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Structural studies on a Pd allyl complex containing a sugar-based thiophosphine chiral auxiliary†

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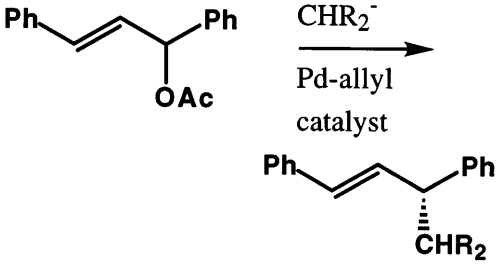
ABSTRACT: A ^{1}H, ^{13}C and ^{31}P NMR study on the enantioselective allylic alkylation catalyst [Pd(η^3-PhCHCHCHPh)(**1**)]CF_3SO_3, **2**, where **1** = (R)-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose)-1-[(*S*)-diphenylphosphino)ferrocenyl]ethylthioether, has shown that (a) the major isomer in solution has the *exo*, *syn/syn* structure, (b) both steric and electronic effects are operative in directing the incoming nucleophile, (c) the thiosugar moiety is sufficiently close to one end of the 1,3-diphenylallyl ligand that at 233 K there is restricted rotation around the C(allyl)—C(*ipso*-phenyl) bond (this latter steric interaction is partially reflected in the ^{13}C chemical shift of the proximate allyl carbon), (d) the ground-state structure reveals a conformation for the six-membered chelate ring in which the methyl group is axial and (e) there is no correlation between the population of the diastereomers in solution and the observed enantiomeric excess.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{31}P NMR; palladium–allyl complex; enantioselective alkylation; structure; restricted rotation

INTRODUCTION

Organometallic reagents have become an integral part of the organic chemists synthetic tool kit.[1] Especially interesting are those metal complexes which function both catalytically and enantioselectively.[2] In this connection, palladium complexes have been extensively employed in the making of new carbon–carbon bonds, e.g. via either cross-coupling or Heck chemistry.[3,4]

Apart from these two reaction types, the palladium-catalyzed enantioselective allylic alkylation has been widely studied,[5–7] with an increasing variety of chiral auxiliaries achieving excellent enantiomeric excesses (*ees*). Much interest has centered on the test reaction involving 1,3-diphenylallyl acetate (or carbonate) substrates, with a suitable carbon nucleophile:



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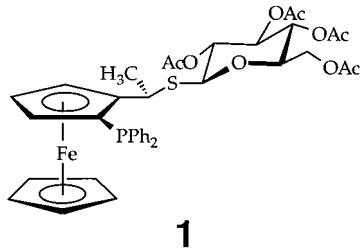
† Dedicated to Professor John D. Roberts on the occasion of his 80th birthday.

although this model has its flaws. This reaction involves oxidative addition of the acetate compound to a transient chiral Pd(0) complex to afford an isolable chiral Pd(II)–1,3-diphenylallyl complex, which is then attacked by the carbon nucleophile in the rate-determining step to afford product and regenerate the Pd(0) complex.[8]

We have been interested in using bidentate chiral sugar-based auxiliaries in enantioselective homogeneous catalysis,[9] and have prepared the phosphinoferrocene thioether **1**, (*R*)-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose)-1-[(*S*)-diphenylphosphino)ferrocenyl]ethylthioether.



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This new auxiliary affords an 88.4% *ee* in the enantioselective allylic alkylation of the racemic test substrate PhCH=CHCH(OAc)Ph using the $CH(CO_2Me)_2$ anion.[10] The attack of the nucleophile is thought to occur at the allyl terminus *trans* to phosphorus, as indicated in Scheme 1. This conclusion is based on the observed product enantiomer (determined using HPLC) plus an x-ray structure of the intermediate diphenylallyl.[10]

