ELSEVIER

Journal of Organometallic Chemistry 525 (1996) 233–238

Journal of Organometallic Chemistry

Enantiodifferentiation of olefinic groups in *cis*-1,2-divinylcyclohexane

Kerstin Nordström [a], Christina Moberg [a,*], Andreas Heumann [b]

[a] *Department of Chemistry, Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden*
[b] *Université d'Aix-Marseille, Faculté de St-Jérome, URA-CNRS 1410, F-130 13 Marseille, France*

Received 4 April 1996; revised 1 May 1996

Abstract

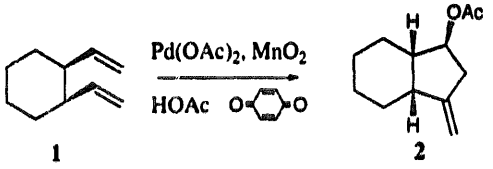
Chirality transfer from asymmetric ligands to the diene in (η^4-*cis*-1,2-divinylcyclohexane) rhodium complexes has been observed, leading to a slight excess of one of the two enantiomeric chair conformations of the cyclohexane ring. The importance of this phenomenon for the palladium-catalyzed oxidative cyclization of (*cis*-1,2-divinylcyclohexane) using chiral carboxylates as nucleophiles is discussed.

Keywords: Palladium; Conformation; Rhodium; Chiral; Diene; Enantioselective

1. Introduction

The ability to differentiate enantiotopic faces, groups or atoms is a key issue in asymmetric synthesis [1]. This achievement can be attained in various ways, by taking advantage of both repulsive and attractive interactions exerted by a chiral reagent or catalyst. A special situation arises when a prochiral compound can occupy two enantiomeric conformations, and when reaction of one conformer leads to a product which is the enantiomer of that obtained by reaction of the other conformer [2,3].

We have thoroughly investigated one such case, involving *cis*-1,2-divinylcyclohexane (**1**). Reaction with acetic acid in the presence of 1,4-benzoquinone and catalytic amounts of palladium(II) acetate and manganese dioxide yields racemic [1*R**,6*S**,7*S**]-7-acetoxy-9-methylenebicyclo[4.3.0]nonane (**2**) as the sole product [4].



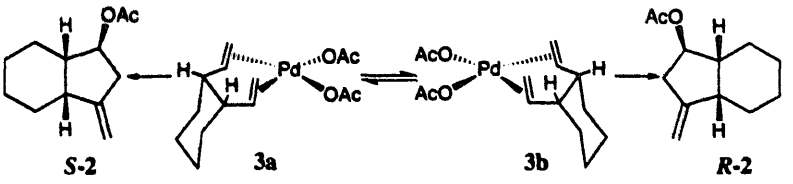
1 2

The initial step of the reaction is the reversible attack of acetate ion on one of the olefinic bonds at the face *trans* to the metal ion [5]. A mechanistic investigation revealed that only reaction at the equatorial olefinic bond leads to product, as demonstrated by the formation of one single pair of enantiomers from the reaction of racemic *cis,cis*-1,2-divinyl-4-(trimethylsilyl)cyclohexane [6]. ^{1}H NMR spectroscopy showed this diene to occupy one single conformation, with the sterically demanding trimethylsilyl group in equatorial position. That addition takes place at the equatorial olefinic bond is expected, since it is unlikely that a tetrahedral center develops in an axial position for steric reasons. The study thus demonstrates not only that the olefinic bonds have different reactivity, but also that the most stable conformation of the diene is probably the one that undergoes reaction. As a consequence of this mechanistic investigation, it could be concluded that each of the two enantiomeric conformers (**3a** and **3b**) of the initially formed palladium diene complex reacts to give a single enantiomer (*S*-**2** or *R*-**2**, Scheme 1).

We have also been able to differentiate the olefinic bonds of *cis*-1,2-divinylcyclohexane in asymmetric synthesis by employing chiral carboxylic acids in place of acetic acid, and obtained one of the two possible stereoisomers in up to 76% *de* [7]. Our earlier finding that only reaction of the equatorial bond leads to product prompted us to investigate the origin of the selectivity of this reaction with chiral carboxylic acids, since in principle the selectivity may arise either via approach of

* Corresponding author.

