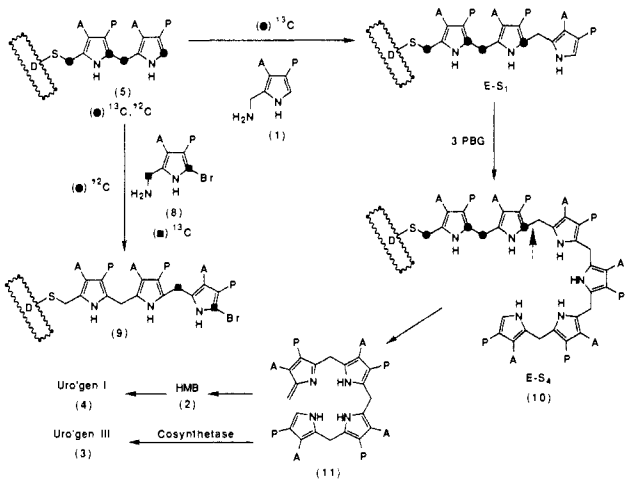
**Scheme III**




ration of the denatured enzyme solution to pH 8. Accordingly, the environment of the thioether in the native enzyme at pH 8 ($\delta$ py-$CH_2$-SR 26.7 ppm) relative to pH 12 ($\delta$ 29.7) must involve shielding by an adjacent residue, an effect which is removed by denaturation at pH 12.

Finally, the monocovalent inhibitor complex[13] (**9**, Scheme III) prepared by incubation of deaminase with [2,11-$^{13}C_2$]-2-bromo PBG (**8**) was analyzed by CMR. The difference spectrum at pH 12 (not shown) displays signals at 24.6 ppm [py-$CH_2$-py (Br)] and 97.5 ppm ($\alpha$-Br pyrrole-C) consistent with loss of ammonia from **8** to give structure **9**. The site of covalent attachment of substrate (and inhibitor) is therefore the free $\alpha$-pyrrole carbon at the terminus of the dipyrromethane in the native enzyme. The above evidence, together with our previous $^3$H NMR results, leads to the structural and mechanistic proposal shown in Scheme III. We suggest that PBG is incorporated into the apoenzyme *before* folding and that the first (kinetic) encounter of PBG deaminase with substrate involves attachment of PBG (with loss of $NH_3$) to the $\alpha$-free pyrrole position of the dipyrromethane to form the $ES_1$ complex (Scheme III). The process is repeated until the "tetra PBG" ($ES_4$) adduct **10** is formed. At this juncture site-specific cleavage of the *hexapyrrole* chain (at →) releases the azafulvene bilane (**11**) which *either* becomes the substrate of uro'gen III synthase, or, in the absence of the latter enzyme, is stereospecifically hydrated[3,8] to HMB (**2**) at pH 12, or is cyclized chemically to uro'gen I (**4**) at pH $\leq$ 8.

The previously reported $^3$H NMR spectra[2] of the $ES_1$ complex are now reinterpreted to accommodate the unexpected finding of a C-C bond between substrate and enzyme, in terms of a broad $^3$H signal at $\delta$ 3.28[2] which could be due to initial (and transitory) attachment of the substrate at the second cysteine residue[10,11] conserved in human and *E. coli* deaminase. Recent independent and complementary work from two other laboratories[9,14] has reached similar conclusions regarding the catalytic site but does not address the question of the covalent linkage to the enzyme or the exact chain length of the oligopyrrolic cofactor. The present study defines both the *number* of PBG units (two) attached to the native enzyme at pH 8 and their head-to-tail relationship (AP-AP) as well as revealing the identity of the nucleophilic group (Cys-SH) which anchors the dipyrromethane (and hence the growing oligopyrrolic chain) to the enzyme. Confirmation of these proposals by X-ray crystallography is in progress.

