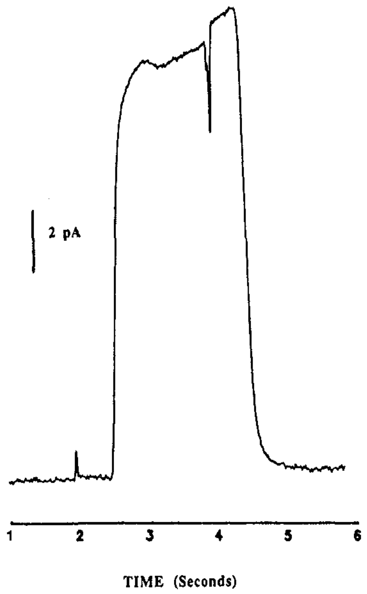

**Figure 3.** Time course of quinone generation at a HRP-modified electrode. Cathodic current monitored at −0.300 V (dc, 200-ms time constant) for the injection of 10 mM catechol (FIA flow rate 1 mL min$^{-1}$). The spikes represent the beginning and end of sample injection (the delay to response corresponds to the dead time of the injection system).

were dipped into a premixed solution containing 3 $\mu$M ExtrAvidin (Sigma) and 0.3 $\mu$M biotinylated horseradish peroxidase (HRP, Pierce Chemical) for 12 h at 4 °C to complete the derivatization (Figure 1).

Surface derivatization can create density of one tether molecule/220 Å$^2$,[7] almost 10 times greater than necessary for complete surface coverage with avidin.[8] The electrochemical properties of the HRP-modified electrode were examined by flow injection analysis.[9] Cyclic voltammetry (25 V s$^{-1}$) was used to provide selective detection of oxygen generated from the autocatalysis of hydrogen peroxide. The enzymatically generated product (Figure 2) was voltammetrically identical with molecular oxygen.[10] The response was linear for $H_2O_2$ between $5 \times 10^{-3}$ and $4 \times 10^{-5}$ M $H_2O_2$ ($r^2 = 0.989$, $n = 5$), with a detection limit of $10^{-5}$ M $H_2O_2$. The selectivity of the measurement was demonstrated by inactivating the surface-bound HRP by boiling the electrode in water for 10 min. After this treatment, the electrode response to hydrogen peroxide was abolished without any loss in sensitivity to molecular oxygen (Figure 2).

The response time of the electrode assembly was evaluated by using catechol as the substrate for HRP catalysis in a flow injection experiment with dc amperometric detection of the enzyme-generated quinone. The $E_{1/2}$ of the catechol/quinone couple was determined by fast-scan cyclic voltammetry (250 V s$^{-1}$) to be 0.187 V vs Ag/AgCl. Therefore, the electrode was poised at −0.300 V vs Ag/AgCl (to ensure complete electrolysis of the quinone generated by the surface-bound HRP) and the cathodic current was monitored continuously versus time. Injection of a 2-s pulse of 10 mM catechol showed a response time less than 300 ms (244 ± 43 ms, $n = 5$) for the HRP-modified electrode (Figure 3). Thus, attachment of an enzyme via a hydrophilic tether through a biotin/avidin coupler produces an electrode that has the size, speed, and sensitivity required for dynamic measurements of in vivo biochemical processes, and the surface coverage of the enzyme can be closely controlled by adjusting the conditions of the surface derivatization reaction.

The other virtue of this immobilization scheme is that the peroxidase can be easily replaced by other enzymes that liberate other redox species. Ultimately, this should lead to an array of well-characterized chemical sensors with rapid response times, each specific for the measurement of a single component in a complex chemical matrix. Of course, the in vitro measurements described here are not as complex as would be expected in vivo. Placement of an electrode into a biological tissue often results in severe degradation of analytical performance due to surface fouling. Nevertheless, a great deal of meaningful information has already been obtained in short-duration experiments (i.e., 4–12 h) with unmodified[11] and enzyme-modified[12] microelectrodes placed in vivo in the mammalian brain.

