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Asymmetric hydrogen-transfer reduction of prochiral and α,β-unsaturated ketones by iridium complexes containing optically pure aminodiphosphine ligands

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Abstract

This work reports the catalytic reduction, via hydrogen-transfer from propan-2-ol, of various α,β-unsaturated ketones or unsymmetrical ketones in the presence of $[Ir(COD)(OMe)]_2$ and the chiral aminodiphosphine ligands (*R*)-$PhC^*H(Me)N(CH_2CH_2PR_2)_2$ (R = Ph, Cy) and (*R*)-(Et)$C^*H(Me)N(CH_2CH_2PPh_2)_2$. In general, these catalyst systems show good activity but modest enantioselectivity. Both the chemoselectivity and the enantioselectivity for the reduction of α,β-unsaturated ketones to optically pure allylic alcohols depend on the nature of the substituent(s) at either the carbon stereocentre or the phosphorus substituents.

Keywords: Hydrogen-transfer reduction; Prochiral ketones; Asymmetric catalysis; Aminodiphoshine ligands; Iridium

1. Introduction

Optically pure alcohols, particularly allylic alcohols, are excellent organic synthons for structural elaborations leading to various biologically active molecules. This chemical versatility constitutes the main reason for the increasing research efforts that are being directed to design and develop efficient routes to optically pure alcohols [1–4]. Homogeneous catalysis using chiral metal complexes is the route of major interest as it may provide large amounts of chiral products at low cost and also allow the obtainment of specifically tailored products through the fine tuning of either the metal complex or substrate.

Unlike prochiral saturated ketones that can be reduced asymmetrically with various transition metal catalysts through hydrogenation, hydrosilylation and hydrogen transfer [1,5–8], α,β-un-

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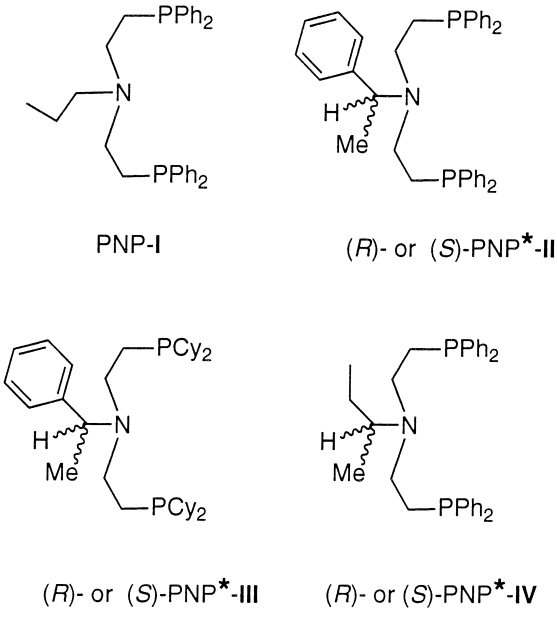
saturated ketones require a precise combination of reaction conditions and ligand/metal systems for their chemo- and/or enantioselective transformation into allylic alcohols [1]. Indeed, most successful catalytic reactions have been performed under hydrogen transfer conditions from secondary alcohols (e.g. propan-2-ol) with metals of the iron- and cobalt-triads coordinated by polydentate ligands [6,9–12]. Most of the effective systems comprise iridium in association with mixed-donor ligands containing both hard (N, O) and soft (P) donor atoms [1,11]. The presence of nitrogen donors reflects the compatibility with the mechanistic peculiarity of the C=O reduction as in the typical hydrogen-transfer reaction, the coordination sphere of the metal comprises hard donor ligands (e.g. nitrogen and alkoxy) and no change in the formal metal oxidation state is apparently required [1]. In turn, phosphorus donors strengthen the inherent basicity of iridium thus favouring the migration of the terminal hydride to the electrophilic C=O carbon atom [9,12]. Finally, the polydentate co-ligands are of fundamental importance for both chemo- and enantioselectivity as they combine a rigid stereochemical control (to disfavour the approach of the substrate via the C=C double bond) with the creation of efficient and easily tunable chiral pockets.

