phosphonates.[14] Thiol exchange with ethanedithiol in an aqueous tetrahydrofuran solution resulted in formation of compound **2b**.

Brevibacterium ammoniagenes was chosen as the enzyme source. While whole cells have been used previously in CoA synthesis,[11] it was expected that for the nucleophile-sensitive thioester analog a partially purified enzyme preparation would be necessary. *Brevibacterium ammoniagenes* was grown following a literature procedure.[11] The two enzymes were initially separated by ion exchange chromatography on DEAE Sepharose.[15] Dephospho-CoA kinase was further purified by dye ligand chromatography on red A-argarose.[16] The enzymes were coimmobilized in polyacrylamide gel.[17]

In preparative enzyme reactions, substrate **2b** was not isolated but was generated from **6c** and ethanedithiol just prior to use and analyzed via HPLC. Reactions were performed by combining compound **2b** (0.42 mmol, 20 mM final concentration), ethanedithiol (10 μL), magnesium chloride (0.5 mL, 0.5 M), ATP (10 mL, 0.1 M in 0.1 M HEPES buffer, pH adjusted to ~6 with LiOH), and inorganic pyrophosphatase (~5 units) in HEPES buffer (11 mL, 0.1 M, pH 7.5) followed by addition of the immobilized enzymes E_1 and E_2 (approximately 0.2 unit of each enzyme). The reaction mixture was stirred at room temperature under nitrogen to minimize oxidation of the thiols. Reaction progress was monitored by HPLC and was judged complete when ATP consumption stopped (2 days). No difference in rates was observed in the enzymatic conversion of **2b** to **1b** versus the rate determinations with the natural substrate. The crude enzyme product was reacted with the amine nucleophile **7** at alkaline pH. Adsorption/desorption on acidified charcoal and ECTEOLA cellulose chromatography[18] followed by C-8 reversed-phase chromatography provided compound **3** (45 mg, 12% from **6a**). The product **3** was characterized by ^1H, ^{31}P, and ^{13}C NMR spectroscopy, elemental analysis, and high-resolution mass spectrometry.[19] This methodology is now being employed in the synthesis of a range of novel CoA analogs for a variety of applications.

In addition to providing convenient access to an unlimited range of CoA analogs, the methodology described here represents a novel concept in utilizing enzymes as catalysts in organic synthesis. This enzymatic synthesis of an easily derivatized analog, followed by introduction of the functionality of interest in a final chemical step, minimizes substrate specificity limitations.[20] We expect that this concept may find similar applications in other classes of compounds.

Acknowledgment. We thank Richard T. Bibart for the synthesis of PAN and Christopher Smith for assistance in enzyme purification. This work was supported by NIH Grant GM 45831.

Registry No. 1b, 142611-88-9; **2b**, 142611-87-8; **3**, 66442-95-3; **4**, 79-83-4; **5a**, 142611-89-0; **5b**, 142611-90-3; **6a**, 142611-91-4; **6b**, 142611-92-5; **6c**, 142611-93-6; **7**, 142611-94-7; ATP, 56-65-5; PhSH, 4985-62-0; $(CH_3O)_2P(O)Cl$, 813-77-4; $HSCH_2CH_2SH$, 540-63-6; dephospho-CoA kinase, 9026-83-9; dephospho-CoA pyrophosphorylase, 9026-99-7.

Supplementary Material Available: Experimental details and characterization data for compounds **1b**, **2b**, **3**, and **5a-7** (6 pages). Ordering information is given on any current masthead page.

(14) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; Mckenna, M. *Tetrahedron Lett.* **1977**, 155.

(15) While a bifunctional enzyme catalyzing these two reactions has been purified from pork liver,[10] the enzyme(s) of *Brevibacterium ammoniagenes* and other microbial species had not to our knowledge been characterized previously. The two reactions were found to be catalyzed by separate enzymes easily separated on ion exchange chromatography. Details of the enzyme isolation are included in the supplementary material.

(16) *Dye-Ligand Chromatography: Applications, Methods, Theory of Mâtrex™ Gel Media*; Amicon Corporation Publications: Lexington, MA, 1980. Scopes, R. K. *Protein Purification: Principles and Practice*; Springer-Verlag: New York, 1987.

(17) Pollak, A.; Blumenfeld, H.; Wax, M.; Baughn, R. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 6324.

