. E. Goeta, J. A. K. Howard, P. J. Low, *J. Organomet. Chem.* **2005**, *690*, 4908–4919.
[20] W. Lackner, C. M. Standfest-Hauser, K. Mereiter, R. Schmid, K. Kirchner, *Inorg. Chim. Acta* **2004**, *357*, 2721–2727.
[21] K. S. Singh, C. Thone, M. R. Kollipara, *J. Coord. Chem.* **2006**, *59*, 333–341.
[22] At these temperatures epimerization of **6b** to **6a** is negligible. Therefore, the isomeric composition of the catalyst remains unchanged during catalysis.
[23] Assuming a similar catalytic rate for both epimers, the calculated enantioselectivity for **6b** is about 14 and 21% *ee*, at −35 and −50 °C, respectively, but in the adduct of opposite configuration.
[24] S.-I. Murahashi, T. Shiota, Y. Imada, *Org. Synth.* **2002**, *9*, 632–636.
[25] SAINT+, Software for CCD Diffractometers, Bruker AXS, Madison, WI, **2000**. G. M. Sheldrick, SADABS, Program for Correction of Area Detector Data, University of Göttingen, Göttingen (Germany), **1999**.
[26] SHELXTL Package (Version 6.10), Bruker AXS, Madison, WI, **2000**. G. M. Sheldrick, SHELXS-86 and SHELXL-97, University of Göttingen, Göttingen (Germany), **1997**.
[27] a) H. D. Flack, *Acta Crystallogr. Sect. A* **1983**, *A39*, 876–881; b) G. Bernardelli, H. D. Flack, *Acta Crystallogr. Sect. A* **1985**, *A41*, 500–511.

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