In earlier work, we have shown that the achiral ligand *n*-$C_3H_7N(CH_2CH_2PPh_2)_2$ (PNP-**I**) and the chiral ligands (*R*)- and (*S*)-$PhC^*H(Me)N(CH_2CH_2PPh_2)_2$ (PNP*-**II**) react with $[Ir(COD)(OMe)]_2$ in propan-2-ol forming excellent catalysts for the chemoselective reduction of the C=O functional group in α,β-unsaturated ketones [10,12]. Using the chiral ligand (*R*)-PNP*-**II**, asymmetric induction was also achieved to give moderate enantioselectivities (the ee's for the reduction of benzylideneacetone did not exceed 54%) [12]. More recently, we have reported the synthesis and characterization of other chiral aminodiphoshine ligands, namely (*R*)- and (*S*)-$PhC^*H(Me)N(CH_2CH_2PCy_2)_2$ (PNP*-**III**) and (*R*)- and (*S*)-$EtC^*H(Me)N(CH_2CH_2PPh_2)_2$



Scheme 1. Molecular sketches of the chiral PNP* ligands.

(PNP*-**IV**), that differ from PNP*-**II** in the substituent(s) at either the stereogenic carbon atom or the phosphorus atoms (Scheme 1) [13].

Herein, we report the results of a study in which the ligands (*R*)-PNP*-**II**, (*R*)-PNP*-**III** and (*R*)-PNP*-**IV** have been employed, in association with $[Ir(COD)(OMe)]_2$, for the hydrogen transfer reduction of various unsymmetrical and α,β-unsaturated ketones. The information obtained has contributed to expand our knowledge of the factors that govern the chemo- and enantioselectivity of these reactions by PNP*/Ir catalysis.

2. Experimental

2.1. Experimental procedure

In a typical experiment, a three-necked thermostatted glass reactor equipped with a condenser, an argon inlet, a rubber septum and a

Table 1
Reduction of ketones with $[Ir(COD)(OMe)]_2$ + PNP-**IV**

entry	substrate	conversion (%)	selectivity (%)	e.e. (%) (config.)
1	$PhCH=CHCOCH_3$	84	51	21 (R)
2		20	46	0
3	$PhCOCH_3$	66	-	0
4	$PhCOCH_2CH_3$	69	-	0
5	$PhCH_2COCH_3$	85	-	0
6	CyCOPh	53	-	5 (R)
7	$(CH_3)_2CHCH_2COCH_3$	32	-	5 (S)

Table 3
Reduction of ketones with $[Ir(COD)(OMe)]_2$ + PNP-**II**

entry	substrate	time (hours)	conversion (%)	selectivity (%)	e.e. (%) (config.)
1[a)]	$PhCH=CHCOCH_3$	45 min	83	92	33 (R)
2[a)]		7	52	100	17 (S)
3[a)]	$PhCOCH_3$	3	87	-	4 (R)
4	$PhCOCH_2CH_3$	5 (6)	79 (83)	-	5 (S)
5	$PhCH_2COCH_3$	2 (3)	88 (96)	-	3 (S)
6	CyCOPh	5	32	-	6 (R)
7	$(CH_3)_2CHCH_2COCH_3$	5 (7)	66 (75)	-	15 (14) (S)

magnetic bar was charged under an argon flow with propan-2-ol (35 ml). Addition of $[Ir(COD)(OMe)]_2$ (0.01 mmol) [14] was followed by addition of the PNP* ligand (0.02 mmol). The resulting pale yellow solution was heated to 60°C. After this mixture was stirred for 10 min at 60°C, the substrate (1 mmol) was added.

2.2. Analytical methods

Product yields and ee's were determined by GC using a Hewlett-Packard 5890 II gas-chromatograph equipped with a MEGADEX DMP β capillary column (25 m $\times$ 0.25 mm, film depth 0.25). Absolute configurations were determined by comparing optical rotations (measured with a Perkin-Elmer 241 polarimeter) to reference data from the literature. Other experimental details are provided in Tables 1–3 that also summarize the results obtained.

