Tetrahedron Vol 47, No 10/11, pp 1965-1976, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00
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EFFECT OF CHARGE DISTRIBUTION ON SELECTIVE HYDROGENATION OF CONJUGATED ENONES CATALYZED BY IRIDIUM COMPLEXES.

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(*Received in UK* 16 *November* 1990)

Abstract

Chemoselectivity in the reduction of substituted conjugated enones catalyzed by iridium/phosphine systems appears to be slightly dependent on the charge distribution around the carbonyl group of the substrates: electron withdrawing groups enhance the reduction rate of the ketonic function. Enantioselectivity, in the case of the catalytic system studied, appears to be related essentially to the steric hindrance in the substrate.

Introduction

Selective reduction of polyfunctional substrates is a key step in the synthesis of many products of interest, and in the last decade several stoichiometric and catalytic systems have been developed to this purpose.
A great number of hydride reducing agents have been used and their properties studied with several functional groups[1]. The reduction of the carbonyl group in the presence of a conjugated olefinic bond is possible with a variety of stoichiometric hydrides, in particular much attention has been devoted to the synthesis of optically active allylic alcohols, which are important chiral building blocks, by means of chiral stoichiometric reagents[2]. Catalytic selective reductions of conjugated enones are more difficult to achieve, nevertheless high yields in allylic alcohol have been obtained in homogeneous phase in the hydrogenation of benzylideneacetone catalyzed by H_3IrP_3 (P = tertiary phosphine)[3]. Asymmetric hydrogenation of the same compound by using $[Ir(S\text{-prolophos})_2]^+$ [S-prolophos= (S)-(-)-N-(diphenylphosphino)-2-diphenylphosphinooxymethylpyrrolidine] gave the allylic alcohol in high yield and 30% e e [4].
Selectivity is clearly a function of steric and electronic interactions between reducing agent and substrate Depending on the system used, the former or the latter or a combination of both can determine the preferential course of the reaction.
Following our previous work mentioned above, we decided to undertake a study on the influences of such parameters and in particular of charge

distribution in the substrate on selectivity in the hydrogenation of various enones in the presence of iridium/phosphine catalysts.
The present work is meant to give some clues about the nature of the catalytic species and the interactions which occur around the metal centre, so as to enable us to gain a better understanding of the factors controlling selectivity in these systems.

Results and discussion

Table 1 reports results obtained in the hydrogenation of various enones catalyzed by $[Ir(cod)(OMe)]_2$ (cod= 1,5-cyclooctadiene) + PEt_2Ph with P/Ir=10. This system was chosen because of its good selectivity in the reduction of the C=O bond of benzylideneacetone[3]. Selectivity in the unsaturated alcohol increases with olefinic bond substitution (runs 1-3, Table 1), and it is higher in the case of alkyl-aryl substrates like benzylideneacetone (run 4), but it drops in the reduction of benzylideneacetophenone (chalcone, run 5).

Table 1
Hydrogenation of enones catalyzed by $[Ir(cod)(OMe)]_2$ + PEt_2Ph[a]

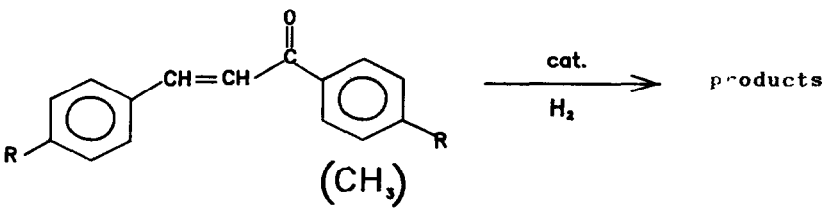
Run	Sub	time(h)	% conv.	A	B	C	selectivity[b]
1.	CH_2=CH-CO-Et[c]	120	35	35	0	0	0
2	Me-CH=CH-CO-Et	66	100	60	0	40	40
3.	Me_2-C=CH-CO-Me	72	24	3	0	21	87
4.	Ph-CH=CH-CO-Me	22	92	5	2	85	92
5.	Ph-CH=CH-CO-Ph	24	85	44	8	33	39

a. Reaction conditions. solvent toluene (50 ml.), [Ir] = $4x10^{-4}$ M, [P]/[Ir]= 10; [sub]/[Ir] = 500, T=100°C, pH_2=20 atm
A = saturated ketone, B = saturated alcohol, C = unsaturated alcohol.
b. Selectivity= (% unsaturated alcohol/ % conversion)x100.
c T=80°C