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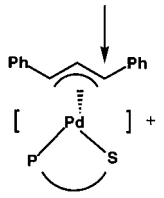
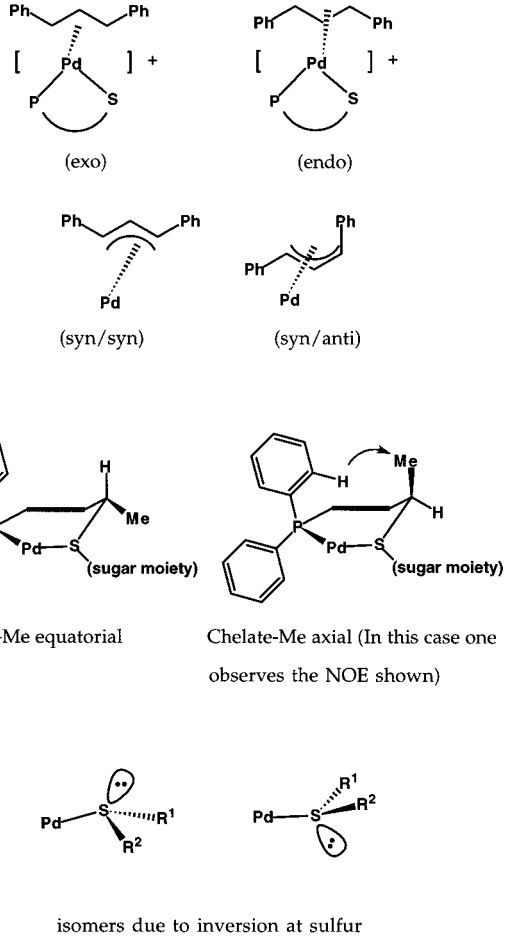


Scheme 1. Abbreviated intermediate allyl complex and the site of attack.

Nevertheless, there are a number of salient and unsettled general and structural questions: (a) how many diastereomers does one observe in solution and what are their structures?; (b) are the isomeric populations related to the observed *ee*?; (c) does one observe solution dynamics which might interconvert any of these isomers? and do the solution dynamics affect the chiral pocket?; and (d) are there NMR parameters which might reflect on allyl bonding, and/or indicate which of the terminal centers is likely to be attacked by the nucleophile?

In connection with structure, one should remember that: (a) for auxiliaries without C_2 symmetry elements, *exo* and *endo* allyl isomers often exist in equilibrium, i.e. there are two possible orientations for the allyl with respect to the auxiliary; (b) there are also possibilities for *syn/syn* and *syn/anti* isomers; (c) the six-membered chelate ring formed can take up two conformations (methyl either pseudo-equatorial or pseudo-axial); and (d) the sulfur atom represents a stereogenic center, thus requiring consideration of two additional isomeric structures and these various possibilities, a–d, are indicated in Scheme 2.



Scheme 2. Possible structural isomers of **2**.

RESULTS AND DISCUSSION

Given the numerous structural alternatives, we undertook an NMR analysis of the solution characteristics of $[Pd(\eta^3\text{-PhCHCHCHPh})(\mathbf{1})]CF_3SO_3$, **2**, shown in Scheme 3, an isolable intermediate in the catalysis.

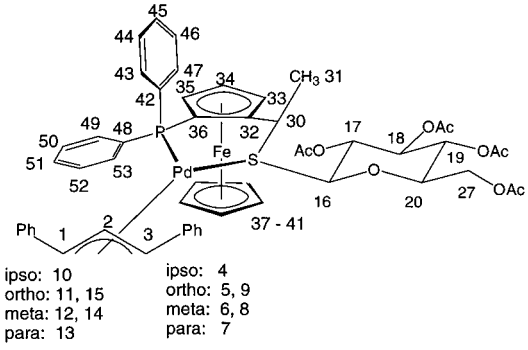
Our NMR approach reflects earlier studies: (a) assign key protons (e.g. the *ortho* protons of the *P*-phenyl rings and the three allyl protons) using a $^{31}P,^{1}H$ correlation; (b) employ NOESY and COSY measurements to assign the chiral auxiliary; (c) use intra-ligand NOEs to obtain a qualitative 3-D structure; and (d) use the phase information in the NOESY spectrum (or in this case ROESY, as the phase information is lost at 233 K) to define exchange pathways. We have previously noted that metal catalysts with moderately large chiral ligands have fairly long correlation times at reduced temperature.[11,12]

The ^{31}P NMR spectrum at room temperature shows two singlets in the ratio of *ca.* 2.7:1. Under the same conditions, the ^{1}H spectrum reveals several broad features; however, from ^{1}H 2-D exchange spectroscopy there are no indications of exchange between the two species. At 233 K the ^{1}H spectrum is sharp and still indicates two species in about the same ratio. At 183 K, the proton spectrum suggests that the equilibrium has shifted to favour the major component (*ca.* 4:1), indicating that this structure might correspond to the x-ray result. Aspects of the dynamics will be discussed after the structural section.