Table 2
Reduction of ketones with $[Ir(COD)(OMe)]_2$ + PNP-**III**

entry	substrate	conversion (%)	selectivity (%)	e.e. (%) (config.)
1	$PhCH=CHCOCH_3$	63	63	5 (S)
2		10	28	4 (R)
3	$PhCOCH_3$	72	-	30 (R)
4	$PhCOCH_2CH_3$	55	-	29 (R)
5	$PhCH_2COCH_3$	37	-	12 (S)
6	CyCOPh	11 (49)	-	57 (30) (R)
7	$(CH_3)_2CHCH_2COCH_3$	4 (36)	-	9 (15) (S)

3. Results and discussion

The reduction of benzylideneacetone to the corresponding allylic alcohol or saturated ketone is catalyzed by all the PNP*/Ir systems under investigation. These, however, exhibit quite different efficiency, chemoselectivity and enantioselectivity. The most active system is provided by (*R*)-PNP*-**II** that gives good conversion (83% in 45 min), good chemoselectivity in allylic alcohol (92%), but moderate ee (33% in the *R* alcohol) (Table 1, entry 1). Substitution of the phenyl substituents at phosphorus for cyclohexyl groups in the ligand (*R*)-PNP*-**III** dramatically decreases the conversion, the chemoselectivity and, especially, the enantioselectivity as the ee is only 5% in the *S* enantiomer (Table 2, entry 1). When, however, the structural change in the PNP* ligand regards the substituents at the stereogenic carbon atom as in (*R*)-PNP*-**IV**, both the chemoselectivity (from 92 to 51%) and the enantioselectivity in allylic alcohol (from 33 to 21%) decrease significantly (Table 3, entry 1). In all the reactions where benzylideneacetone is reduced with low chemoselectivity, the saturated ketone is reduced very slowly to the saturated alcohol. A similar trend is observed for the reduction of 3-methyl-2-cyclohexen-1-one for which (*R*)-

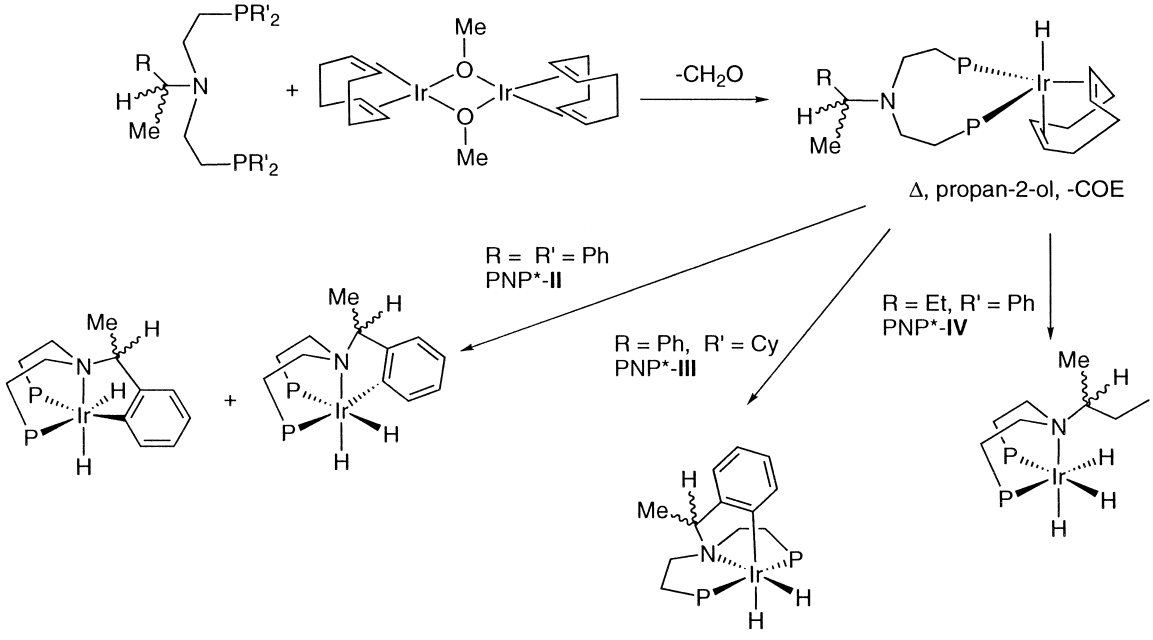
PNP*-**II** again provides the best results in every sense (see entry 2 in Tables 1–3). This α,β-unsaturated ketone, however, is not as easily reducible as benzylideneacetone.