**Acknowledgment.** We thank the National Institutes of Health for generous support of this work (Grants GM32596 and DK32034) and the Robert A. Welch Foundation for a Fellowship (to M.D.G.). We also thank Dr. G. Müller (Stuttgart) for a reference specimen of 2-bromo PBG[15] and Dr. B. Bachman (*E. coli* Genetic Stock Center, Yale University) for *E. coli* strain SASX41B.

(13) A 1:1 adduct between enzyme and inhibitor was confirmed by nondenaturing polyacrylamide gel electrophoresis described in a forthcoming paper.[12]

(14) Warren, M. J.; Jordan, P. M. *FEBS Lett.* **1987**, *225*, 87.

(15) The use of 2-bromo PBG as covalent inhibitor of deaminase was first suggested to us by Dr. G. Müller whom we thank for details regarding its preparation.

## Translocation of Radical Sites by Intramolecular 1,5-Hydrogen Atom Transfer

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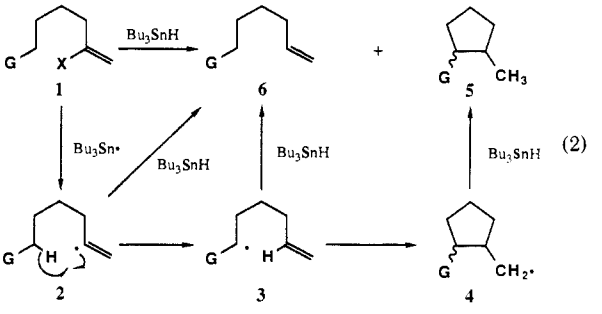
Modern free radical-based synthetic methods often apply trialkyltin hydrides to mediate chain reactions.[2] In the tin hydride method, a wide variety of carbon-heteroatom bonds serve as radical precursors (eq 1). Carbon-hydrogen bonds, by far the

$$R\text{-}X + Bu_3Sn^{\bullet} \rightarrow R^{\bullet} + Bu_3SnX \qquad (1)$$

X = halogen, thiophenyl, selenophenyl, xanthate, etc. X ≠ H

simplest "radical precursors", can never be directly used since the transfer of hydrogen atoms to tin radicals is significantly endothermic. We now report a collection of related reactions in which a free radical is produced indirectly from a carbon-hydrogen bond following initial generation of a radical at a remote site. The site of the radical is then translocated by intramolecular 1,5-hydrogen atom transfer[3] prior to the occurrence of a hexenyl radical cyclization.[4,5]

There are two variations on this theme. In one, the radical is first generated on the alkene that is destined to become the acceptor for the subsequent cyclization.[6] In the other, the radical is first generated in a protecting group. Equation 2 provides a




(2)

detailed sequence of propagation steps for the first variation.

(1) Recipient of a Sloan Foundation Fellowship, 1985-1987. Dreyfus Teacher-Scholar, 1985-1989. Eli Lilly Grantee, 1985-1987. Merck Faculty Development Awardee, 1986-1987. NIH Research Career Development Awardee, 1987-1992.

(2) Reviews: Curran, D. P. *Synthesis* **1988**, 417, 489. Neumann, W. P. *Synthesis* **1987**, 665. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(3) Hydrogen atom transfer is a fundamental reaction of organic free radicals which is a key step in transformations such as the Kharasch, Barton, and Hofmann-Löffler-Freytag reactions. Remote functionalization by intramolecular H-atom transfer has been extensively studied by Breslow. For a leading reference, see: Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045.

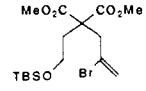
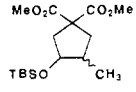
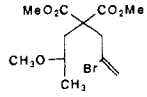
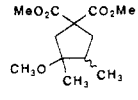
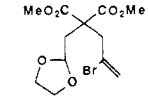
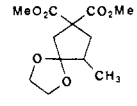
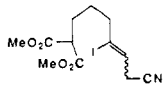
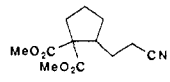
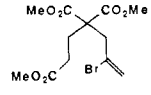
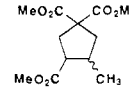
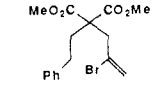
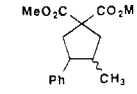
(4) (a) An example of 1,5-H atom transfer prior to an addition reaction has been reported by Giese. Giese, B.; Dupuis, J.; Hasskerl, T.; Meixner, J. *Tetrahedron Lett.* **1983**, *24*, 703. (b) For a Kharasch reaction where cyclization follows H-atom transfer, see: Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772.

