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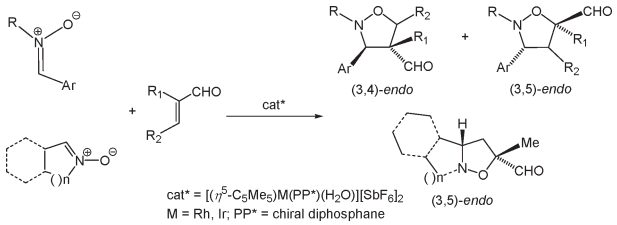

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Asymmetric 1,3-dipolar cycloaddition reactions between enals and nitrones catalysed by half-sandwich rhodium or iridium diphosphane complexes

Ainara Asenjo, Fernando Viguri,* M. Pilar Lamata, Ricardo Rodríguez, María Carmona, Luis A. Oro and Daniel Carmona*

The aqua complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (M = Rh, Ir; PP* = chiral diphosphane) catalyse the asymmetric 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated aldehydes. Enantioselectivity up to 99% ee was achieved.

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Catalysis Science & Technology

PAPER

Asymmetric 1,3-dipolar cycloaddition reactions between enals and nitrones catalysed by half-sandwich rhodium or iridium diphosphane complexes†

Cite this: DOI: 10.1039/c4cy01533a

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Received 21st November 2014,
Accepted 4th February 2015

DOI: 10.1039/c4cy01533a

www.rsc.org/catalysis

The aqua complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (M = Rh, Ir; PP* = chiral diphosphane) have been tested as catalysts for the asymmetric 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated aldehydes. Quantitative conversions with very high regioselectivity, perfect *endo* selectivity and excellent enantioselectivity (up to 99% ee) were achieved. The stereochemical outcome was analyzed on the basis of the stereoelectronic properties of the intermediate enal complexes of the formula $[(\eta^5\text{-}C_5Me_5)M(PP^*)(enal)][SbF_6]_2$.

Introduction

Among the wide variety of asymmetric organic syntheses, cycloadditions are highly attractive processes which allow the construction of several new stereogenic centres with stereochemical control in a single step.[1] In particular, the 1,3-dipolar cycloaddition reaction (DCR) constitutes an efficient approach for the preparation of five-membered heterocyclic rings[2] that complements the hetero-Diels–Alder reaction.

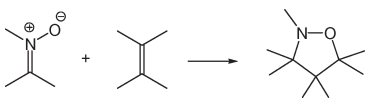
One of the most studied DCRs has been the cycloaddition of nitrones to alkenes (Scheme 1)[2,3] probably due to the fact that the resulting optically active isoxazolidines can be easily converted into biologically active compounds such as amino alcohols, amino acids, alkaloids and β-lactams.[3b,4] Moreover, contrary to other 1,3-dipoles, most nitrones are stable compounds that do not require *in situ* formation.[4b]

However, in sharp contrast to the wide application of metal complexes as catalysts in asymmetric Diels–Alder cycloadditions,[5] enantioselective versions of DCR catalysed by metallic compounds are very scarce.[2,3] The first example of transition-metal catalysed asymmetric DCR between alkenes and nitrones was reported in 1994 by Gothelf and Jørgensen.[6] In this work, alkenoyloxazolidinones were employed as alkenes (Chart 1) and the authors argued that κ^2O,O' chelation to the metal of this type of alkene was much more favoured compared to the coordination of the nitrone.[7] Bidentate chelate coordination activates the alkene for a normal electron-demand DCR and fixes the coordination plane of the prochiral dipolarophile, making good stereoselection possible. Consequently, most research in this field was focused on bidentate dipolarophiles such as alkenoyloxazolidinones.[2,3]

However, in 2002, Kündig *et al.* showed that enals, which are monodentate dipolarophiles, can be activated by properly tuned one-point binding iron and ruthenium complexes toward the asymmetric catalytic DCR with nitrones. Highly enantioenriched isoxazolidines were obtained in high yield.[8] In the same year, Yamada's group published that a cationic cobalt(III) complex containing an optically active β-ketoiminato ligand catalysed the DCR of enals and nitrones to afford the corresponding isoxazolidines in high yield with excellent *endo* selectivity and high enantioselectivity.[9]

A number of reports dealing with this class of DCR have been since then published. Thus, Kündig, Yamada, Kanemasa, Maruoka and Doyle have reported on the use of chiral diphosphinito/M(II) (M = Fe, Ru),[10] β-ketoiminato/cobalt(III),[11] DBFOX/M(II) (M = Ni, Mg, Zn or Co),[12] BINOL/Ti(IV),[13] and carboxamidate/dirhodium(II/III)[14] complexes, respectively, as catalysts for this kind of reaction.