**Acknowledgment.** This work was supported, in part, by the Office of Naval Research (T.H.M.; N00014-89-J-3071) and a Presidential Young Investigater Award (W.G.K.) from the National Science Foundation (CHE-8957394). The donation of Jeffamine ED-600 by Texaco, the loan of a stainless steel injector from Professor Steven Angle, and the donation of the latest revision of voltammetry software by Dr. Eric Kristensen are gratefully acknowledged.

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(7) The extent of surface coverage was assessed by derivatizing the surface with an electroactive amine, 3,4-dihydroxyphenethylamine (dopamine), in place of the Jeffamine ED-600. Chronocoulometry (−0.4 V to +0.4 V, $\tau$ = 100 ms) showed a 50-pC increase in the charge observed at the carbon surface due to the oxidation of surface-bound dopamine. This corresponds to one dopamine molecule/220 Å$^2$ (based on a geometrical surface area of 350 $\mu$m$^2$), similar to that found by Chi-Sing Tse and Kuwana (*Anal. Chem.* **1978**, *50*, 1315–1318) for macroscopic glassy carbon electrodes. Electrochemical measurements were performed on an EI-400 potentiostat (Ensman Instruments, Bloomington, IN) where all voltammetric waveforms were generated and current acquired via a PC-AT microcomputer (Zenith Data Systems) interfaced via an A/D//D/A interface (Labmaster DMA, Scientific Solutions, Solon, OH).

(8) The cross-sectional area of avidin can be calculated from crystallographic data to be on the order of 2000 Å$^2$ (Weber, P. C.; Ohlendorf, D. H.; Wendoloski, J. J.; Salemme, F. R. *Science* **1989**, *243*, 85–88).

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(10) All flow injection components were stainless steel to prevent atmospheric oxygen from entering into the system. All solutions were rigorously degassed with nitrogen before use.

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# Insertion Chemistry of $Cp_2Zr(\eta^2\text{-}C,N\text{-}CH_2\{6\text{-Me-pyrid-2-yl}\})^+$: Facile Zirconium-Mediated Functionalization of Methyl C–H Bonds of 2,6-Lutidine

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The rich insertion chemistry of three-membered metallacycles such as $Cp_2M$(benzyne), $Cp_2M$(olefin), and $Cp_2M(pyridyl)^+$ (M = group 4 metals) provides a general approach to metal-mediated C–C bond formation.[1–3] In contrast, the insertion chemistry of

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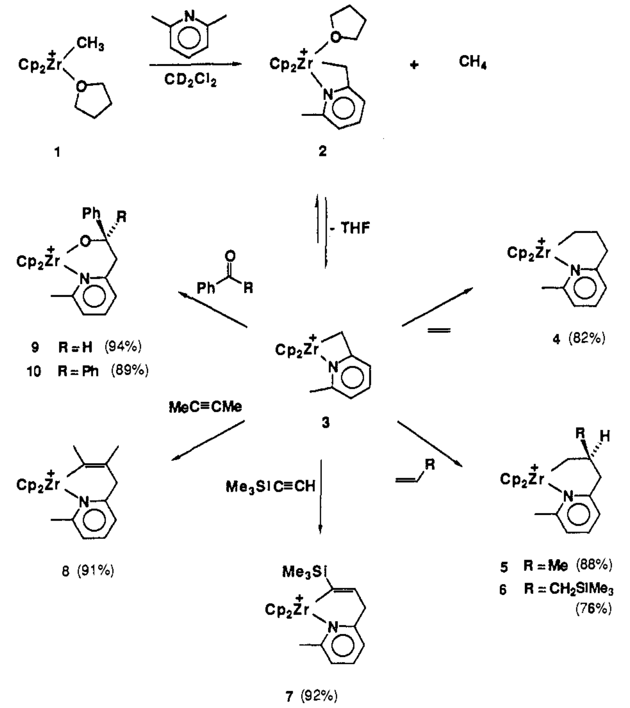
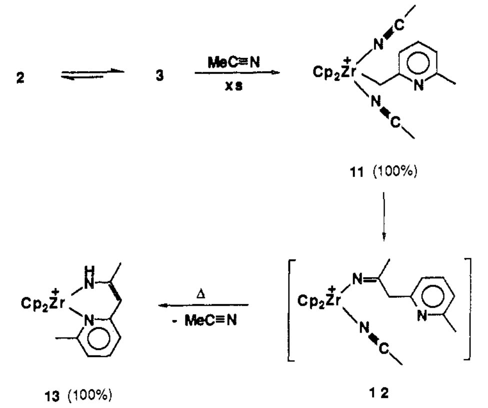
0002-7863/91/1513-1833$02.50/0