While for the aliphatic enones the steric hindrance on the C=C bond clearly affects the selectivity in favour of the carbonyl group's reduction, the replacement of the methyl group with a phenyl one requires a more careful analysis of both steric and electronic parameters, which could give contributions in the same direction or be in competition with each other.

Generally speaking, in hydrogenation reactions catalyzed by metal phosphine complexes, several variables can influence the reaction rate and selectivity, namely the structure of the substrate and its coordination ability to the metal, as well as the charge distribution in the catalytic species. We proposed that in the case of H_3IrP_3 the steric hindrance on the metal largely accounts for the selectivity observed[3]. On the other hand, an influence of the phosphine basicity[5] has not been found in this case and the effect of changes of the charge distribution in the substrate molecule has not been determined so far. Various phosphines have been used by some authors[6,7] in ketone and olefin hydrogenation reactions catalyzed by rhodium and iridium complexes, and the results seem to indicate that a higher electron density on the metal enhances the reaction rate, which is partly related to the easier formation of the dihydride intermediate. On the other hand, ketone hydrogenation is thought to require the presence of basic ligands around the metal centre In the transfer hydrogenation of α,β -unsaturated aldehydes, the system $[Ir(cod)Cl]_2$ + $P(o\text{-}MeOPh)_3$ gives a selective catalyst for reduction of the carbonyl group, probably because of interaction between the oxygen atom of the anisyl group of the phosphine and the iridium atom, which makes the coordinated hydrogen more hydridic in character[8]. Iridium complexes with aminophosphines have been found to be very active in the hydrogen transfer reduction of benzylideneacetone even in the absence of base, and selective towards C=O reduction, such behaviour was attributed to the basic properties of the ligands, which would favour hydride transfer to the substrate[9]. Iridium/phosphine systems were also used in selective hydrogenation of cinnamic aldehyde, but no significant correlation between phosphine basicity and yield in unsaturated alcohol was found[10]

The charge distribution on the substrate can also give some information on the catalytic system. With this aim in mind, we synthesized and used benzylideneacetone and chalcone derivatives substituted on the phenyl ring(s) in para-position with groups having different electronic effects, minimizing in this way steric influences. The reaction studied is schematized below, and results are summarized in Tables 2,3 and 4 (see exp section for procedure and experimental details).



The % conversion reported includes all hydrogenation products, i.e. unsaturated alcohol, saturated ketone and some saturated alcohol formed by reduction of the latter (the allylic alcohol is not reduced under the same conditions). The reaction is always very selective towards reduction of the carbonyl group with all the benzylideneacetone derivatives (except for the dimethylamino one)(Table 2), but there are some differences in terms of reduction rate. In the case of chalcone derivatives, selectivities are much lower, but still some sort of trend is visible. Selectivity is usually slightly lower in the first few hours of reaction, and this is apparently due to the time required for the complete formation of the selective species from the precursor[3b]. The reduction rates of the carbonyl group vary in a relatively marked way, whereas those of the C=C bond (% conversion - % unsaturated alcohol) seem to be little affected by the nature of the substituent. In order to see the general qualitative trend of the reactions with the various substituents, the three series of data have been collected in Fig. 1, where the % in unsaturated alcohol after 24 hours of reaction is plotted against the electron withdrawing ability of the different groups, which is best expressed by their Hammett σ, and data are fitted with the least-squares method. The mechanism of carbonyl reduction is assumed to be the same whichever is the substituent, and to be independent of the concomitant reduction of the olefinic bond.