(5) For some interesting examples where 1,5-hydrogen atom transfer has intervened in reactions conducted by the tin hydride method, see: Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666. Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878. Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409.

(6) Very recently, an example of this approach has appeared in which an allylic hydrogen is transferred. Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81.

0002-7863/88/1510-5900$01.50/0 

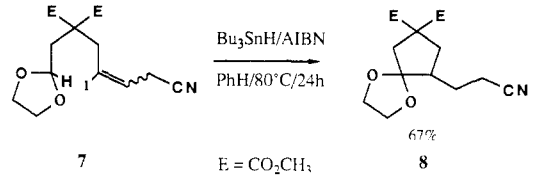
**Table I.** 1,5-Hydrogen Atom Transfer to a Vinyl Radical

| entry | precursor | method[a] | cyclic products | ratio cyclic/reduced[b] | yield of cyclic products[c] (cis/trans)[d] |
|---|---|---|---|---|---|
| a |  | B |  | 91/9 | 66%[e] (40/60) |
| b |  | B |  | 86/14 | 78% (18/82) |
| c |  | B |  | 58/42 | 38%[f] |
| d |  | A |  | >95/5 | 87% |
| e |  | B |  | 76/24 | 60%[g] (82/18) |
| f |  | B |  | 78/22 | 53%[f] (39/45/16[h]) |

[a] Method A, syringe pump addition of the tin hydride and AIBN; method B, Stork catalytic procedure, see text. [b] The reduced product refers to the dehalogenated cyclization precursor. [c] Isolated yield of cyclic products after chromatographic purification. [d] Where relevant, stereochemistry was generally assigned by γ-gauche effects in the $^{13}C$ NMR spectra. [e] Isolated yield after desilylation to the alcohol. [f] Reduced alkene was oxidized by treatment of the reaction product with mCPBA to facilitate separation. [g] Reduced alkene was oxidized by treatment of the reaction product with ozone to facilitate separation. [h] A third minor cyclic product in this case was tentatively identified as the 6-endo product.

Treatment of a vinyl halide **1** with tri-*n*-butyltin hydride results in the formation of vinyl radical **2**. 1,5-Hydrogen atom abstraction by the reactive vinyl radical can then produce the stabilized radical **3**. Hexenyl radical cyclization (**3** → **4**) is then followed by standard chain transfer to give **5**. This sequence can be derailed to give the directly reduced product **6** if either the H-atom transfer or the cyclization is slow relative to bimolecular hydrogen atom abstraction by **2** or **3** from tin hydride. Standard experimental techniques to minimize the concentration of the tin hydride should favor the formation of **5** over **6** by suppressing the rate of all bimolecular reactions involving tin. To ensure that intramolecular 1,5-hydrogen atom transfer is sufficiently rapid to propagate a chain, a radical stabilizing group (G) is introduced to weaken the C–H bond.

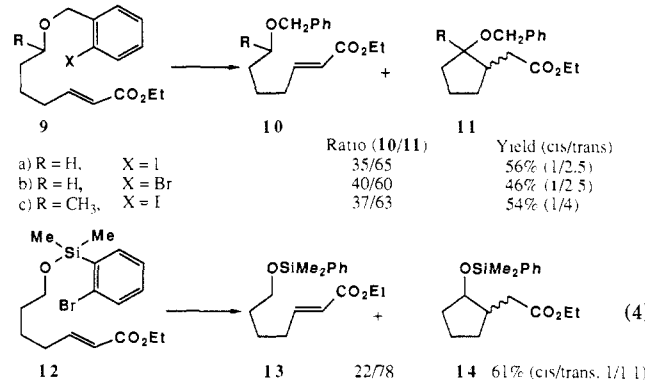
A representative example of the process is outlined in eq 3. Addition of a 0.02 M benzene solution of tri-*n*-butyltin hydride (containing 5 mol % AIBN) by syringe pump drive over 24 h to a 0.02 M benzene solution of vinyl iodide **7**[7] gave cyclic ketal **8** in 67% yield after standard chromatographic purification. There