The Structure of 2

The solution structural data were taken from the spectra measured at 233 K. Selected NMR chemical shifts (determined via COSY, NOESY and C,H-correlation measurements) are given in Table 1.

As allyl protons in a pseudo-*trans* position to a ^{31}P spin show relatively large spin–spin coupling constants, the $^{31}P,^{1}H$ correlation pinpointed the two terminal allyl H3 protons in the isomers. Based on the observed strong NOE contacts between the allyl protons H1 and H3, (see Fig. 1), and the usual (but not always reliable)



Scheme 3. Intermediate **2** (numbering system for the major diastereomer).

Table 1. Chemical shifts[a] for the two diasteromeric isomers of **2**

^{1}H	Major	Minor
1 (allyl, *trans* to S)	4.98	5.60
2	6.96	6.65
3 (allyl, *trans* to P)	6.11	5.47
5	7.71	7.71
6,8	7.64–7.68	
9	7.97	7.71
11	6.80	7.15
12,14	7.02	
14	7.02	
15	6.80	7.15
16	2.70 (d, 9.9)	3.78
17	5.06 (d, d, 9.5)	5.17
18	4.50 (d, d, 9.7)	4.91
19	4.81 (d, d, 9.8)	4.97
20	4.81 (d, t, 10.3, 2.4)	
27[1]/27[b]	4.11/3.91	4.00/3.75
30	4.71	4.71
31	0.91	1.12
33	4.56	4.51
34	4.42	4.37
35	3.65	3.53
37–41 (Cp)	4.33	4.10
43	6.42	
44,46	7.07	
45	7.28	
47	6.42	
49,53	7.54	
^{31}P	8.84	13.68
^{13}C		
1 (*trans* to S)	82.7	89.7
2	109.7	111.6
3 (*trans* to P)	101.6	92.8

[a] At 233 K. Chemical shifts in ppm, CD_2Cl_2. Ratio major/minor = 2.7
^3J(H,H) (Hz) in parentheses.

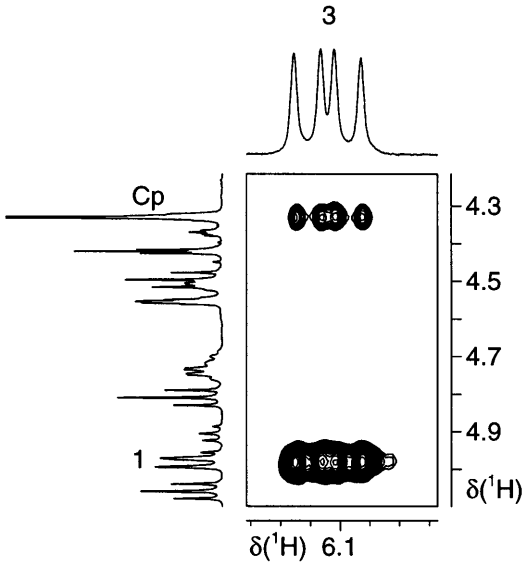
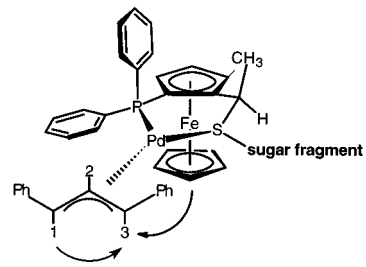


Figure 1. Section of the ROESY spectrum showing the H1,H3 intra-allyl NOE and the H3 to η^5-Cp NOE (233 K, CD_2Cl_2, 500 MHz).

geometric dependence of ^3J(H,H) spin–spin couplings on geometry, it was clear that *both* isomers have *syn/syn* geometry in the allyl. The ^3J(H,H) value is not completely reliable in complexes since coordination of the allyl distorts the *anti* protons *ca.* 30° out of the allyl plane,[13–15] thus markedly changing the dihedral angles between the central proton H2 and the *anti* protons H1 and H3. Despite this, it is often, but not always, possible to use this coupling constant to differentiate between *syn* and *anti* structures. The H1,H3 NOE is more reliable.