Table 2
Hydrogenation of X-C_6H_4-CH=CH-CO-Me catalyzed by $[Ir(cod)(OMe)]_2$ + PEt_2Ph[a]

X	% conversion	% yield: A	B	C	selectivity[b]
4-$N(CH_3)_2$	64	7	9	48	75
4-OCH_3	68	4	0	64	94
H	92	5	2	85	92
4-Cl	77	5	0	72	93
4-CF_3	97	5	2	90	93
2-OCH_3	77	2	2	73	95

a. Reaction conditions solvent toluene (50 ml.); [Ir]= 4×10^{-4} M, [P]/[Ir] = 10, [sub]/[Ir] = 75; T= 100°C, pH_2= 20 atm
Reaction time· 24 hours.
A = saturated ketone, B = saturated alcohol, C = unsaturated alcohol.
b. Selectivity= (% unsaturated alcohol/ % conversion)x100.

The overall picture so obtained shows that the pattern is roughly the same in the three cases. The higher selectivities observed for unsubstituted

enones could be ascribed to some sort of steric and/or electronic interaction in the catalyst/substrate adduct, which favours reduction of C=O. The fact that ortho-substituted derivatives are reduced with roughly the same selectivity as the para-substituted ones (Tables 2 and 3) seems to rule out a simple steric hindrance on the olefinic bond coordination as the cause of this effect

Table 3
Hydrogenation of X-C_6H_4-CH=CH-CO-Ph catalyzed by $[Ir(cod)(OMe)]_2$ + PEt_2Ph[a]

X	% conversion	% yield: A	B	C	selectivity
4-$N(CH_3)_2$	52	45	7	0	0
4-OCH_3	67	51	4	12	18
H	85	44	8	33	39
4-Cl	88	48	15	25	28
4-CF_3	96	61	3	32	33
2-OCH_3	54	41	3	10	18

a. Same system and reaction conditions as in Table 2.

Table 4
Hydrogenation of Ph-CH=CH-CO-C_6H_4-X catalyzed by $[Ir(cod)(OMe)]_2$ + PEt_2Ph[a]

X	% conversion	% yield. A	B	C	selectivity
4'-OCH_3	83	55	10	18	22
H	85	44	8	33	39
4'-F	89	50	13	26	29
4'-Cl	86	45	14	27	31
4'-CF_3	94	38	27	29	31

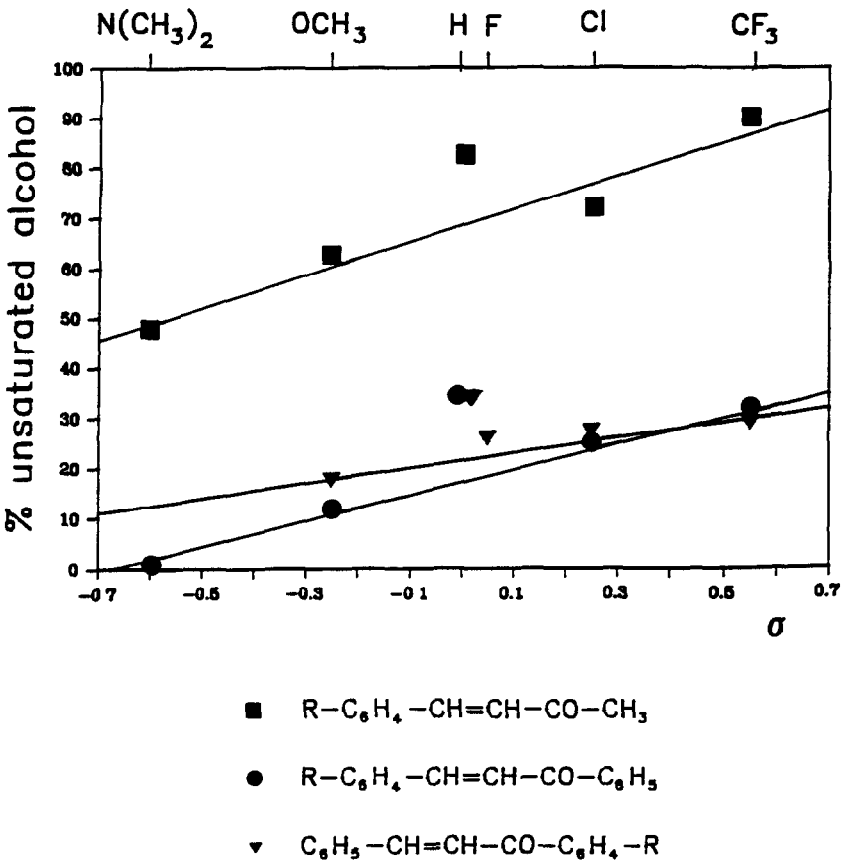
a. Same system and reaction conditions as in Table 2