7 E = $CO_2CH_3$ 8 (3)

was no evidence for the formation of the directly reduced (uncyclized) product under these conditions. Table I contains a variety of related examples. Protected alcohols (entries a and b), acetals (entry c), esters (entries d and e), and phenyl rings (entry f) all serve as groups which facilitate radical translocation by weakening the adjacent C–H bond.[6,8] In each of the examples, cyclic products predominated over reduced/uncyclized products under conditions of high dilution.[9] The formation of significant amounts of reduced/uncyclized products was more pronounced with vinyl bromides, which are poorer halogen donors than vinyl iodides and require higher tin hydride concentrations to maintain viable chains. Indeed, with the slow syringe drive addition of tin hydride (method A), vinyl bromides were sometimes recovered unreacted. Reproducible results were obtained with the vinyl bromides by using the catalytic tin hydride method of Stork (method B, 10% $Bu_3SnCl$, 10% AIBN, 2 equiv of $NaCNBH_3$, *tert*-butyl alcohol; 0.05 M, reflux 4–6 h).[9,10]

In the second strategy, a modified "protecting group"[11] serves as a site for generation of the initial radical. This protecting group, which contains halogen, is converted to its standard form during the radical reaction. Several applications of this concept are illustrated in eq 4. Reduction of *o*-bromobenzyl derivatives **9a–c**




9 10 11

| | | Ratio (10/11) | Yield (cis/trans) |
|---|---|---|---|
| a) R = H, | X = I | 35/65 | 56% (1/2.5) |
| b) R = H, | X = Br | 40/60 | 46% (1/2.5) |
| c) R = $CH_3$, | X = I | 37/63 | 54% (1/4) |

12 13 22/78 14 61% (cis/trans, 1/1.1) (4)

under the Stork conditions provided about a 50% isolated yield

(7) Vinyl iodide **7** and the precursor for Table I, entry d were prepared by atom transfer addition of iodoacetonitrile to an alkyne (Kim, D., unpublished results). The details of this new method will be reported separately.

(8) For pertinent mechanistic studies of substituent effects on hydrogen atom abstraction, see: Beckwith, A. L. J.; Brumby, S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1801. Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455. Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609. Beckwith, A. L. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615.

(9) In one case (Table I, entry a), reduction in the presence of $Bu_3SnD$ gave a reduced/uncyclized product with the deuterium label on the vinyl carbon. This shows that this uncyclized product results from a failure of the H-atom transfer and not of the cyclization.

(10) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

(11) Such protecting groups are usually not required for the radical reaction itself but are often needed for previous or subsequent steps in a synthetic sequence.

of the cyclic product **11**, alongside lesser amounts of the directly reduced product **10**. A sequence of propagation steps analogous to that outlined in eq 2 (halogen abstraction, 1,5-H atom transfer, cyclization, chain transfer) accounts for the formation of **11**, which now contains a simple benzyl group. The (*o*-bromophenyl)dimethylsilyl group[12] is readily introduced by standard silylation conditions, and, in the example studied, it provided a better ratio of cyclic to reduced products than did the *o*-bromobenzyl group. The reduction of **12** under the Stork conditions provided a 61% isolated yield of **14**.

The option to place a radical precursor at a site other than that where the radical is ultimately required can simplify the preparation of substrates for complex synthetic applications. Variations of the translocation strategy outlined herein should provide access to a variety of stabilized radicals for use in cyclization or addition reactions.

**Acknowledgment.** We thank the National Institutes of Health (GM33372) for funding of this work and Hoffmann-LaRoche for unrestricted support.