(18) Shimizu, S.; Esumi, A.; Komaki, R.; Yamada, H. *Appl. Environ. Microbiol.* **1984**, *48*, 1118. Shimizu, M.; Nagase, O.; Okada, S.; Hosokawa, Y.; Tagawa, H.; Abiko, Y.; Suzuki, T. *Chem. Pharm. Bull.* **1967**, *15*, 655.

(19) Data available in supplementary material.

(20) In parallel reactions, direct enzymatic synthesis of compound **3** from the corresponding acetonyldethiophosphopantetheine analog (see ref 13) was found to proceed at a rate less than 5% that of the rate of conversion of **2b** to **1b**.

Double C-H Activation at the α-Carbon of Cyclic Ethers by $Tp^*Ir(C_2H_4)_2$

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The activation of C-H bonds by pyrazolyl borate complexes of rhodium and iridium is receiving increased attention.[1,2] We recently demonstrated[3] that the complex $Tp^*Ir(H)(CH{=}CH_2)(C_2H_4)$ (**2**) ($Tp^* = HB(3,5\text{-}Me_2\text{-}pz)_3$) undergoes intramolecular coupling of the vinyl and ethylene ligands with formation of the allylic complex $Tp^*Ir(H)(\eta^3\text{-}CH_2CHCHMe)$ (**3**). Now we show that the hydride-vinyl **2** is also capable of regioselectively activating the two C-H bonds of the O-bearing methylene groups of cyclic ethers (e.g., tetrahydrofuran (THF)) with formation of Fischer-type carbene derivatives, which also contain an Ir-H and an Ir-butyl functionality.

Heating a THF solution of the bis(ethylene) complex **1** (60 °C, 8 h) quantitatively leads to a mixture of two complexes in a 1:1 ratio. One of them is the already mentioned allyl **3**, while for the other, **4**, analytical and spectroscopic studies (including 2D ^1H-^1H and ^1H-^{13}C NMR experiments) suggest the formulation shown in Scheme I. This has been confirmed by X-ray studies,[4] whose results are shown in Figure 1.

Formation of **4** constitutes an unprecedented double dehydrogenation of one of the α-methylene groups of tetrahydrofuran.[5]

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[‡] CSIC-Universidad Complutense.

(1) (a) Barrientos, C.; Ghosh, C. K.; Graham, W. A. G.; Thomas, M. J. *J. Organomet. Chem.* **1990**, *394*, C31. (b) Ghosh, C. K.; Hoyano, J. K.; Krentz, R.; Graham, W. A. G. *J. Am. Chem. Soc.* **1989**, *111*, 5480. (c) Ghosh, C. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1989**, *111*, 375. (d) Ghosh, C. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1987**, *109*, 4726.

(2) (a) Fernández, M. J.; Rodríguez, M. J.; Oro, L. A.; Lahoz, F. J. *J. Chem. Soc., Dalton Trans.* **1989**, 2073. (b) Tanke, R.; Crabtree, R. H. *Inorg. Chem.* **1989**, *28*, 3444.

(3) Pérez, P. J.; Poveda, M. L.; Carmona, E. *J. Chem. Soc., Chem. Commun.* **1992**, 8; *J. Chem. Soc., Chem. Commun.* **1992**, 558.

(4) Crystal data for $Tp^*Ir(H)(n\text{-}C_4H_9)(=\overline{C(CH_2)_3O})$: triclinic, $P\bar{1}$; a = 10.435 (8) Å, b = 10.809 (4) Å, c = 13.888 (2) Å, α = 81.54 (2)°, β = 68.43 (4)°, γ = 63.02 (3)°, V = 1298.8 (6) Å^3, Z = 2, ρ_{calcd} = 1.58 g cm^{-3}; λ (Mo Kα) = 0.710 69 Å (graphite monochromator); final R = 0.026, R_w = 0.029. The metal-bound hydrogen atom, H(1), was located in a final difference Fourier synthesis as the highest peak in the map.