A general increase in selectivity towards reduction of the carbonyl group can be seen with electron withdrawing groups, although differences are not very marked especially for chalcone derivatives

Similar results were found by other authors with different reduction systems Electron withdrawing groups in para-substituted acetophenone derivatives give higher yields in the alcohols with a ruthenium complex in the presence of Et_3N^+ $H_2PO_2^-$.n H_2O as hydrogen source[11] A similar effect was found by Beaupere et al. in the hydrogen transfer reduction of benzylideneacetone derivatives catalyzed by $HRh(PPh_3)_4$, whereby hydridic properties

were assigned to this rhodium complex[12]. Sasson and Blum studied a similar system which gave different results, probably owing to differences in the rate determining step[13].

Fig. 1



The key feature of all these reduction systems seems to be the nucleophilic character of the coordinated hydrogen, which in turn is enhanced whenever the metal centre is enriched in electron density

Back to our system, the complex H_3IrP_3, to act as a catalyst, must either

dissociate one phosphine ligand or eliminate hydrogen in order to make sites available for coordination of the substrate. The latter possibility seems more plausible, since the iridium species with two phosphines would catalyze C=C reduction[3]; also, the system is still active and selective even at high P/Ir ratios. It follows that the catalytic species present in solution should be an iridium complex with three phosphines coordinated, which render the metal centre fairly electron rich. This in turn makes the coordinated hydrogen more nucleophilic, hence more available to be transferred onto a positive centre like the carbon atom of the carbonyl group. Our results are in agreement with the suggestion that the catalytic species should be rather "hydridic" in character, since reduction of C=O is faster when the carbon atom's electrophilicity is higher. In summary, as far as this system is concerned, the steric hindrance on the catalytic species is necessary to achieve chemoselectivity in the reduction of conjugated enones, while electronic parameters enhance or depress the C=O reduction, hence affecting selectivity in the case of chalcone derivatives.

These results lead us to consider the possibility to undertake a study on more subtle correlations, that is to say on the effect of charge distribution in the substrate on the stereoselectivity in the asymmetric reduction of enones to allylic alcohols. The nature of these influences is not well understood, and there is little work in the literature on this subject.

Capillon and Guette reported that in the asymmetric reduction of phenylalkylketones with a chiral aromatic Grignard reagent, the absolute configuration of the products and the enantiomeric excess (e.e.) depend on electronic effects of the substituents, and explained this result in terms of donor-acceptor interactions between the phenyl rings of reagent and substrate[14]. A different interpretation of the same result was given by Nishio and Hirota, by invoking CH/π interactions in the transition state[15].

Werz et al. have very recently found a correlation between the electronic properties of a rhodium-diop catalyst and the optical yield in the asymmetric reduction of acylaminoacrylate and acylaminocinnamate derivatives, by introducing various substituents on the ligand's phenyl rings in para-position[16]. Although this study is limited to electron donating groups, the authors did find a linear dependence of the e e. on the Hammett σ of the substituents. This effect is ascribed to electronic and solvation factors.

In this work, we used a particular chiral catalyst and various substituted chalcone derivatives as substrates. Following our previous results in the asymmetric hydrogenation of benzylideneacetone catalyzed by Ir/phosphine systems[4], the complex $[Ir(S,S\text{-diop})_2]^+$ [(S,S)-diop= (+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] was chosen as the catalyst for these reactions, because of its good chemoselectivity.