Various unsymmetrical ketones have been examined. The conversions to the corresponding alcohols are not too sensitive to the structure of the chiral ligand, though a decrease in the order PNP*-**II** > PNP*-**IV** > PNP*-**III** may be noticed. The ee's are generally very low for PNP*-**II**, nonexistent for PNP*-**IV** and moderate for PNP*-**III**. The bulkiness and flexibility of the cyclohexyl substituents seem to be the factors that control the catalytic activity of the (*R*)-PNP*-**III**/Ir system in terms of both conversion and enantioface discriminatiom (vide infra). In particular, the reduction of the sterically demanding cyclohexyl phenyl ketone that is achieved with low conversion (11%) but with rather good ee (57%) reflects the structural affinity between substrate and chiral ligand (Table 2, entry 6).

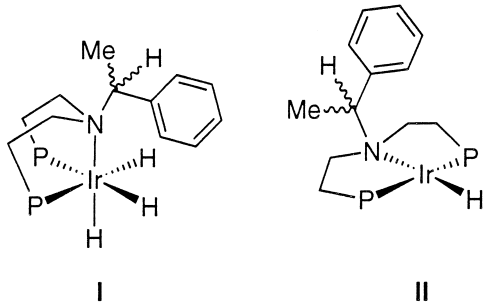
In all cases, monitoring of the ee with time showed the absence of racemization of the allylic alcohols in the experimental conditions considered. Ee's of reaction mixtures were observed to slowly decrease for prolonged times, however.

From a perusal of the catalytic data, one may readily infer that phenyl substituents at either the stereogenic carbon atom or the phosphorus donors have a positive influence on both the rate of reduction and the transfer of chirality, particularly in the case of α,β-unsaturated ketones. The reasons for this beneficial effect are evident as one looks at the different reactivity of the PNP* ligands towards $[Ir(COD)(OMe)]_2$ in propan-2-ol [13]. They all are capable of cleaving the methoxy bridges to form mononuclear Ir(COD)hydrido intermediate species. These, however, show distinct reactions with propan-2-ol (Scheme 2).

With PNP*-**IV**, a trihydride complex is obtained, which is fairly stable with respect to the reductive elimination of H_2 as a thermal step. In contrast, with PNP*-**II** and PNP*-**III**, (*o*-metalated)dihydride species are formed that structurally differ from each other only in the conformation of the tridentate ligand, e.g. meridional or facial. It has experimentally been



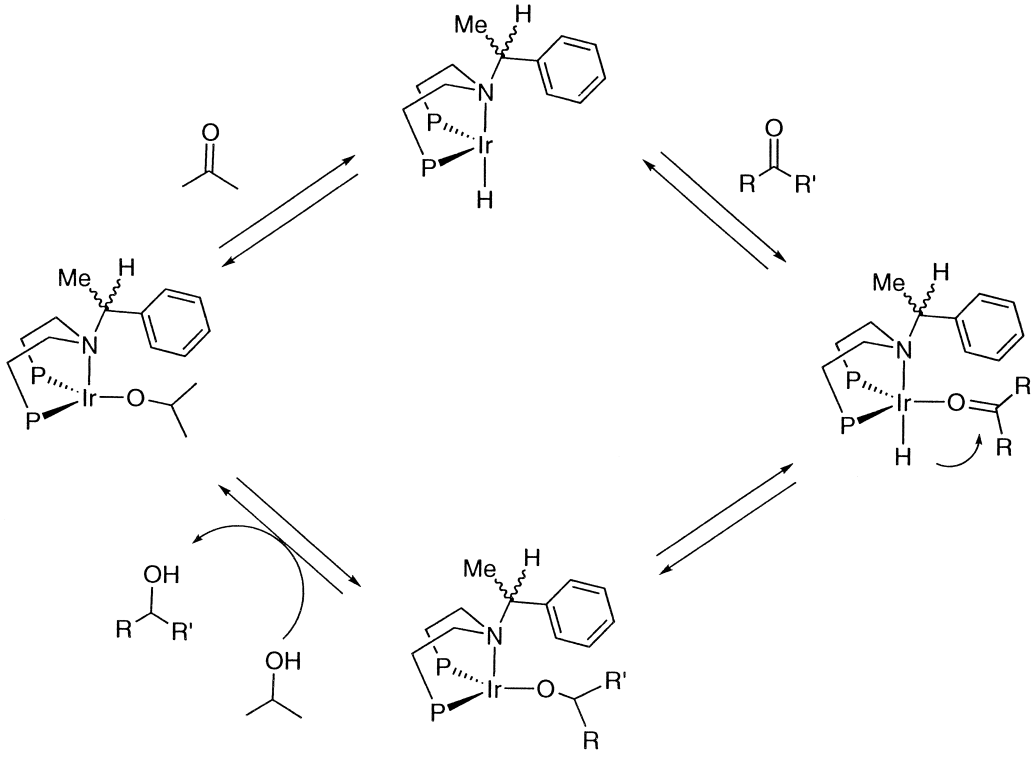
Scheme 2. Reactivity pattern of $[Ir(COD)(OMe)]_2$ with the various PNP* ligands.