(5) Radical C-H activation of THF by transition metal compounds is a known process. See: Bevan, P. C.; Chatt, J.; Diamantis, A. A.; Head, R. A.; Heath, G. A.; Leigh, G. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1711. Setsune, J.; Ishimaru, Y.; Moriyama, T.; Kitao, T. *J. Chem. Soc., Chem. Commun.* **1991**, 556. Double α-C-H abstractions from phosphines[6a,b] and amines[6c] are also known. We are not aware, however, of such an activation of ethers, although very recently a 1,1-elimination of molecular hydrogen from 1,3-dimethoxypropane by a bare transition metal ion in the gas phase was reported: Prüsse, T.; Fiedler, A.; Schwarz, H. *J. Am. Chem. Soc.* **1991**, *113*, 8335. Dehydrogenation of one of the α-methylene groups of tetrahydrofuran with formation of lactone is selectively effected by the powerful oxidant RuO_4. See: Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682. Raychandhuri, S. R.; Ghosh, S.; Salomon, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 6841.

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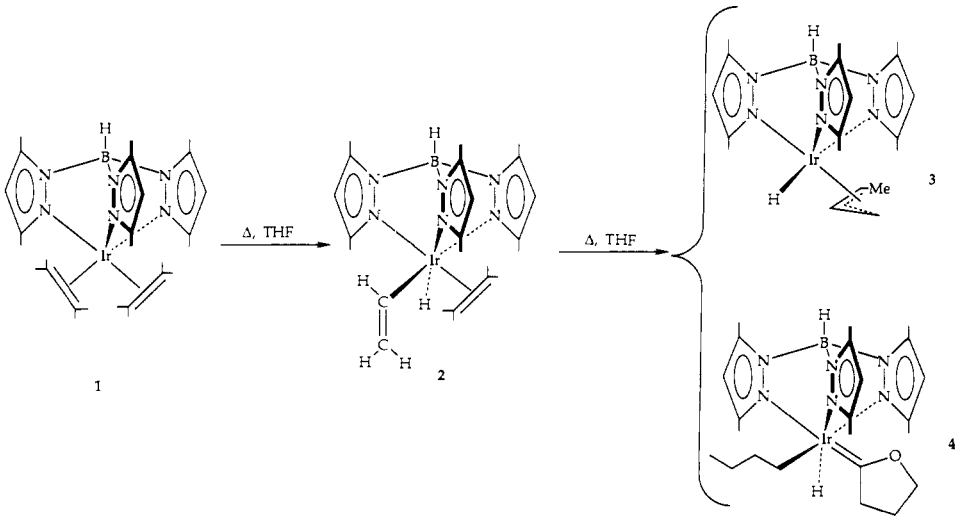
Scheme I[a]



[a] The Tp* ligand in **1** may be bidentate. See refs 1b and 2b.

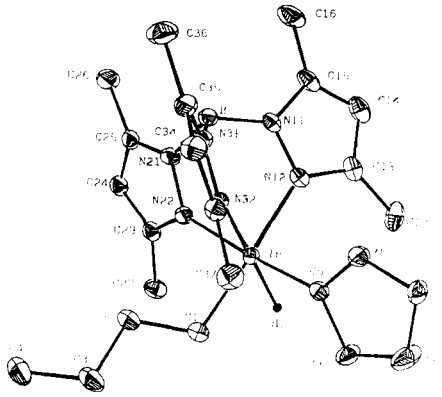


Figure 1. ORTEP diagram for **4** and atom labeling scheme. Important bond distances (Å) and angles (deg) include the following: Ir–H(1) 1.8 (1), Ir–C(1) 2.106 (5), Ir–C(5) 1.881 (5); C(1)–Ir–C(5) 92.0 (3), Ir–C(5)–C(6) 131.4 (5), Ir–C(5)–O 120.8 (4), C(6)–C(5)–O 107.8 (5).

In a formal sense, one of the abstracted H atoms ends up as a hydride ligand while the other becomes incorporated into the hydrocarbon fragment resulting from the coupling of the two molecules of ethylene. Reactivity studies show that **4** does not form from **3** and THF. Furthermore, complexes **3** and **4** originate from **1** as a result of different, competitive pathways through a common intermediate, the hydride–vinyl **2**. This has been demonstrated by NMR monitoring of the thermal activation of **1** and, moreover, by the direct and faster conversion of pure **2**[3] (60 °C, THF, 4 h) into the same 1:1 mixture of **3** and **4**.