PII S0022-328X(96)06440-6



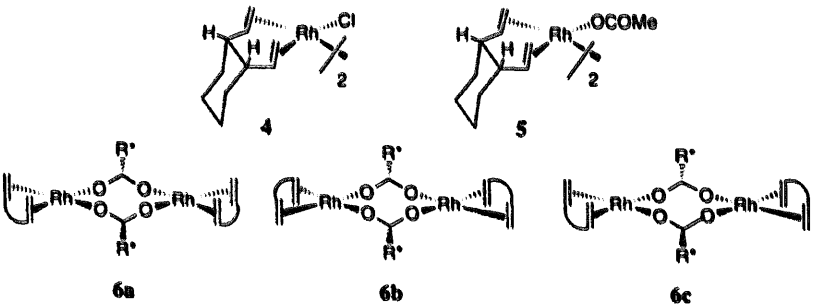
Scheme 1.

the chiral acid or by complexation of this acid to palladium (exchange of acetate for chiral carboxylate was indeed demonstrated to occur). We have therefore studied the effect of chiral ligands on the conformation of metal complexes of the diene, in particular whether a chiral ligand is able to stabilize one of the two enantiomeric conformations. The results of this investigation are presented here.

2. Results

Palladium diene complexes with chiral carboxylates as counter ions were unsuitable for the desired study, since such complexes are unstable in that the anion readily attacks the diene. Attempted studies of cationic palladium as well as platinum complexes containing chiral derivatives of acetylacetonate also failed, since pure products were difficult to obtain, possibly as a consequence of the formation of two diastereomers. A less complicated situation was expected using rhodium(I) instead of palladium(II), since an olefinic bond coordinated to Rh(I) is not attacked by the nucleophile, and neutral complexes are formed upon complexation with mono-anions. Bis[(η^4-*cis*-1,2-divinylcyclohexane)rhodium(I) chloride] (**4**) could readily be prepared, and from this complex also bis[(η^4-*cis*-1,2-divinylcyclohexane)rhodium(I) acetate] (**5**), by reaction with silver acetate, in analogy to previously known diene complexes (diene–Rh–acetate complexes, see Ref. [8]). Exchange of diene in complex **5** was slow on the NMR timescale, as shown by the observation of different signals for the coordinated and free diene in the ^{1}H NMR spectrum, thus allowing the study of different isomers using this technique.

Chiral complexes could also be obtained as with the acetate complex **5**, using silver salts of chiral carboxylic acids. We were pleased to find that out of three different possible isomers (**6a–c**), a single complex containing two chemically identical dienes seemed to form from **4** and silver (*R*)-*O*-(2,4-dichlorophenyl)lactate, according to ^{1}H NMR spectroscopy (probably with either structure **6a** or **6b**, since the third possible isomer is expected to show different signals for the two dienes, being diastereotopic). That complex **6** was a dimer was ascertained by the observation of signals from diastereoisomeric complexes (with homochiral and heterochiral carboxylate ligands respectively) when racemic lactate was employed in place of the enantiomerically pure compound.



The room temperature ^{1}H NMR spectrum of the C_2-symmetric complex thus obtained showed different signals for the six olefinic protons of the diene, the difference in chemical shift between the two internal olefinic protons being as large as 0.62 ppm. At −40 °C, flipping of the cyclohexane rings was slow enough to allow for the observation of separate signals for the protons of equatorial and axial vinylic substituents, and at −70 °C a well-resolved spectrum was obtained. Three different conformers with the cyclohexane rings in chair conformation are possible, two of which retain their C_2 symmetry (the isomer lacking C_2 symmetry is shown in Fig. 1). This implies that, upon cooling, each signal may split into up to four different signals (one signal from each C_2-symmetric conformer and two signals from the non-symmetric conformer), a phenomenon that was indeed observed for several of the signals. For example, one of the internal olefinic protons was split

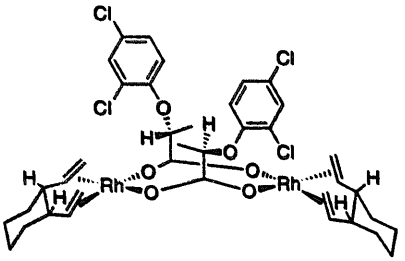
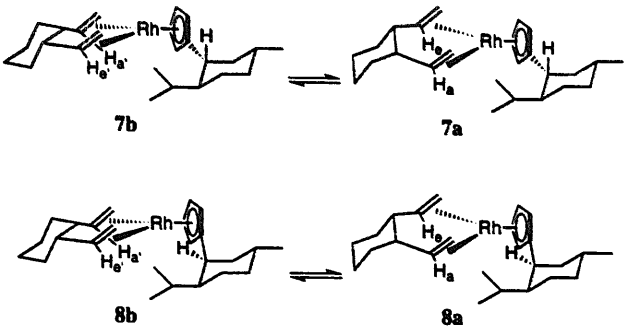