Asymmetric hydrogenations were carried out under the experimental conditions reported in table 5, in the presence of 1 equivalent diop to depress ligand dissociation. The optical yields were determined by ^{31}P NMR of the diastereoisomers of the allylic alcohol derivatives obtained by reaction with optically active phospholane (Anderson-Shapiro reagent; see exp. section), after the validity of this method was confirmed by comparing results obtained on benzylideneacetone with optical rotation measurements. A series of substituted chalcones was considered for these experiments, since for these substrates no interference occurs between NMR signals of the allylic alcohol derivatives and those of the saturated ones. The ^{31}P NMR spectrum run in the case of chalcone (run 1, Table 5) is reported as an example in Fig. 2, where the two major peaks are due to the diastereoisomers of the allylic alcohol derivatives. Some selected results are collected in Table 5. A larger number of experiments was run on different substrates, and results show that chemoselectivity in this case appears to be practically insensitive to substituents on the phenyl rings. As far as enantioselectivity is concerned, we can say that the presence of a substituent group in para-position on either phenyl ring leads to an increase of the optical yield in the allylic alcohols, and that electronic properties of such group have little or no influence at all on the e.e within the experimental errors (compare runs 2,3 and 4 in Table 5) The e.e's obtained for the saturated alcohols seem to parallel those reported for the allylic ones.

Fig. 2

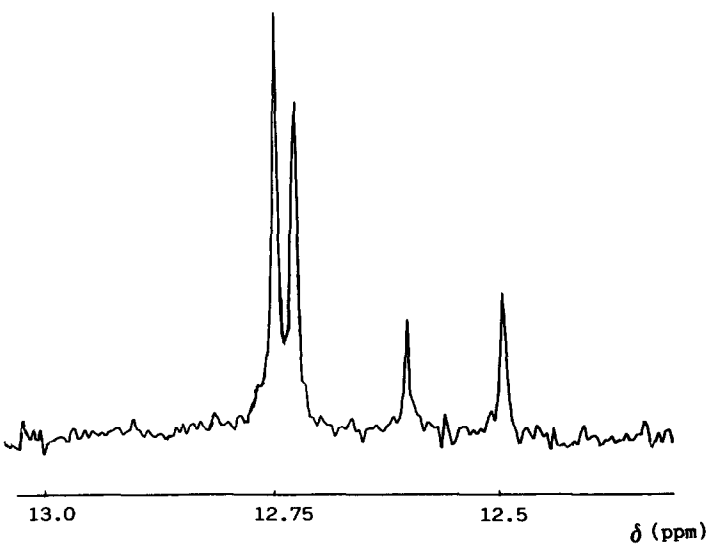


Table 5
Asymmetric hydrogenation of 4-X-C_6H_4-CH=CH-CO-C_6H_4-4'-Y catalyzed by $[Ir(diop)_2]^+$ in the presence of 1 equivalent diop[a]

Run	X	Y	t(h)	% conv.	% uns.alc.	% sel.	% e.e.[b]
1	H	H	14	96	73	75	13
2	CH_3	H	38	90	74	80	25
3	CF_3	H	47	99	62	63	24
4	H	CH_3	22	94	74	79	25
5	H	CF_3	47	67	47	70	*

a. Conditions as in Table 2. [Sub]/[Ir]=100.
b. Enantiomeric excess (± 2-3%). Absolute configuration unknown.
* No peak separation at ^{31}P NMR (see exp. section).