In this context, we have developed catalytic systems based on chiral cationic half-sandwich complexes of the general



Scheme 1 DCR between nitrones and alkenes.

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic characterization data of the 1,3-dipolar cycloaddition catalytic results. See DOI: 10.1039/c4cy01533a

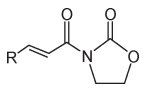


Chart 1 3-Alkenoyloxazolidinones.

formula $[(\eta^n\text{-ring})M(L^1L^2)^*(H_2O)]^{2+}$ (M = Rh(III), Ir(III), Ru(II); $(L^1L^2)^*$ = chiral bidentate ligand) which are well suited for the DCR of alkenes and nitrones.[7c,15] In particular, notable results have been obtained with catalysts based on the chiral fragment $(\eta^5\text{-}C_5Me_5)M\{(R)\text{-prophos}\}$ (M = Rh(III), Ir(III)) for the DCR between enals[7c,15a,c] or methacrylonitrile[15d,e] and nitrones. These 16 e^- metallic fragments exhibit several remarkable structural features.[7c,15a,c] First, they coordinate enals in a completely diastereoselective fashion; only (S_M,R_C)-$[(\eta^5\text{-}C_5Me_5)M\{(R)\text{-prophos}\}(enal)]^{2+}$ diastereomers are detected (Scheme 2a). Therefore, a single catalyst will be present in the reaction medium. Second, the five-membered M–P–C–C–P chelate, formed through the coordination of the (*R*)-prophos ligand, displays a λ conformation, with the methyl substituent occupying a pseudo-equatorial position (Scheme 2b). The resulting stereochemistry determines the chiral bias of the catalyst pocket where the enal is located and, therefore, where catalysis will take place. Third, coordinated enals adopt an *s-trans* conformation and an *E* configuration around the carbonyl double bond (Scheme 2a). Finally, the M–O rotamer is fixed by attractive CH/π interactions established between a phenyl group of the diphosphane and the aldehyde proton. In summary, these fragments are well suited to act as enantioselective catalysts for organic processes involving enals. In fact, excellent enantiomeric excesses have been obtained in the cycloaddition reactions of cyclopentadiene[16] or nitrones[7c,15a] to enals.

We anticipated that, most probably forced by the bulky C_5Me_5 ring, the substituent on the diphosphane backbone determines the M–P–C–C–P chelate conformation. Therefore, it would play a key role in defining the geometry of the catalyst chiral pocket by tuning the spatial disposition of the four PPh_2 phenyl groups. Thus, studying the influence of substituents bulkier than methyl on the stereoselection of the abovementioned cycloaddition reactions will be interesting. In this line, we have recently reported that complexes of the general formula $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ [M = Rh(III), Ir(III); PP* = (*R*)-phenphos, (*R*)-benphos, (*R*)-valphos, (*R*)-cyphos] (**1–8**), in which phenyl, benzyl, isopropyl or cyclohexyl substituents replace the methyl group of the (*R*)-prophos ligand (Scheme 3), generate efficient systems for the Diels–Alder reaction between methacrolein and cyclopentadiene. Enantiomeric excesses up to 96% were obtained.[17]

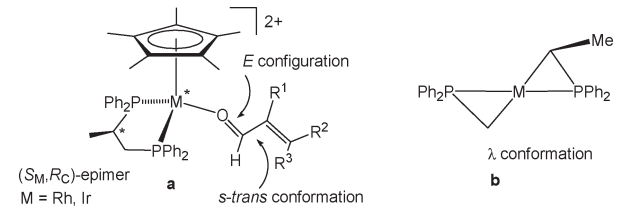
On the other hand, when catalysts based on the chiral fragment $(\eta^5\text{-}C_5Me_5)M(R)$-prophos were applied to the 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxide to methacrylonitrile, low enantiomeric excesses were obtained.[15d,e] When methacrylonitrile coordinates the metallic chiral fragment, two epimers at the metal are formed and it has been shown that each epimer induces the preferential formation of each one of the two enantiomers of the cycloaddition product.[15d] Hence, the configuration of the metal governs the stereochemical outcome. However, despite the fact that methacrolein complexes containing the diphosphane ligand (2*R*,4*R*)-norphos (Scheme 3) were also obtained as a mixture of the two epimers at the metal, they gave rise to the most enantioselective systems for the Diels–Alder reaction between methacrolein and cyclopentadiene. In this case, it has been shown that the configuration of the diphosphane controls the sign of the enantioselectivity of the cycloadduct.[17]