Fig. 1. One of the possible conformers of bis[η^4-*cis*-1,2-divinylcyclohexane)rhodium(I) (*R*)-(*O*-2,4-dichlorophenyl)lactate] (**6**).

into four signals, one at ca. 4.35 ppm (overlapping with quartets originating from the acid part of the complex) and the remaining three at 4.23, 4.06 and 3.93 ppm, the former as a broad apparent quartet and the two latter as apparent broad triplets. This coupling pattern is consistent with the observation of diastereomeric conformers, with quartets originating from the protons on the axial olefinic bonds and the triplets from those on the equatorial bonds. That different patterns are observed for the two kinds of proton is consistent with the expected geometry, the angle between H_e and the closest allylic proton on the cyclohexane ring being approximately 90°, a situation resembling that previously observed for dichloro(η^4-*cis*,*cis*-1,2-divinyl-4-(trimethylsilyl)cyclohexane)palladium [6] and for dichloro(η^4-*cis*-1,2-divinylcyclohexane)palladium at −90 °C [9]. With a statistical distribution of isomers, a 1:1:1:1 ratio of the signals from each proton is expected. It is interesting to note that the integrals of the signals originating from one of the internal protons are not equal, the ratio of signals originating from a conformer with that proton on a vinyl group in axial to those of the same proton on a group in equatorial position instead being 1:0.6. For the second internal proton, the expected inverse ratio was observed. These results demonstrate that one chair conformation of the cyclohexane ring was slightly preferred over the other.

To further verify this observation, a simpler system with fewer possibilities for isomerism was desired. Deprotonated chiral cyclopentadienes have been used extensively as chiral ligands in asymmetric synthesis, and a large variety of such compounds has been described [10]. Among the known compounds, menthyl- and neomenthylcyclopentadiene have been employed in the synthesis of Ti(IV) and Zr(IV) [11] compounds. Since (η^4-cycloocta-1,5-diene)(η^5-cyclopentadienyl)rhodium [12,13] and (+)-(η^4-cycloocta-1,5-diene)(η^5-neomenthylcyclopentadienyl)rhodium [14] have also been described, this type of complex was considered as another useful model for the palladium complexes involved in the catalytic reaction under study, since one single isomer was expected in each case.

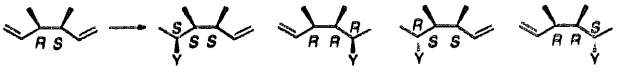
Reaction of bis[(η^4-*cis*-1,2-divinylcyclohexane)-rhodium(I) chloride] with [(−)-menthyl)cyclopentadienyl]lithium and [(+)-neomenthylcyclopentadienyl]lithium afforded complexes **7** and **8** respectively. Analogous to known metal complexes containing a neomenthylcyclopentadienyl ligand [11,15], the cyclopentadienyl ring is thought to occupy an axial position in the cyclohexane ring. The ^{1}H NMR spectra at room temperature showed separate signals for all six olefinic protons in **7**, whereas the signals for the internal olefinic protons in **8** overlapped. On cooling the samples, similar changes took place in the two cases, further verifying that the cyclohexane rings in the menthyl part of the complexes assume chair conformations with the isopropyl and methyl groups occupying equatorial positions. The dynamic process observed in the olefinic region of the spectrum was therefore attributed to conformational changes in the diene part of the molecule (Scheme 2). In each case, three signals for the internal olefinic protons were observed at −55 °C (500 MHz). The spectrum of complex **8** was also recorded at −80 °C (400 MHz), at which temperature the signals were resolved into two broad quartets (at 3.78 and 3.62 ppm) in a ratio of 0.6:1 and one broad triplet (at 3.50 ppm), the integral of which was of the same size as the sum of those of the two quartets. This shows that the ratio between the two conformers of **8** is ca. 0.6:1. From this experiment it could thus again be concluded that one of the two enantiomeric cyclohexane conformations was slightly preferred over the other.