The unexpected but marked NOE from the allyl proton H3 of the major isomer to the five equivalent protons of the lower η^5-Cp ring (also shown in Fig. 1, and indicated in Scheme 4) is indicated in **3** and supports an *exo* structure for this isomer. In the minor isomer one observes NOEs from the *P*-phenyl *ortho* protons H43,47 to *both* H1 and H3, thus supporting an *endo* structure.

Interestingly, in both isomers, there are strong NOEs from these same *P*-phenyl *ortho* protons H43,47 to the six-membered ring chelate methyl groups. This NOE (see Fig. 2), indicated in Scheme 2 by an arrow, shows these methyl groups to be pseudo-axial. This represents a rare arrangement for this type of ferrocene ligand. In more than a dozen chelating bisphosphine– and phosphine–pyrazole ferrocene-type complexes, this methyl is *always* pseudo-equatorial.[16]



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Scheme 4. Major isomer, **3**, showing NOE from allyl H3 to Cp and from H1 to H3. These support the *exo*, *syn/syn* structure.

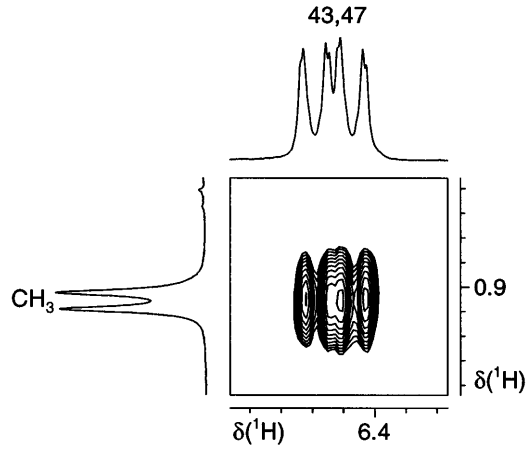
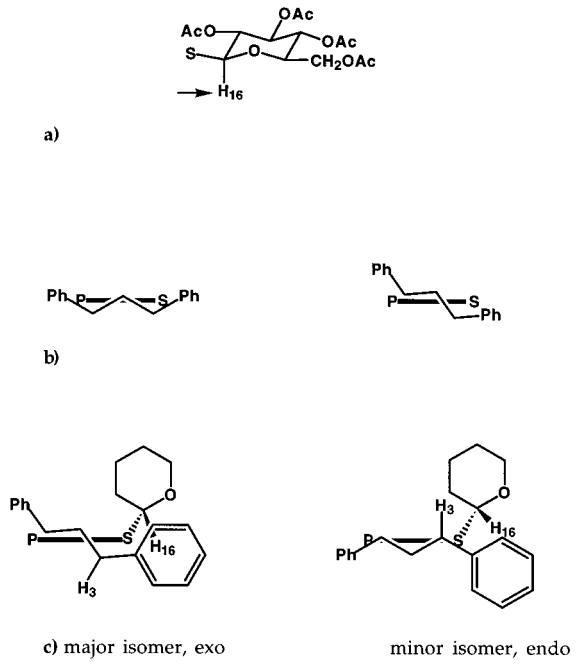


Figure 2. NOE from the chelate-ring methyl group to the *P*-phenyl *ortho* protons H43,47 (233 K CD_2Cl_2, 500 MHz).



Scheme 5. (a) Thioglucose fragment showing H16. (b) View from behind the allyl showing both routine (left) and rotated (right) 1,3-diphenylallyl ligands. The P—Pd—S coordination plane is shown as a dark bar. (c) Fragments showing H16 in the major isomer, left, relative to the allylphenyl and H16 in the minor isomer, right.