**Supplementary Material Available:** Spectroscopic characterization of all cyclic products in eq 3 and 4 and Table I (6 pages). Ordering information is given on any current masthead page.

(12) (*o*-Bromophenyl)dimethylsilyl chloride was prepared by silylation of *o*-bromophenyllithium. See: Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1980**, *193*, 283. This procedure was modified as follows: dimethyldichlorosilane was added before *n*-butyllithium, and the product was isolated by nonaqueous workup (evaporation of the THF, dilution with hexane, filtration, and concentration). We thank Drs. Richard Elliott and Thomas Fevig for the preparation of this silyl chloride.

## Cationic Chromium(III) Alkyls as Olefin Polymerization Catalysts

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*Received April 12, 1988*

Chromium-based catalysts are used in the commercial coordination polymerization of small olefins.[1] A particular catalyst of this type is prepared by deposition of chromocene ($Cp_2Cr$) on silica.[2] The species thus generated is thought to retain one cyclopentadienyl ligand, which is not incorporated into the growing polymer chain. We are exploring the reactivity of a class of paramagnetic chromium alkyls containing cyclopentadienyl ligands ($C_5H_5$ or $C_5Me_5$).[3] These compounds appear to be close structural models of the active site proposed for the heterogeneous catalyst. Herein we describe a number of cationic chromium(III) alkyls, some of which are catalysts for the polymerization of ethylene and propene.

Abstraction of chloride from dimeric alkyl complexes of the type $[Cp^*Cr(R)Cl]_2$ in the presence of Lewis bases yielded a series of mononuclear chromium complexes (see Scheme I).[4] Like their precursors, these compounds feature 15 valence electrons only. However, in contrast to the dimeric starting materials, and due to their monomeric nature, they exhibit the full effective magnetic moment of three unpaired electrons per chromium atom. For example, when 2.0 equiv of $TlPF_6$ were added to a THF solution of $Cp^*Cr(Et)Cl]_2$ containing 4.0 equiv of pyridine, the color of the solution changed from purple to brown and a grey precipitate (TlCl) formed. Filtration, removal of solvent, and recrystallization of the solid residue from THF/pentane yielded analytically pure $[Cp^*Cr(py)_2Et]^+PF_6^-$ (**1**) in 74% yield.[5] The crystal structure of **1** was determined by X-ray diffraction (see Figure 1).[6] The compound consisted of well-separated cations and $PF_6^-$ anions. The chromium atom exhibited the pseudooctahedral coordination environment of a three-legged piano stool. The chromium–carbon distance (Cr–C1, 2.09 Å) was essentially the same as that in the structurally characterized dimer $[CpCr(Me)Cl]_2$. The Cr–C1–C2 angle (113°) was slightly larger than the perfect tetrahedral angle, presumably reflecting the steric demand of the metal fragment. Despite the electron-deficient nature of the complex, no indication of an agostic M–H–C interaction[7] between the chromium atom

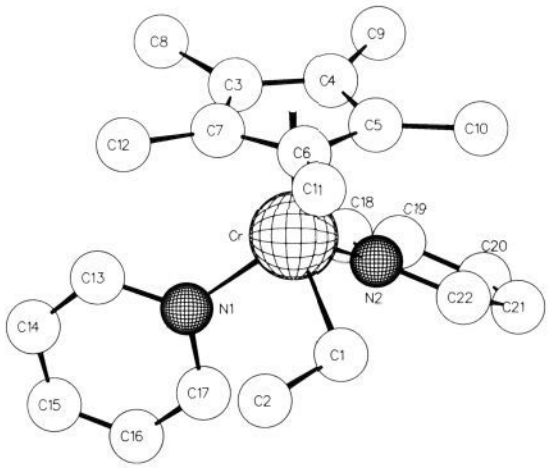
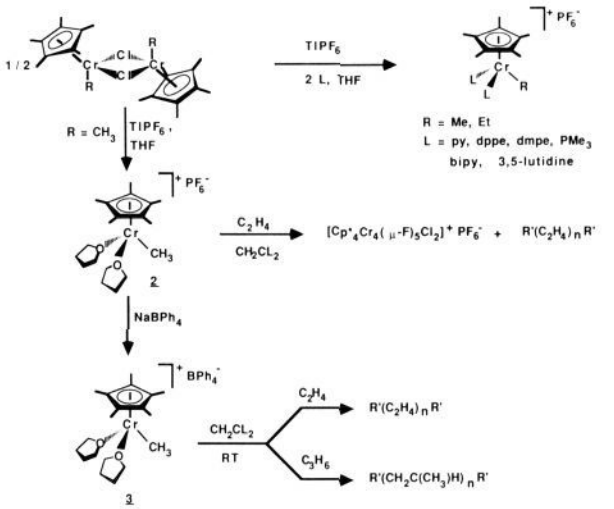