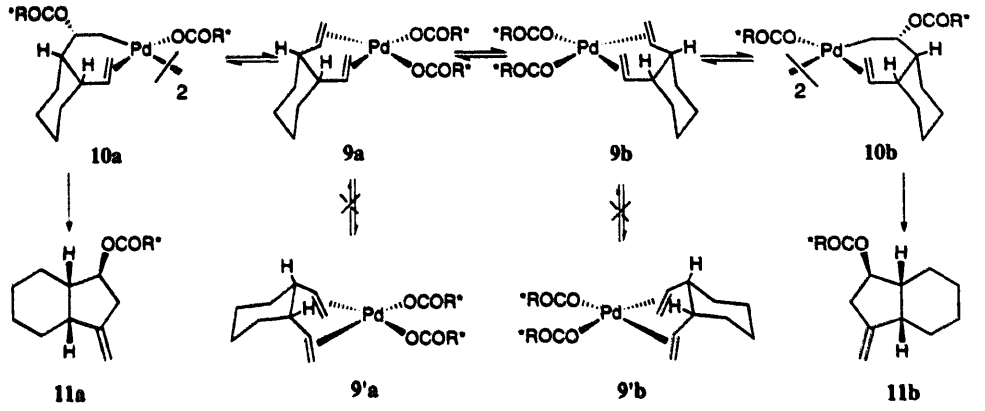
Scheme 2.

3. Discussion

The stereoselectivity in the palladium-catalyzed oxidative cyclization involves both enantiotopic group selection and diastereoface selection, and thus the possible formation of four different stereoisomers, as shown schematically in Scheme 3.



Scheme 3.



Scheme 4.

The diastereoselectivity originates from the presence of only one palladium–diene complex in the case of *cis*-1,2-divinylcyclohexane (i.e. the diastereomeric complexes analogous to **9'a** and **9'b** were not observed); with several other dienes, a mixture of two diastereomeric complexes was observed, a situation leading to the formation of mixtures of diastereomeric products. The enantiotopic group selection originates in the different reactivity of the two enantiotopic olefinic groups.

The rate-determining step in the oxidative cyclization is the insertion of the olefinic group into the palladium–carbon σ-bond in the σ,π-complex **10** (Scheme 4). This step results in a σ-palladium complex which rapidly undergoes β-elimination to give the final product **11**. The activation barrier for the conformational equilibrium between **9a** and **9b** is thought to be small, as indicated by separate signals for the conformers in the ^{1}H NMR spectrum only below ≈ 40 °C for the analogous rhodium complexes, probably resulting in Curtin–Hammet conditions [3]. The product ratio (**11a**:**11b**) will therefore be determined by the relative rates of reaction of the diastereomeric intermediates **10a** and **10b**. In case the reaction of σ,π-complex **10** is exothermic, the transition state, according to Hammond's postulate, should resemble the starting material. The difference in stability between **10a** and **10b** is therefore expected to be reflected in the overall stereoselectivity of the reaction.

What we have been able to study here is the different stability of conformers **9a** and **9b**. The importance of this difference for the overall selectivity, however, is not clear. With the high barrier for conformational change in 4-(*tert*-butyldimethylsilyl)-1,2-divinylcyclohexane, the ratio of conformers seems to be important for the ratio of products, the stable conformer being the one undergoing reaction. If there is a difference in stability between conformers **9a** and **9b**, it is reasonable to believe that this might be reflected in a difference in stability of complexes **10a** and **10b**.

The ability of a chiral carboxylate ligand coordinated to a metal ion to transfer chirality to a diene bound to the same metal ion, the phenomenon observed in rhodium(I) complexes **6–8**, could thus be one factor involved in the stereoselection of the palladium-catalyzed oxidative cyclization of *cis*-1,2-divinylcyclohexane using (*R*)-*O*-(2,4-dichlorophenyl)lactic acid as nucleophile. Although the present study is not able to prove this assumption, it seems clear that if a large difference in stability between the two initially formed conformers of the initially formed palladium–diene complex could be achieved, this would be reflected in the stereoselectivity of the overall reaction. The ratio of conformational diastereomers in the two cases studied here corresponds to a *de* of ca. 25%. This is close to the selectivity observed in the catalytic reaction using this nucleophile (17% *de*). [Higher diastereoselectivity (up to 76%) was observed only upon the addition of molecular sieves to the reaction mixture.] More generally, induced conformational enantiomerism, previously studied using cyclodextrins as chiral receptors [16], is probably an important phenomenon in asymmetric catalysis. [A preliminary ^{1}H NMR spectroscopic study of *cis*-1,2-divinylcyclohexane encapsulated in α-cyclodextrine indicated the presence of diastereotopic olefinic groups. A suitable solvent allowing low temperature studies was not found, however, since the complex was found to be stable only in water [17].]