With all these concerns in mind, in the present paper, we report on the application of well-defined chiral diphosphane compounds **1–10** (Scheme 3) to the DCR of the nitrones depicted in Scheme 4 to the α,β-unsaturated aldehydes methacrolein, acrolein, *trans*-crotonaldehyde and *trans*-2-methylbutenal. The influence of the substituent on the backbone of the chiral diphosphane as well as the role of the stereogenic centres (metal and diphosphane) in controlling the enantioselectivity will be studied. The resulting selectivity will be rationalized on the basis of the structural parameters determined for the model cationic methacrolein intermediates $[(\eta^5\text{-}C_5Me_5)M(PP^*)(enal)][SbF_6]_2$ (M = Rh, Ir) whose molecular structures have been previously reported.[7c,15a,c,17]

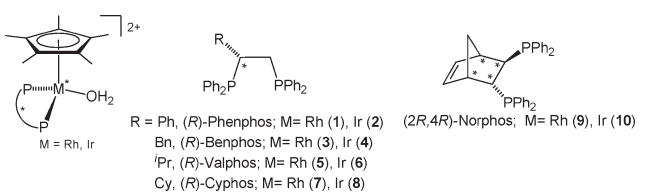
Results and discussion

DCR of nitrones Ia and V to methacrolein

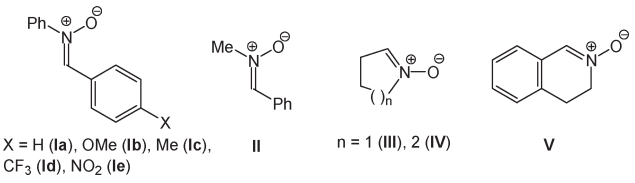
First, the activity of the aqua complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (**1–10**, Scheme 3) for the DCR of linear *N*-benzylideneaniline *N*-oxide (**Ia**) and cyclic 3,4-dihydroisoquinoline *N*-oxide (**V**) nitrones (Scheme 4) to methacrolein was tested. Table 1 lists a selection of the results together with the reaction conditions employed. The collected results are the average of at least two comparable reaction runs. Catalysts were *in situ* prepared by treatment of the aqua



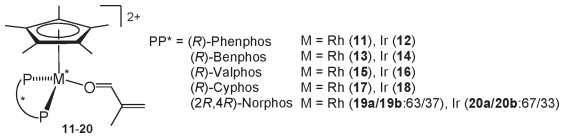
Scheme 2 (a) Coordinated enal complexes. (b) λ Conformation of the M–P–C–C–P chelate.



Scheme 3 Chiral diphosphane rhodium and iridium precursor catalysts.



Scheme 4 Employed nitrones.



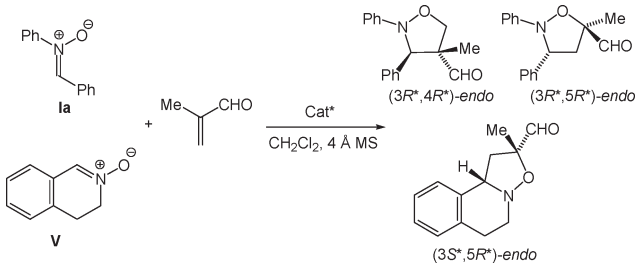
precursors **1–10** with an excess of methacrolein, in the presence of 4 Å MS, before the nitrones were added. The cyclic nitrone **V** was added over a 10 h period to avoid undesired nitrone coordination.[7c] Catalytic conditions were selected according to the results obtained upon applying the (*R*)-prophos analogues of complexes **1–10** as catalysts.[7c,15c] Under these conditions, the methacrolein complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(methacrolein)][SbF_6]_2$ (**11–20**, eqn (1)) were the sole metallic complexes present in solution according to NMR measurements. Moreover, the preparation of complexes **11–18** was completely diastereoselective; the epimer of the *S* configuration at the metal was the only isomer detected. However, for complexes **19** and **20**, which contain the (2*R*,4*R*)-norphos ligand, a mixture of diastereomers, S_{Rh}-**19**/R_{Rh}-**19** and S_{Ir}-**20**/R_{Ir}-**20** in 63/37 and 67/33 molar ratios, respectively, was formed.[17]