Determining the geometry at the stereogenic sulfur center in the major isomer is not simple, although there are suggestive data. The proton chemical shifts for the anomeric sugar methine, H16, (see Scheme 5), in the two isomers are observed at $\delta = 2.70$ (major) and $\delta = 3.78$ (minor). We attribute this difference to an anisotropic effect from the proximate allyl phenyl group. One should remember that the allyl is most likely rotated, as shown in Scheme 5. This rotation is not a prerequisite for the shielding, but the NOE from H3 to the Cp, mentioned above, and the fact that the allyl is rotated in the solid state require that we do not ignore this structural feature.

In any case, the low frequency shift of H16 is assigned to the differing positions of H16, relative to the allyl phenyl. In support of this we note that there is (a) a strong NOE between H3 and H16 in the major (and also in the minor) isomer and (b) modest-to-strong NOEs from H16 to the two **non-equivalent** *ortho* protons, H5 and H9, of this proximate phenyl group (see Fig. 3). The observation of these non-equivalent *ortho* protons is consistent with a close approach of the sugar moiety to this allyl phenyl, with resulting restricted rotation around the C(allyl)—C(*ipso*-phenyl) bond. Given these chemical shift and NOE data, we assign the sugar moiety in the major isomer to a **pseudo-equatorial** position with the sulfur lone-pair directed down into the relatively open space below the P—Pd—S coordination plane, in agreement with Gillespie *et al.*'s ideas on valence lone pairs.[17] As we observe several NOEs from the H17 and H19 sugar methine groups to the chelate ring methyl, we can eliminate a structure, for the major isomer, with the sugar moiety below and the sulfur lone-pair directed away from (above) the coordination plane.

We cannot be so precise with respect to the minor isomer. We observe similar NOEs from the H17 and H19 sugar methine groups to the chelate ring methyl group, suggesting a similar placement of the thio sugar relative to the chelate ring. Further, as noted above, there is an NOE from the allyl H3 to the sugar proton H16, supporting a structure with the sugar moiety

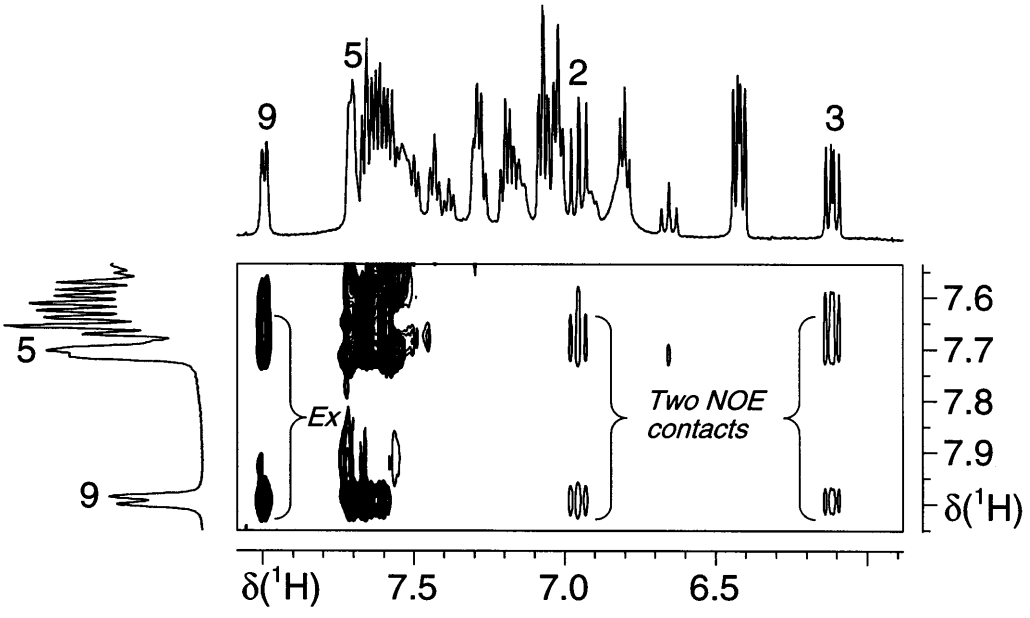
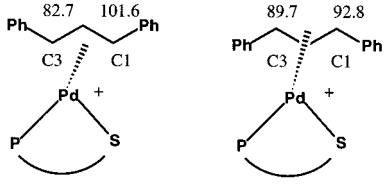