Mechanistic studies aimed at clarifying this transformation are presently being pursued. At this stage we note that the process is likely initiated by insertion of the olefin into the Ir–H bond of **2** to give an unsaturated Ir–Et species.[7] In accord with this, the reaction of **2** with PMe_3 at 60 °C affords the thermally stable ethyl complex $Tp^*Ir(CH_2CH_3)(CH{=}CH_2)(PMe_3)$.[8] As for the C–H activation reaction, whether or not it needs anchimeric assistance by O-coordination of THF is presently not known. Heteroatom coordination seems to be required for the metalation of Lewis bases,[6,9] but in the present case the intermediacy of a "C–H σ-bond complex" is also conceivable, such a species having being recently proposed in some olefinic C–H activations.[10]

Table I. Thermal Decomposition of Complex **1** in Cyclic Ethers[a]

Solvent		Me			
	3 (40%) + [Ir] (60%)	3 (45%) + [Ir] Me (55%)	3 (20%) + [Ir] (50%) + [Ir] (30%)	3	3 (60%) + [Ir] (40%)

[a] All reactions were performed at 60 °C to completion (ca. 8 h). Percentage yields are in parentheses and refer to the crude materials (^{1}H NMR). The new carbene derivatives are purified by chromatography and/or crystallization. [Ir] ≡ Tp*Ir(H)(*n*-Bu) [b] Mixture of the two possible diastereoisomers (1:1 ratio). [c] No carbene formed in more than trace amounts.

The cyclic carbene ligand present in the molecules of **4** is a common functionality in transition metal carbene chemistry,[11] including that of iridium.[12] In no case, however, have compounds of this type been obtained from THF. Other five- and also six-membered cyclic ethers undergo analogous C–H activations (Table I), provided a CH_2O functionality exists (2,5-Me_2THF and 2,2,5,5-Me_4THF afford exclusively the allylic species **3**). As shown in Table I, the five-membered heterocycles seem to be more reactive than those containing six-membered rings, and on the other hand, the presence of two heteroatoms in the ring favors the C–H activation reaction. Curiously enough, tetrahydropyran, $C_5H_{10}O$, does not yield an oxycarbene analogous to **4**. This is probably due to a larger kinetic barrier of steric origin associated

(6) (a) Gibson, V. C.; Graimann, C. E.; Hare, P. M.; Green, M. L. H.; Bandy, J. A.; Grebenik, P. D.; Prout, K. *J. Chem. Soc., Dalton Trans.* **1985**, 2025. (b) Gibson, V. C.; Kee, T. P.; Carter, S. T.; Sanner, R. D.; Clegg, W. *J. Organomet. Chem.* **1991**, *418*, 197. (c) Rosenberg, E.; Kabir, S. E.; Hardcastle, K. I.; Day, M.; Wolf, E. *Organometallics* **1990**, *9*, 2214.

(7) A related C–H activation process followed by hydride transfer to an alkene ligand has been reported recently by Ghosh and Graham.[1c]

(8) Unpublished results from this laboratory.

(9) For some examples of α-monometalations, see: Rabinovich, D.; Parkin, G. *J. Am. Chem. Soc.* **1990**, *112*, 5381 and references cited therein (M-$(PMe_3)_n$ complexes). Jordan, R. F. *Adv. Organomet. Chem.* **1991**, *32*, 325 (pyridine derivatives). Hanton, L. R.; Kemmit, T. *J. Chem. Soc., Chem. Commun.* **1991**, 700 and references therein (metalation of thioethers).

(10) Kafafi, Z. H.; Hange, R. H.; Margrave, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 7550.

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(12) For some recent examples, see: O'Connor, J. M.; Pu, L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 6232.

with this transformation, which causes the reaction to proceed exclusively through the alternative pathway leading to the allyl **3**. Work directed toward a better understanding of this and other aspects of these interesting transformations is presently under way.

Acknowledgment. We thank Dr. Brevard (Bruker Spectrospin, France) for the 2D NMR experiments carried out with complex **4**. M.C.N. and P.J.P. thank the Spanish Ministry of Education (MEC) for research grants. O.B. and E.C. thank the EEC for the award of a research grant (Contract No. SC1* 481). We also gratefully acknowledge generous support from the Dirección General de Investigación Científica y Técnica (Proyecto PB87-0201-C03-01) and the Junta de Andalucía.