**Figure 1.** The molecular structure of the $Cp^*Cr(py)_2Et$ cation. The $PF_6$ counterion is omitted for clarity. Selected bond distances: Cr–C1, 2094 (12) Å; Cr–N1, 2.083 (9) Å; Cr–N2, 2.085 (9) Å; C1–C2, 1.521 (17) Å. Interatomic angles: C1–Cr–N1, 92.8 (4)°; C1–Cr–N2, 94.2 (4)°; N1–Cr–N2, 88.1 (3)°; Cr–C1–C2, 113.2 (8)°.

**Scheme I**




(1) (a) Karol, F. J. *Catal. Rev. Sci. Eng.* **1984**, *26*, 557. (b) Sinn, H.; Kaminsky, W. *Adv. Organomet. Chem.* **1980**, *18*, 99.

(2) (a) Karol, F. J.; Karapinka, G. L.; Wu, C.; Dow, A. W.; Johnson, R. N.; Carrick, W. L. *J. Polym. Sci. A-1* **1972**, *10*, 2621. (b) Karol, F. J.; Brown, G. L.; Davison, J. M. *J. Polym. Sci., Polym. Chem. Ed.* **1973**, *11*, 413.

(3) (a) Richeson, D. S.; Hsu, S.-W.; Fredd, N. H.; Van Duyne, G.; Theopold, K. H. *J. Am. Chem. Soc.* **1986**, *108*, 8273. (b) Richeson, D. S.; Mitchell, J. F.; Theopold, K. H *J. Am. Chem. Soc.* **1987**, *109*, 5868. (c) Thomas, B. J.; Mitchell, J. F.; Leary, J. A.; Theopold, K. H. *J. Organomet. Chem*, in press (crystal structure and characterization of $[Cp^*_4Cr_4(\mu\text{-}F)_5Cl_2]PF_6$.

(4) Satisfactory elemental analyses have been obtained for all compounds reported herein. Details of the syntheses and full characterizations will be reported in a full paper.

(5) **1**: $^1$H NMR (THF-$d_8$) 22.4, 18.9, –13.0 ppm; IR (KBr) 3587 (w), 3080 (m), 2919 (s), 2856 (s), 2728 (w), 1604 (s), 1487 (s), 1445 (s), 1382 (s), 1217 (m), 1130 (m), 1065 (s), 1012 (s), 846 (vs), 765 (s), 708 (s), 640 (s), 556 (vs), 443 (m), 401 (m) cm$^{-1}$; mp 165–170 °C; $\mu_{eff}$ = 3.87 $\mu_B$ at 298 K. Anal. Calcd for $C_{22}H_{30}CrF_6N_2P$: C, 50.87; H, 5.82; N, 5.39. Found: C, 50.83; H, 5.97; N, 5.27.

(6) Black cubes from THF/$Et_2O$; monoclinic $P2_1/c$; $a$ = 8.810 (2) Å, $b$ = 15.425 (3) Å, $c$ = 17.792 (3) Å, $\beta$ = 89.34 (9)°; $Z$ = 4; R = 0.083, $R_w$ = 0.099.

(7) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395.

0002-7863/88/1510-5902$01.50/0 