Enantioface discrimination is clearly determined by the chiral arrangement in the catalyst-substrate adduct in the transition state, and electronic interactions can contribute by favouring or disfavouring one or the other face and hence the e e. Noyori et al. brought a significant example of these effects in the asymmetric hydrogenation of arylalkylketones with BINAL-H[17]. In this case, n/π type electronic repulsions in the transition state apparently prevail over steric effects in determining the absolute configuration of the products

In our system, we can conclude that steric parameters essentially control both chemo- and enantioselectivity in the case of $[Ir(diop)_2]^+$, and this result is connected to the considerable bulkyness of the dihydride which is thought to be the catalytic species in this reaction[4]. In this case the coordination ability of the substrate through the olefinic or the ketonic function is apparently crucial for selectivity. Also, the apparent lack of a trend with charge distribution is an indication that the hydrogen transfer to the carbon atom of the C=O bond is not a slow step in the catalytic cycle. The reaction rate here could be determined by the oxidative addition of hydrogen to the Ir(I) precursor.

On the other hand, a dependence of the optical yield on electronic parameters cannot be excluded for different catalytic systems and substrates. In the asymmetric hydrogenation of para-substituted acetophenones catalyzed by the "in situ" system $[Ir(cod)(OMe)]_2$ + diop, the enantiomeric excess does seem to be dependent on the nature of the substituent the para-chloro derivative, for example, is reduced with 18% e.e. as compared with the 31% e.e. obtained from the unsubstituted ketone. Further investigations, however, are needed to confirm these results The cationic complex

$[Ir(diop)_2]^+$ turned out to be much less active in this reaction. Interactions of the type CH/π, as well as donor-acceptor interactions between the substrate molecule and the phenyl rings of the ligands could take place for this kind of compounds, and be responsible for differences in the optical yields. Although we showed that in the case of benzylideneacetone[4] the cationic precursor and the "in situ" one give the same e.e., electronic parameters might exert a different influence in the two systems.

In conclusion, both steric and electronic parameters can play an important role in hydrogenation reactions. The predominance of one or the other in determining selectivity is apparently determined by the nature of the catalytic species, the charge distribution in the adduct catalyst-substrate and the mechanism of reaction, so that a generalization is often hazardous In our case, steric hindrance in the catalytic intermediate seems to be crucial for selectivity in allylic alcohol, whereas the electronic density around the reduction centre has an influence in the case of H_3IrP_3. The effect of charge distribution in the substrate on the optical yield in asymmetric reductions is not yet understood, and more information is needed on this particular subject

Experimental section

Chemicals

Toluene was distilled before use

Phosphines were purchased from Strem Chemicals and used as received

$[Ir(cod)(OCH_3)]_2$ was prepared according to the literature[18].

$[Ir(diop)_2]$ BPh_4 was synthesised by slight modification of standard procedure[19].

(4R,5R)-(+)-2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane-2-oxide was supplied by Aldrich Chemicals and stored under nitrogen in a refrigerator

Substrates

1-penten-3-one, 4-hexen-3-one and 2-methyl-2-penten-3-one (mesityloxide) (Aldrich) were distilled in vacuo before use

Benzylideneacetone and chalcone (Fluka) were recrystallized three times from propan-2-ol

Benzylideneacetone and chalcone derivatives were synthesized by condensation of the appropriate aldehyde with acetone or acetophenone in the presence of base[20] After recrystallization from ethanol 95%, the overall yields were in the range 60-70% The products were identified by m p. and

^1H NMR by comparison with literature data. Their purities were determined by GLC (>98%).

Hydrogenation reactions

All reactions were carried out in a stainless steel autoclave according to the procedure described previously[4]. The reproducibility of results reported in tables 1-5 is within 2-3%.

The composition of the mixture of products (± 1%) was determined by GLC using a Perkin Elmer Sigma 3B chromatograph equipped with an HWD detector, using helium as carrier gas and two different wide-bore capillary columns (CP Sil-5B and Supelcowax 10).

In the case of asymmetric hydrogenations, at the end of reaction the solution was concentrated and passed through silica to separate the catalyst. The solvent was then evaporated and the residue dried in vacuo for several hours. Optical yields were determined by ^{31}P NMR on a Bruker WP 80 spectrometer after reacting the product mixture with 1 equivalent of (4R,5R)-(+)-2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane-2-oxide, according to the Anderson-Shapiro method[21]. The reactions were performed in a dry box using dry reagents Nevertheless, in some cases the optical yield determination was not possible or it was unreliable because of formation of byproducts and/or hydrolysis products The spectra obtained were compared with those run on racemic mixtures. The peak separations for the allylic alcohols were of 0.5-0 7 Hz The chemical shifts in fig. 2 are referred to H_3PO_4 85% (downfield positive).