Note Added in Proof. We have recently learned that some Russian workers have observed the formation in very low yields of oxycarbene ligands derived from tetrahydrofuran in a photochemically induced radical process. See: Ustynyuk, N. A.; Vinogradova, V. N.; Kravtsov, D. N.; Oprunenko, Y. F.; Batsanov, A. S.; Struchkov, Y. T. *Organometallic Chem. USSR* **1991**, *4*, 155. We thank Dr. M. J. Winter (University of Sheffield) for bringing this work to our attention.

Supplementary Material Available: Tables of crystal and intensity collection data, bond distances and angles, atomic coordinates, and thermal parameters for Tp*Ir(H)(*n*-C_4H_9)(=C-$(CH_2)_3O$) (4 pages); listing of observed and calculated structure factors (38 pages). Ordering information is given on any current masthead page.

Stepwise Metal-Assisted Reduction of η^4-Coordinated Benzene to Cyclohexene

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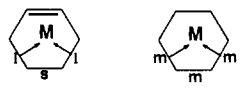
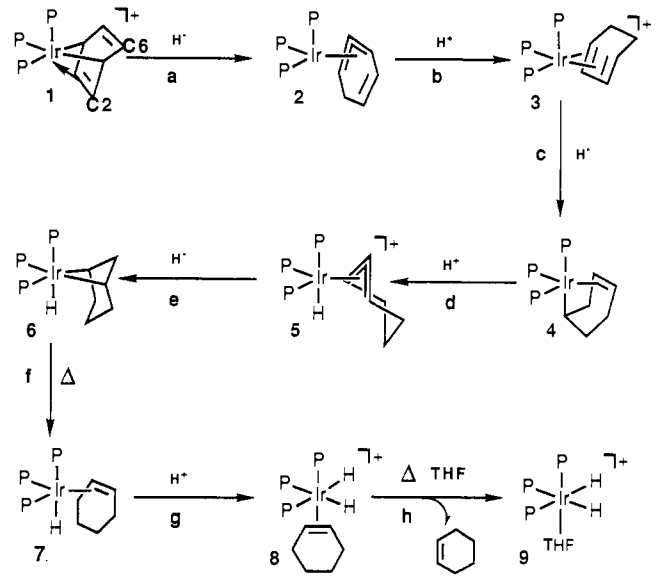
The chemical reactivity of benzene coordinated in an η^4 fashion[1] is unexplored, but it is anticipated to be unusual (e.g., different from that of cyclohexadiene) since it is established that the pattern of C/C bond lengths of this ligand (**A**; s = short, m = medium, l = long) differs markedly from that of cyclohexadiene (and all conjugated dienes) coordinated to the late transition metals (**B**).[2] We report here the regiochemistry of reduction of η^4-benzene coordinated to $[MeC(CH_2PPh_2)_3]Ir^+$ ((triphos)Ir^+).



A **B**

Treatment[3] (Scheme I) of (triphos)Ir(η^4-benzene)$^+$ with a 5-fold excess of $LiHBEt_3$ in THF at 25 °C gives (1 h) yellow (triphos)Ir(η^3-cyclohexadienyl) (**2**).[4,5] The ^1H NMR spectrum of **2** at 20 °C shows seven resonances for the cyclohexadienyl ring, which indicates that migration of Ir to the uncomplexed vinyl carbons, if it occurs at all, is slow.

Scheme I



Compound **2** is protonated immediately (by $HBF_4{\cdot}OEt_2$, HSO_3CF_3, or even EtOH) in THF to give (triphos)Ir(η^4-cyclohexadiene)$^+$ (**3**).[6,7] This molecule shows phosphorus site exchange which is rapid at 20 °C but slowed (AM_2 $^{31}P\{^1H\}$ NMR pattern) at −50 °C; the variable temperature $^{13}C\{^1H\}$ NMR spectrum shows mirror symmetry, with P-C coupling consistent with the phosphorus site exchange.

Treatment of **3** with 5 equiv of $LiHBEt_3$ in THF gives immediate and complete transformation to **4**, a cyclohex-1-en-4-yl complex, by delivery of hydride to the internal carbon of the diene.[8,9] The lack of mirror symmetry in the ^{13}C NMR spectrum shows that the C_6H_9 ring is *not* bound by three contiguous carbons to Ir (i.e., η^3-allyl), and the one large J(PC) value to an sp^3-hybridized carbon (10.0 ppm) suggests a structure with that carbon trans to P in a trigonal bipyramid.