According to the data listed in Table 1, iridium catalysts are slightly more active and selective than the rhodium-based homologues. Typically, quantitative conversions are observed after 15–25 hours of reaction at −25 °C. Reactions with the linear nitrone **Ia** were, in general, faster than those with the cyclic nitrone **V**. Perfect *endo* selectivity was obtained in all cases. While with nitrone **Ia** the 3,4-*endo* regioisomer was preferably formed, the 3,5-*endo* isomer was the sole product obtained with nitrone **V**. In most cases good ee values were achieved. In particular, the best enantioselectivity was achieved when catalysts based on the diphosphanes (*R*)-cyphos and (2*R*,4*R*)-norphos were used (entries 7–10 and 18–20).

DCR of nitrones Ib–Ie, II, III and IV to methacrolein

The high enantioselectivity shown by the (*R*)-cyphos (**7**, **8**) and (2*R*,4*R*)-norphos (**9**, **10**) complexes prompted us to study their catalytic activity in the DCR of nitrones **Ib–Ie**, **II–IV**

Table 1 Enantioselective DCR of nitrones **Ia** and **V** to methacrolein[a]



Entry[a]	Catalyst precursor	Nitrone	t^b (h)	Conv.[c,d] (%)	3,4/3,5 (*endo*)[d]	ee[e] (%)
1	**1** (Rh/phenphos)	**Ia**	15	94	61/39	76/36
2	**2** (Ir/phenphos)		15	100	75/25	74/39
3	**3** (Rh/benphos)		15	100	62/38	86/66
4	**4** (Ir/benphos)		15	100	75/25	88/73
5	**5** (Rh/valphos)		15	97	62/38	82/70
6	**6** (Ir/valphos)		15	98	78/22	86/78
7	**7** (Rh/cyphos)		15	79	62/38	90/78
8	**8** (Ir/cyphos)		15	100	77/23	91/84
9	**9** (Rh/norphos)		15	100	66/34	95/83
10	**10** (Ir/norphos)		15	100	81/19	96/85
11	**1** (Rh/phenphos)	**V**	25	82	—/100	64
12	**2** (Ir/phenphos)		15	90	—/100	70
13	**3** (Rh/benphos)		25	70	—/100	77
14	**4** (Ir/benphos)		15	100	—/100	80
15	**5** (Rh/valphos)		25	85	—/100	68
16	**6** (Ir/valphos)		15	97	—/100	84
17	**7** (Rh/cyphos)		25	100	—/100	84
18	**8** (Ir/cyphos)		15	100	—/100	98
19	**9** (Rh/norphos)		25	83	—/100	92
20	**10** (Ir/norphos)		15	90	—/100	97

[a] Reaction conditions: catalyst 0.06 mmol (5 mol%), methacrolein 8.4 mmol, 100 mg of 4 Å molecular sieves, and nitrone 1.2 mmol in 4 mL of CH_2Cl_2, at −25 °C. [b] Total reaction time; addition of the cyclic nitrone **V** was accomplished over 10 h. [c] Based on nitrone. [d] Determined by ^{1}H NMR. [e] Determined by integration of the corresponding ^{1}H NMR signals of the diastereomeric (*R*)-(+)-methylbenzylimine derivatives (nitrone **Ia**) or with the use of the chiral shift reagent Eu(hfc)$_3$ (nitrone **V**).

(Scheme 4) to the same enal. Table 2 lists a selection of the results.

Isoxazolidines were obtained with perfect *endo* diastereoselectivity. Perfect or almost perfect 3,5-regioselectivity was achieved with nitrones **II–IV**. Good ee values were achieved in all cases.