Acknowledgments

Authors thank C.N.R. (Roma), Progetto Finalizzato Chimica Fine II, and the University of Trieste for financial support.

References

1. a) Brown, H.C., Krishnamurthy, S., Tetrahedron, 1979, 35, 567 and ref. therein.
b) Kim, S , Ahn, K H., J. Org. Chem., 1984, 49, 1717
2 a) Noyori, R., Tomino, I.; Yanada, M.; Nishizawa, M , J. Am. Chem. Soc , 1984, 106, 6717.

b) Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V., J. Org. Chem., 1987, 52, 5406.

c) Brown, H.C.; Cho, B.T.; Park, W.S., ibid., 1988, 53, 1231.

d) Midland, M.M.; McLoughlin, J.I.; Gabriel, J., ibid., 1989, 54, 159.

3. a) Farnetti, E.; Pesce, M.; Kaspar, J.; Spogliarich, R.; Graziani, M. J. Chem. Soc., Chem. Commun., 1986, 746.

b) Farnetti, E., Kaspar, J.; Spogliarich, R.; Graziani, M., J. Chem. Soc., Dalton Trans., 1988, 947.

4. Spogliarich, R.; Farnetti, E.; Kaspar, J.; Graziani, M.; Cesarotti, E., J. Mol. Catal., 1989, 50, 19.

5. Tolman, C.A., Chem. Rev., 1977, 77, 313.

6. Vastag, S.; Heil, B.; Mark, L., J. Mol. Catal., 1979, 5, 189.

7. Uson, R.; Oro, L.A.; Fernandez, M.J., J. Organometal. Chem., 1980, 193, 127.

8. a) Visintin, M., Spogliarich, R., Kaspar, J; Graziani, M., J. Mol. Catal., 1984, 24, 277.

b) Visintin, M., Spogliarich, R., Kaspar, J.; Graziani, M., ibid, 1985, 32, 349.

9. Farnetti, E.; Nardin, G.; Graziani, M., J. Chem. Soc., Chem. Commun., 1989, 1264.

10. Farnetti, E.; Pesce, M., Kaspar, J., Spogliarich, R.; Graziani, M., J. Mol. Catal., 1987, 43, 35

11. Khai, B.Th.; Arcelli, A., J. Org. Chem., 1989, 54, 949 .

12. Beaupere, D.; Nadjo, L.; Uzan, R.; Bauer, P., J. Mol. Catal., 1983, 20, 185.

13. Sasson, Y.; Blum, J., J. Org. Chem., 1975, 40, 1887.

14 Capillon, J.; Guette, J.P., Tetrahedron, 1979, 35, 1817

15. Nishio, M.; Hirota, M., Tetrahedron, 1989, 45, 7201.

16.a) Werz, U.; Brune, H.A., J. Organometal. Chem., 1989, 363, 377

b) Werz, U ; Brune, H.A., ibid, 1989, 365, 367.

17 Noyori, R., Tomino, I , Tanimoto, Y., Nishizawa, M., J. Am. Chem. Soc., 1984, 106, 6709.

18 Uson, R., Oro, L.A., Cabeza, J.A , Inorg. Synth., 1985, 23, 126.

19. Brown, J.M.; Dayrit, F.M., Lightowler, D., J. Chem. Soc., Chem. Commun., 1983, 414.

20 a) Drake, N.L., Allen, P Jr., Organic Syntheses, Coll., Vol 1, Gilman, H and Blatt, A H Eds., Wiley and Sons Publ., New York, 1958, p. 77.

b) Kohler, E.P., Chadwell, H M , ibid., 1958, p. 78.

21 Anderson, R.C., Shapiro, M.J., J. Org. Chem , 1984, 49, 1304.