Protonation (stoichiometric $HBF_4{\cdot}OEt_2$ in THF at 25 °C) of **4** yields a monohydride cation, **5**, in which the cyclohex-1-en-4-yl ligand has been isomerized to an η^3-allyl bonding mode.[10,11] The hydride signal shows large (129 Hz) coupling to one phosphorus, suggesting a location trans to one phosphorus and cis (15 Hz) to the other two.

Hydride transfer (5 equiv of $LiHBEt_3$ in THF) to the cation **5** occurs to the central carbon of the allyl group to yield **6**,[12] whose

(4) Selected spectral data: $^{31}P\{^1H\}$ NMR (−70 °C, THF-d_8) δ_A = −17.64 (dd), δ_M = −19.46 (dd), δ_Q = −24.11 (dd), J_{AM} = 28, J_{AQ} = 15, J_{MQ} = 22 Hz; ^1H NMR (20 °C, THF-d_8) 6.78 (br, 1 H), 4.89 (br d, J = 8 Hz, 1 H), 4.65 (br, 1 H), 3.68 (br, 1 H), 3.43 (br, 1 H), as well as lines at 2.0 and 1.6 ppm (masked by triphos CH_2 and CH_3) detected by $^1H^1H$-COSY experiments.

(5) In THF, compound **2** transforms (slowly at 20 °C or within 2 h at 50 °C) into (triphos)$Ir(H)_2(C_6H_5)$ by apparent oxidative addition of two C–H bonds ($Ir^I \rightarrow Ir^{III}$). This product was made independently by thermal (60 °C) oxidative addition of benzene following elimination of ethane from (triphos)$Ir(H)_2Et$.

(6) Selected spectral data: $^{31}P\{^1H\}$ NMR (−50 °C, CD_2Cl_2) δ_A = −19.45, δ_M = −24.11, J_{AM} = 8 Hz; $^{13}C\{^1H\}$ NMR (20 °C, CD_2Cl_2) vinylic carbons at 85.24 (s), 53.74 (q, J_{CP} = 10 Hz), and 25.59 (q, CH_2, J_{CP} = 3 Hz).

(7) This compound can be independently synthesized in 80% yield by reflux (3 h in THF) of **1** in the presence of 30 equiv of 1,3-cyclohexadiene.

(8) Selected spectral data: $^{31}P\{^1H\}$ NMR (20 °C, CD_2Cl_2) δ_A = −20.07, δ_M = −22.52, δ_Q = −32.61, J_{AM} = 18, J_{AQ} = 48, J_{MQ} = 17 Hz; $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 20 °C) 47.2 (ddd, J_{CP} = 35, 8, 3, vinyl), 22.96 (dd, J_{CP} = 31, 7, vinyl), 10.00 (dd, J_{CP} = 68, 5, Ir–C alkyl).

(9) In contrast to **2**, **4** is stable to ethanol.

(10) Selected spectra data (20 °C, CD_2Cl_2): $^{31}P\{^1H\}$ NMR AM_2 with δ_A = −16.59, δ_M = −26.74, J_{AM} = 25 Hz; $^{13}C\{^1H\}$ NMR 84.85 s (1 C, allylic), 59.11 (d, J_{CP} = 26 Hz, 2 allylic C), 26.49 (s, 2 C), 23.78 (d, J_{CP} = 4 Hz, 1 C); ^1H NMR −11.16 (dt, J_{PH} = 129, 15, Ir–H); IR (Nujol) 2200 cm^{-1} (Ir–H).

(11) Cation **5** was independently synthesized in 70% yield by reflux of **1** (7 h in THF) with 20 equiv of cyclohexene.

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[‡] Istituto per la Studio della Stereochimica ed. Energetica dei Composti di Coordinazione.

(1) Bianchini, C.; Caulton, K. G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T. J.; Meli, A.; Peruzzini, M.; Rauscher, D. J.; Streib, W. E.; Vizza, F. *J. Am. Chem. Soc.* **1991**, *113*, 5127.

(2) Erker, G.; Krüger, C.; Müller, G. *Adv. Organomet. Chem.* **1988**, *24*, 1.

(3) All cations were employed as BPh_4^- salts.

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