DCR of nitrone Ia to other enals

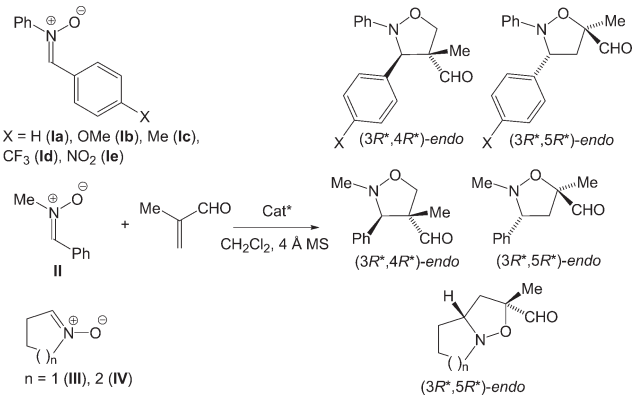
Finally, the study was extended to the DCR of nitrone **Ia** to the enals acrolein, *trans*-crotonaldehyde and *trans*-2-methylbutenal employing complexes **7–10** as catalyst precursors. Table 3 collects the results obtained together with the reaction conditions. Catalysts were prepared *in situ* by treating the aqua precursors $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (**7–10**) with an excess of the corresponding enal in the presence of 4 Å MS.

The DCR catalytic outcome was very sensitive to the nature of the dipolarophile. The rate and selectivity of the reaction were strongly affected by the presence of substituents in the α- or β-position. Probably due to steric reasons, the rate decreased with substitution and, in particular, low conversions were obtained (≤40%) after three days at −25 °C with α,β-disubstituted *trans*-2-methylbutenal (entries 9 and 10). Perfect *endo* diastereoselectivity was observed and, in contrast to methacrolein, only 3,4-regioisomers were obtained for these enals (see entries 7–10, Table 1). In general, good to excellent ee values were achieved. The highest enantioselectivity was reached for acrolein when the norphos complexes **9** and **10** were employed as catalyst precursors (entries 3 and 4).

Diastereo- and regioselectivity

The observed preference for the selective formation of *endo* cycloadducts is in good agreement with the previous studies on Lewis acid catalysed cycloaddition reactions.[10a,d,18,19] Regioselectivity is controlled by both steric and electronic factors.[2e,20] With electron deficient alkenes, such as enals, coordination of the carbonyl oxygen to the metallic Lewis acid should make the β-carbon of the enal more electrophilic. Accordingly, the attack of the nitrone oxygen should become more favoured at the β-position rendering 3,4-regioisomers (Scheme 5a).[18,19] In our case, electronically controlled

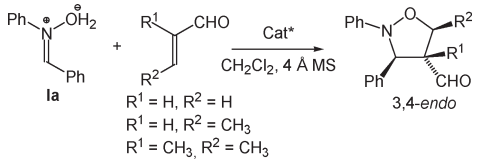
Table 2 Enantioselective DCR of nitrones **Ib–Ie**, **II–IV** to methacrolein[a]



Entry[a]	Catalyst precursor	Nitrone	t^b (h)	Conv.[c,d] (%)	3,4/3,5 (*endo*)[d]	ee[e] (%)
1	**7** (Rh/cyphos)	**II**	24	61	2/98	90
2	**8** (Ir/cyphos)			91	1/99	95
3	**9** (Rh/norphos)			95	1/99	98
4	**10** (Ir/norphos)			99	1/99	99
5	**7** (Rh/cyphos)	**III**	15	80	—/100	80
6	**8** (Ir/cyphos)			89	—/100	75
7	**9** (Rh/norphos)			81	—/100	70
8	**10** (Ir/norphos)			86	—/100	80
9	**7** (Rh/cyphos)	**IV**	15	100	—/100	94
10	**8** (Ir/cyphos)			100	—/100	95
11	**9** (Rh/norphos)			100	—/100	92
12	**10** (Ir/norphos)			100	—/100	95
13	**10** (Ir/norphos)	**Ib**	15	100	97/3	93/—
14	**10** (Ir/norphos)	**Ic**	15	99	94/6	96/—
15	**10** (Ir/norphos)	**Ia**	15	100	81/19	96/85
16	**10** (Ir/norphos)	**Id**	15	99	46/54	96/81
17	**10** (Ir/norphos)	**Ie**	15	21	30/70	96/83

[a] Reaction conditions: see footnote of Table 1. Reactions with nitrone **II** were carried out at −10 °C. [b] Total reaction time; addition of the cyclic nitrones **III** and **IV** was accomplished over 10 h. [c] Based on nitrone. [d] Determined by ^{1}H NMR. [e] Determined by integration of ^{1}H NMR signals of the diastereomeric (*R*)-(+)-methylbenzylimine (nitrones **Ib–Ie**, **II**) or (*S*)-mandelic acid (nitrone **IV**) derivatives, or by using the chiral shift reagent Eu(hfc)$_3$ (nitrone **III**).