**Scheme I**



**Scheme II**



related four-membered metallacycles, such as $\overline{\text{Cp}_2\text{ZrCH}_2\text{Si}(\text{Me}_2)\text{CH}_2}$, $\overline{\text{Cp}_2\text{HfCH}_2\text{CH}_2\text{CH}_2}$, and $\overline{\text{Cp}_2\text{TiCR}{=}\text{CR}'\text{CH}_2}$, appears to be limited to polar substrates.[1k,4] We report here that the four-membered azazirconacycle $\text{Cp}_2\text{Zr}(\eta^2\text{-}N,C\text{-CH}_2\{6\text{-Me-pyrid-2-yl}\})^+$ (**3**)[3c] undergoes facile insertion reactions with a variety of polar and nonpolar substrates. These reactions provide the basis for the Zr-mediated functionalized of the methyl C–H bonds of 2,6-lutidine.

As a part of our ongoing efforts to develop synthetic organic applications of cationic $\text{Cp}_2\text{Zr(R)(L)}^+$ complexes,[3,5] we recently reported the preparation of $\text{Cp}_2\text{Zr}(\eta^2\text{-}N,C\text{-CH}_2\{6\text{-Me-pyrid-2-yl}\})(\text{THF})^+$ (**2**) via the reaction of $\text{Cp}_2\text{Zr(Me)(THF)}^+$ (**1**) with 2,6-lutidine (Scheme I).[3c] Other cationic four-membered metallacycles were similarly prepared.[3c] In $\text{CH}_2\text{Cl}_2$ solution, **2** undergoes extensive THF dissociation to yield isolable **3**.

The insertion chemistry of **3** (generated in situ from **2**) is summarized in Scheme I. Complex **3** reacts with olefins such as ethylene, propene, and allyltrimethylsilane at 55 °C ($\text{ClCH}_2\text{CH}_2\text{Cl}$, 20 h) to afford six-membered metallacycles **4–6**, respectively. The $^1$H and $^{13}$C NMR spectra of **5** and **6** unambiguously establish the 1,2-insertion regiochemistry.[6] (Trimethylsilyl)acetylene and 2-butyne insert rapidly into the Zr–C bond of **3** at 23 °C ($\text{CH}_2\text{Cl}_2$, 1.0 h) to afford metallacycles **7** and **8**.[6] The $^1$H NMR spectrum of **7** exhibits a doublet for py-$\text{CH}_2$ ($\delta$ 3.53) and a triplet ($\delta$ 6.72) for the vinylic proton and confirms the assigned regiochemistry. Additionally, the $^{13}$C NMR spectra of **7** and **8** exhibit the expected low-field quaternary Zr–C(vinyl) resonances ($\delta$ 217.3 and 190.0, respectively). Complex **3** also reacts very rapidly with benzaldehyde and benzophenone at 23 °C ($\text{CH}_2\text{Cl}_2$, 10 min) to afford metallacycles **9** and **10**.[6] The $^1$H NMR py-Me resonances for **4–10** all appear in the range $\delta$ 1.9–2.1, similar to the resonances for **2** ($\delta$ 2.08) and **3** (2.27) and significantly upfield of the resonances for 2,6-lutidine ($\delta$ 2.46), consistent with N-coordination. Similar upfield shifts of py-Me resonances have been observed for related pyridyl complexes.[3a-c]