4. Conclusion

It has been shown that it is possible to some extent to enforce a chiral conformation by chirality transfer from a ligand to a diene, both bound to Rh(I). Our previous finding that only attack on the equatorial double bond in the palladium-catalyzed oxidative cyclization leads to product, suggests that if the diene were to be locked in one chair conformation efficient enantiodifferentiation of the olefinic bonds would be possible.

5. Experimental

5.1. General procedures

^{1}H NMR spectra were recorded at 250, 400 or 500 MHz and ^{13}C NMR spectra at 100.6 MHz.

Cis-1,2-divinylcyclohexane obtained from Lancaster and rhodium(III) chloride hydrate from Aldrich were used as received. Neomenthylcyclopentadiene was prepared from (1*R*,2*S*,5*R*)-menthyl tosylate [18] by slight modification of a literature procedure [11] (DMSO as solvent and butyllithium as base in place of THF/Na). Menthylcyclopentadiene was prepared by a similar procedure from cyclopentadienyllithium and (1*S*,2*S*,5*R*)-neomenthyl bromide [19]. (*R*)-*O*-(2,4-dichlorophenyl)lactic acid was prepared from (L)-lactic acid as previously described [7].

5.2. Bis[(η^4-cis-1,2-divinylcyclohexane)rhodium(I) chloride] (4)

This complex was prepared analogously to bis(η^4-1,5-cyclooctadiene)rhodium(I) chloride [12] by heating *cis*-1,2-divinylcyclohexane and $RhCl_3$ hydrate in ethanol (59%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.42 (m, 2H), 3.40 (d, J = 8 Hz, 2H), 2.47 (d, J = 12 Hz, 2H), 2.5–2.3 (m, 2H), 1.9–1.7 (m, 6H), 1.6–1.4 (m, 2H).

5.3. Bis[(η^4-cis-1,2-divinylcyclohexane)rhodium(I) acetate] (5)

Complex **4** (7 mg) was reacted with silver acetate (1 equiv.) in $CDCl_3$ in an NMR tube. ^{1}H NMR: δ 4.33 (m, 2H), 3.10 (d, J = 8 Hz, 2H), 2.50 (d, J = 12 Hz, 2H), 2.45–2.25 (m, 2H), 2.0–1.60 (m, 4H), 1.78 (s, 3H), 1.60–1.20 (m, 4H).

5.4. Bis[(η^4-cis-1,2-divinylcyclohexane)rhodium(I) (R)-(O-2,4-dichlorophenyl)lactate] (6)

(*R*)-(*O*-2,4-Dichlorophenyl)lactic acid (2.35 g, 10 mmol) in CH_2Cl_2 (20 ml) was extracted with 0.5 M aqueous NaOH (20 ml). The aqueous phase was neutralized and $AgNO_3$ (1 equiv.) was slowly added while heating at 100 °C. After cooling, the precipitate formed was filtered off and washed thoroughly with water and then dried. A fraction of the silver salt obtained (27 mg) was stirred with complex **4** in CH_2Cl_2 at ambient temperature. The solvent was evaporated and the residue dissolved in CD_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 2.4 Hz, 1H), 7.13, dd, J = 8.8 and 2.4 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 4.42 (q, J = 6.7 Hz, 1H), 4.36–4.24 (m, 1H), 3.73–3.63 (m, 1H), 3.25 (d, J = 7.6 Hz, 1H), 2.56 (d, J = 12.5 Hz, 1H), 2.50 (d, J = 7.6 Hz, 1H), 2.30 (d, J = 12.5 Hz, 1H), 2.25–2.05 (m, 1H), 1.9–1.4 (m, 8H), 1.36 (d, J = 6.7 Hz, 3H).

5.5. (η^4-Cis-1,2-divinylcyclohexane)(η^5-(1R,2S,5R)-menthylcyclopentadienyl)rhodium (7) and (η^4-cis-1,2-divinylcyclohexane)(η^5-(1S,2S,5R)-menthylcyclopentadienyl)rhodium (8)

Complexes **7** and **8** were prepared analogously to (η^4-cycloocta-1,5-diene)(η^5-cyclopentadienyl)rhodium [10] from bis(η^4-*cis*-1,2-divinylcyclohexane)rhodium(I) chloride and (menthylcyclopentadienyl)lithium or (neomenthylcyclopentadienyl)lithium respectively.

7. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 5.21 (m, 1H), 5.03 (m, 1H), 4.85 (m, 1H), 4.77 (m, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 2.73 (d, J = 7.5 Hz, 1H), 2.53 (d, J = 7.5 Hz, 1H), 2.20 (br d, J = 13 Hz, 1H), 2.06 (dt, J = 3 and 11 Hz, 1H), 1.9–1.0 (m, 20H), 0.98 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 7 Hz, 3H), 0.78 (d, J = 7 Hz, 3H).

8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (m, 1H), 5.13 (m, 1H), 4.89 (m, 1H), 4.36 (m, 1H), 3.80–3.68 (m, 2H), 2.77 (m, 1H), 2.71 (dd, J = 8 and 2 Hz, 1H), 2.55 (dd, J = 8 and 2 Hz, 1H), 2.18 (d, J = 12 Hz, 1H), 1.9–1.0 (m, 20H), 0.97 (d, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.78 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 111.96, 89.21, 88.40, 84.87, 83.85, 65.99, 65.87, 65.33, 65.20, 48.57, 43.66, 37.21, 35.77, 35.60, 30.92, 29.98, 29.73, 29.50, 27.91, 24.52, 23.90, 23.56, 22.88, 21.94, 20.74.

Acknowledgements

We are indebted to Dr. Tobias Rein for valuable discussions. This work was supported by the Swedish Natural Science Research Council.

References

[1] R.S. Ward, *Chem. Soc. Rev.*, *19* (1990) 1; C.S. Poss and S.L. Schreiber, *Acc. Chem. Res.*, *27* (1994) 9; S.R. Magnuson, *Tetrahedron*, *51* (1995) 2167.
[2] J.K. Whitesell and S.W. Felman, *J. Org. Chem.*, *45* (1980) 755.
[3] N.S. Zefirov, *Tetrahedron*, *33* (1977) 2719.
[4] T. Antonsson, C. Moberg, L. Tottie and A. Heumann, *J. Org. Chem.*, *54* (1989) 4914.
[5] C. Moberg, L. Sutin and A. Heumann, *Acta Chem. Scand.*, *45* (1991) 77; C. Moberg and L. Sutin, *Acta Chem. Scand.*, *46* (1992) 1000.
[6] C. Moberg, L. Sutin, I. Csöregh and A. Heumann, *Organometallics*, *9* (1990) 974.
[7] L. Tottie, P. Bæckström, C. Moberg, J. Tegenfeldt and A. Heumann, *J. Org. Chem.*, *57* (1992) 6579.
[8] R.P. Hughes, in G. Wilkinson and F.G.A. Stone, *Comprehensive Organometallic Chemistry*, Vol. 5, Pergamon, Oxford, 1982, p. 277.
[9] L. Sutin and C. Moberg, unpublished results.
[10] R.L. Halterman, *Chem. Rev.*, *92* (1992) 965.
[11] E. Cesarotti, H.B. Kagan, R. Goddard and C. Krüger, *J. Organomet. Chem.*, *162* (1978) 297.
[12] J. Chatt and L.M. Venanzi, *J. Chem. Soc.*, (1957) 4735.

[13] J.W. Kang, K. Moseley and P.M. Maitlis, *J. Am. Chem. Soc.*, *91* (1969) 5970.
[14] J.A. Ramsden, D.J. Milner, H. Adams, N.A. Bailey, A.J. Smith and C. White, *Organometallics*, *14* (1995) 2575.
[15] P.A. Schofield, H. Adams, N.A. Bailey, E. Cesarotti and C. White, *J. Organomet. Chem.*, *412* (1991) 273; Y. Ma and R.G. Bergman, *Organometallics*, *13* (1994) 2548 and 4648 (corrections).
[16] K. Kano, M. Tatsumi and S. Hashimoto, *J. Org. Chem.*, *56* (1991) 6579; K. Kano, S. Arimoto and T. Ishimura, *J. Chem. Soc., Perkin Trans. 2*, (1995) 1661 and references cited therein.
[17] L. Tottie and C. Moberg, unpublished results.
[18] S. Winstein, B.K. Morse, E. Grunwald, H.W. Jones, J. Corse, D. Trifan and H. Marshall, *J. Am. Chem. Soc.*, *74* (1952) 1127.
[19] A. Wagner, M.-P. Heitz and C. Mioskowski, *Tetrahedron Lett.*, *30* (1989) 557.