Table 3 Enantioselective DCR of enals to nitrone I[a]



Entry[a]	Catalyst precursor	Enal	t^b (h)	Conv.[c,d] (%)	e. e.[e] (%)
1	**7** (Rh/cyphos)		16	100	81
2	**8** (Ir/cyphos)		16	100	90
3	**9** (Rh/norphos)		16	100	96
4	**10** (Ir/norphos)		16	100	98
5	**7** (Rh/cyphos)		72	85	63
6	**8** (Ir/cyphos)		25	100	79
7	**9** (Rh/norphos)		16	100	91
8	**10** (Ir/norphos)		25	89	93
9	**8** (Ir/cyphos)[e]		72	31	72
10	**10** (Ir/norphos)[e]		72	37	85

[a] Reaction conditions: catalyst 0.03 mmol (5 mol%), enal 4.2 mmol, 100 mg of 4 Å molecular sieves and nitrone 0.6 mmol in 4 mL of CH_2Cl_2, at −25 °C. [b] Based on nitrone. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] Catalyst 0.06 mmol (10 mol%).

3,4-regioisomers were obtained for the diarylnitrones **I** (see Tables 1–3). In this line, the 3,4-*endo*/3,5-*endo* ratio correlates with the electron-donor ability of the substituents on the nitrone. While electron-donor substituents give high 3,4/3,5 ratios (entries 13 and 14, Table 2), the amount of the 3,4-regioisomer strongly diminishes in the presence of electron-withdrawing groups (entries 16 and 17, Table 2).

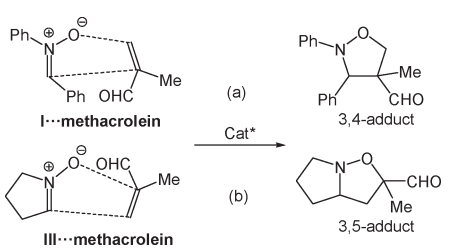
However, DFT studies carried out on the BH_3-catalysed reaction between cyclic 1-pyrrolidine *N*-oxide (**III**) and methacrolein, performed by Salvatella *et al.*,[19] predict the preferential formation of 3,5-*endo* cycloadducts. This preference has been attributed to the occurrence of a stabilizing (possibly electrostatic) interaction between the oxygen dipole and the carbonyl carbon from the polarophile (Scheme 5b). This proposal accounts for the experimental results reported in the present paper collected in Tables 1 and 2.

Enantioselectivity

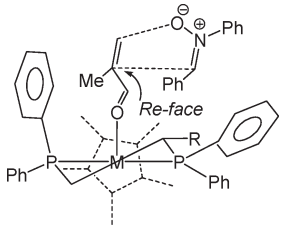
As stated in the Introduction, the intermediate enal complexes **11–18** present a highly stable S_M,R_C absolute configuration, the M–P–C–C–P chelate exhibits a λ conformation and the coordinated enal adopts an *s-trans* conformation and an *E* configuration around the carbonyl double bond. Furthermore, the M–O rotamer is fixed by attractive CH/π interactions established between a phenyl group of the chiral diphosphane and the aldehyde proton. As a result, the C_α-*Re*-face of the enal is more accessible to the nitrone approach than the C_α-*Si*-face which is sheltered by one phenyl ring of the diphosphane (Scheme 6).

The absolute configuration determined[21] for the major 3,4-adduct of the reaction between methacrolein and nitrone **Ia** was 3*R*,4*R*-*endo*,[7c] that for the major adduct of methacrolein with nitrones **III** and **IV** was 3*R*,5*R*-*endo*,[8] and that with nitrone **V** was 3*S*,5*R*-*endo*.[8] Finally, the absolute configuration of the major 3,4-*endo* adduct of the reaction between *trans*-crotonaldehyde and nitrone **Ia** was 3*S*,4*R*,5*S*.[15c] In all cases, the absolute configuration of the adducts implies a nitrone approach to the C_α-*Re*-face of the enal, which is in good agreement with the conclusion from the structural studies.