Scheme 3. Possible geometries of the 16e$^-$ fragment [IrH(PNP*-**II**)].

proved that the intramolecular C–H insertion reaction is reversible [12,13]. The de-orthometalation reaction occurring in solution, however, generates transient monohydrido complexes with different structure and stereochemistry depending on the PNP* ligand. The steric hindrance provided by the cyclohexyl substituents on the phosphorus atoms forces PNP*-**III** to adopt a *mer* conformation [13]. Accordingly, the resulting 16e$^-$ Ir(I) monohydrido species has a square-planar structure with the chiral substituent rather away from the expected site of reduction (see structure **II** in Scheme 3). In contrast, the de-orthometalation reaction undergone by the PNP*-**II** derivative produces a 'butterfly-shaped' 16e$^-$ fragment **I** [13] that has a higher energy as compared to the square-planar one [15,16] and also contains the chiral appendage closer to the site of reduction [12].

Based on these simple structural and electronic considerations as well as the mechanism previously proposed for the reduction of benzylideneacetone by PNP*-**II**/Ir (Scheme 4) [12], one may try to rationalize, even though qualitatively, the different catalytic activity exhibited by the present PNP* ligands. In particular, the major efficiency of the PNP*-**II** system may be related to the larger equilibrium concentration of the catalytically active species in the reaction mixture (e.g. the electronically and co-



Scheme 4. Proposed reaction mechanism for the hydrogen transfer reduction of ketones catalyzed by [IrH(PNP*-**II**)].

ordinatively unsaturated species [IrH(PNP*)] [12]). Indeed, PNP*-**II** forms neither a stable trihydride complex, like that with PNP*-**IV**, nor a square-planar species, like that with PNP*-**II** (Scheme 3). Square-planar d^8 metal complexes are generally stable and do not easily interact with weak ligands such as ketones [17] unless energy is provided to induce a structural change towards the butterfly conformation with C_s symmetry.

As for the transfer of chiral information to the alcohol products, we believe that a crucial role is played by the substituent(s) at either the stereocentre or the P atoms. In particular, the combination of cyclohexyl and phenyl substituents, as in PNP*-**III**, seems to be appropriate to effectively orientate the more flexible ketones bearing alkyl and phenyl substituents (Table 2). Following this concept, the PNP-**II** ligand bearing exclusively phenyl substituents would be (and actually it is) suited for a better interaction with the structurally rigid α,β-unsaturated ketones, especially benzylideneacetone for which phenyl–phenyl stacking effects may also be important [10].

Finally, the exclusive presence of alkyl substituents on the carbon stereocentre apparently detracts qualities for asymmetric catalysis (Table 3). This may be due to various causes, which include the lack of efficient stacking with the phenyl groups of the ketones as well as the lack of intramolecular C–H activation (due to the higher thermodynamic barrier to insertion into sp^3-hybridized C–H bonds [18,19]) that in the PNP*-**II** and PNP*-**III** iridium complexes contributes to bring the stereocentre near to the site of reduction.

4. Conclusions

Iridium in association with three different chiral aminodiphosphine ligands has been used to reduce various unsymmetrical or α,β-unsaturated ketones via hydrogen transfer from propan-2-ol. It has been found that the substituents at either the carbon stereocentre or the phosphorus donors in the aminodiphosphine ligands determine both the efficiency and the chemo-/enantioselectivity of the catalysts generated in situ by reaction with $[Ir(COD)(OMe)]_2$. These catalyst systems show good activity but quite modest enantioselectivity, however. Since the poor enantioface discrimination might be related to the position of the stereocentre with respect to the site of reduction (see also Ref. [20]), it would appear that, for effective production of asymmetric catalysis, the chiral auxiliary be positioned closer to the phosphorus donors. We are at present pursuing these studies with a new generation of PNP* ligands having the stereocentre(s) incorporated into the P–N arms.

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