Figure 3. Slice through the ROESY spectrum showing (a) exchange of the two non-equivalent allyl phenyl *ortho* protons, H5 and H9 (filled-in cross peaks), and (b) their NOEs to the allyl protons H3 and H2, as open cross peaks. H2 is a triplet due to two approximately equal splittings from H1 and H3; H3 is a doublet of doublets arising from ^{31}P and ^{1}H coupling (233 K, CD_2Cl_2 , 500 MHz).

above the coordination plane. Since the allyl has *syn/syn* geometry, we believe the structure of the minor isomer differs only in the relationship of the allyl to the chiral auxiliary.

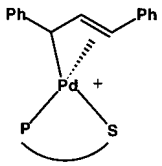
Bonding and carbon chemical shifts

Previous studies[18–20] have shown that terminal allyl ^{13}C chemical shifts are capable of reflecting bonding characteristics in allyl–palladium complexes. For **2** these data are given in Scheme 6.



Scheme 6. ^{13}C data for the terminal allyl carbons.

Allowing that the tertiary phosphine has a stronger *trans* influence than the thioether,[21,22] one expects the carbon resonance for the allyl terminus pseudo-*trans* to the P-donor at higher frequency. However, the observed difference in the major isomer, $\Delta\delta = 18.9$ ppm, is large. We attribute this separation to both electronic and steric effects with an additional steric weakening of the Pd—C allyl bonding as a result of the proximate sugar ring [which is noted above to be close enough to result in restricted rotation around the C(allyl)—C(*ipso*-phenyl) bond]. This asymmetry in the allyl bonding can be pictured in its extreme 'ene-yl' form, as **4**. Structure **4** suggests that the terminal allyl carbon pseudo-*trans* to the P-donor will be the more electrophilic and, consistent with the catalytic result,[10] more susceptible to attack from the nucleophile.



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Dynamics and catalysis

The catalytic experiments are carried out at, or slightly above, room temperature. For the major isomer, close inspection of the proton spectrum at ambient temperature reveals that the three allyl resonances are relatively sharp; however, many of the sugar methine signals (and especially H16) are broad. It is unlikely that the thioether dissociates, as this should strongly affect the H1 and H3 allyl protons, which, in turn, often reflect on dynamics.[24] Moreover, an *ee* of 88% would be surprising if the chiral pocket were so markedly disturbed. At ambient temperature the allyl *ortho* protons, H5,9, are now found as a broad signal of integral two, instead of the two well resolved resonances at 233 K. Clearly this ring is now slowly rotating, thus inducing (relatively slow) motions in the sugar ring with concomitant broadening of its proton resonances. In any case, the **chiral pocket cannot be very rigid at this temperature** owing to these dynamics. As rigidity can be important,[25] this may explain why, although auxiliary **1** works well, other chelates are better.[7]

Although all of these structural data and conclusions are useful, they need not reflect on the enantioselective step in the catalysis should the transition-state structure be significantly different. However, if the reaction mechanism involves an 'early' transition state, this might 'remember' some of these structural features. In any case, the observed *ca.* 2.7:1 ratio of the two isomers does not correlate with the experimental *ee* of 88% (*ca.* 94% *S*: 6% *R*), implying differences in the rates of attack of the nucleophile and/or as yet uncharacterized equilibria.

EXPERIMENTAL

The complex **2** has been prepared by us previously.[10] The two-dimensional $^{31}P,^{1}H$-correlation and COSY measurements were carried out at 500 MHz for ^{1}H as reported previously.[9–13] The ROESY (and although not discussed, NOESY) spectra for **2** were measured twice at 233 K (500 MHz, CD_2Cl_2), with a 0.4 s spin-lock. The carrier frequency was initially set in the middle of the proton spectrum; however, in a second measurement, it was set at *ca.* 5.8 ppm, which proved superior.

Acknowledgments

It is a pleasure for P.S.P. to dedicate this paper to Professor J. D. Roberts, who, without realising it, is responsible for the senior author's interest in organometallic chemistry. P.S.P. thanks the Swiss National Science Foundation and the ETH for support and the Johnson-Matthey Research Foundation, Reading, UK, for the loan of precious metals.

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