The excellent enantioselectivities achieved for the norphos derivatives strongly indicate that, as for the Diels–Alder reaction between methacrolein and cyclopentadiene,[17] enantioselectivity is not governed by the configuration at the metal but by that of the chiral ligand. Therefore, both metal epimers induce a preferential nitrone attack through the C_α-*Re*-face of the coordinated enal, affording equally configured cycloadducts.



Scheme 5 Regioselectivity in DCR of nitrones to methacrolein.



Scheme 6 Proposed model of the nitrone **Ia** approach to the more accessible C_α-*Re*-face of the coordinated methacrolein.

Conclusions

In summary, the aqua complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (M = Rh, Ir; PP* = chiral diphosphane) catalyse efficiently the DCR between a variety of nitrones and enals. In the corresponding catalytic intermediate complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(enal)][SbF_6]_2$, the enal is confined into the chiral pocket formed by the metal surrounded by the $\eta^5\text{-}C_5Me_5$ group and the chiral diphosphane ligand. The resulting stereoelectronic features of the coordinated enal favour a highly regioselective, *endo* attack of the nitrone, preferentially through the C_α-*Re*-face of the enal. Cycloadducts with perfect *endo* diastereoselectivity, high or perfect regioselectivity and enantioselectivity up to 99% were obtained. The presence of substituents different from methyl on the backbone of the diphosphane maintains yields and regioselectivities. Enantioselectivities were significantly improved especially by the cyphos ligand. Excellent ee values were achieved for the norphos derivatives, in which enantioselectivity is controlled not by the metal but by the chiral diphosphane.

Experimental section

General comments

All solvents were dried over appropriate drying agents, distilled under argon and degassed prior to use. All preparations have been carried out under argon. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-300 (300.13 MHz), Bruker AV-400 (400.16 MHz) or Bruker AV-500 (500.13 MHz) spectrometer. Chemical shifts are expressed in ppm upfield from $SiMe_4$. Analytical high performance liquid chromatography (HPLC) was performed on an Alliance Waters (Water 2996 PDA detector) instrument using a chiral column, Daicel Chiralcel OD-H (0.46 cm × 25 cm) or Chiralpak AD-H (0.46 cm × 25 cm).

The complexes $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (**1–10**) were prepared according to literature procedures.[17]

Catalytic procedure

At −25 °C, the corresponding metallic complex $[(\eta^5\text{-}C_5Me_5)M(PP^*)(H_2O)][SbF_6]_2$ (0.03 or 0.06 mmol, 5 or 10 mol%) was dissolved in CH_2Cl_2 (3 mL). A freshly distilled enal (4.20 mmol) and 50 or 100 mg of activated 4 Å molecular sieves were added and the suspension was stirred for 30 min. A solution of the corresponding nitrone (0.60 mmol) in CH_2Cl_2 (1 mL) was added. Cyclic nitrones (**III–V**) were added dropwise using a syringe pump over 10 h. After stirring at the corresponding temperature for the appropriate reaction time, 20 mL of hexane was added. After filtration over Celite, the solution was evaporated to dryness. The residue was purified by chromatography (SiO_2). Conversion and regioselectivity were determined on the crude mixture by ^1H NMR analysis in C_6D_6 (nitrones **I**, **II** and **V**) or in $CDCl_3$ (nitrones **II** and **IV**). Enantioselectivity was determined by NMR or HPLC analysis (see footnote of Tables S1–S3; for details see the ESI†).

Acknowledgements

We thank the Ministerio de Economía y Competitividad of Spain (CTQ2012-32095) and Gobierno de Aragón (Grupo Consolidado: Catalizadores Organometálicos Enantioselectivos) for financial support. A. A. acknowledges IUCH for a grant. R. R. acknowledges CSIC and European Social Fund for a JAE grant. M. C. acknowledges Gobierno de Aragón and CSIC for a DGA grant.

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21 The absolute configuration of the major 3,4-*endo* cycloadduct derived from the DCR of methacrolein to nitrone **Ia** (3*R*,4*R*), that of the major 3,5-*endo* adducts with nitrones **III** (3*R*,5*R*), **IV** (3*R*,5*R*) and **V** (3*S*,5*R*) and that of the major 3,4-*endo* adduct of the reaction between *trans*-crotonaldehyde and nitrone **Ia** (3*S*,4*R*,5*S*) have been established by comparing their NMR and HPLC data (detailed in the ESI†) with those reported in the literature ref. 7*c*, 8, and 15*c*.