Treatment of **3** with excess $\text{CH}_3\text{CN}$ at 23 °C (5 min) followed by removal of volatiles yields the thermally sensitive bis-$\text{CH}_3\text{CN}$ complex **11** (Scheme II).[6,7] Key $^1$H NMR data for **11** include

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[6] Detailed synthetic procedures and complete characterization data for **4–13** are provided in the supplementary material. NMR yields are near quantitative in all the insertion reactions; isolated yields are reported in Scheme I. The counterion is $\text{BPh}_4^-$ in all cases. Key NMR data for **5**: $^1$H NMR $\delta$ 2.70 (dd, $J$ = 16.2, 1.7 Hz, 1 H, py-C$H_2$), 2.55 (t, $J$ = 12.5 Hz, 1 H, $\text{ZrCH}_2$), 2.30 (dd, $J$ = 16.2, 9.9 Hz, 1 H, py-C$H_2$), 2.10 (m, 1 H, $\text{ZrCH}_2$C$H$(Me)), 1.11 (obscured by CH($Me$), 1 H, $\text{ZrCH}_2$); $^{13}$C NMR $\delta$ 64.3 ($\text{ZrCH}_2$), 48.3 (py-$C$H$_2$). Key NMR data for **6**: $^1$H NMR $\delta$ 2.73 (dd, $J$ = 15.7, 2.2 Hz, 1 H, py-C$H_2$), 2.63 (t, $J$ = 12.5 Hz, 1 H, $\text{ZrCH}_2$), 2.35 (dd, $J$ = 16.0, 9.5 Hz, 1 H, py-C$H_2$), 2.13 (m, 1 H, $\text{ZrCH}_2$C$H$($\text{CH}_2\text{SiMe}_3$)), 1.15 (br d, $J$ = 12.7 Hz, 1 H, $\text{ZrCH}_2$); $^{13}$C NMR $\delta$ 65.4 ($\text{ZrCH}_2$), 49.8 (py-$C$H$_2$). Key $^1$H NMR data for **9**: $\delta$ 5.51 (dd, $J$ = 9.5, 2.6 Hz, 1 H, ZrOC$H$(Ph)), 3.34 (dd, $J$ = 15.3, 2.7 Hz, 1 H, py-C$H_2$), 3.19 (dd, $J$ = 15.3, 9.6 Hz, 1 H, py-C$H_2$), 2.08 (s, 3 H, Me). Key $^1$H NMR data for **10**: $\delta$ 3.93 (s, 2 H, py-C$H_2$), 2.13 (s, 3 H, Me).

a resonance for coordinated $CH_3CN$ which is slightly shifted from that of free $CH_3CN$ and a py-Me resonance at $\delta$ 2.40.[7] The latter indicates that the py group is substantially or completely dissociated in $CD_2Cl_2$ solution. Thermolysis of **11** in $CD_2Cl_2$ (55 °C, sealed tube, 12 h) followed by drying under vacuum affords **13** (Scheme II).[6] When this reaction is monitored by $^1H$ NMR spectroscopy, the $CH_3CN$-insertion product **12** is observed as a transient intermediate (Scheme II).[7] Cyclization via $CH_3CN$ displacement followed by tautomerization (or vice versa) of **12** affords the thermodynamically favored conjugated metallacycle **13**. Similar 1,3-hydrogen shifts have been observed in related systems.[1j,4c,8] The $^1H$ NMR spectrum of **13** exhibits singlets at $\delta$ 2.00 and 1.96 for the py-*Me* and NHC(*Me*)= groups, a broadened singlet at $\delta$ 5.81 for the vinylic proton, and a broad resonance at $\delta$ 6.79 for NH. The py-*Me* resonance at $\delta$ 2.00 establishes that the py group in **13** is coordinated to Zr. The FTIR spectrum of **13** exhibits an NH absorbance at 3320 $cm^{-1}$.

The high reactivity of **2** is ascribed to the extensive formation of the reactive THF-free species **3** in solution and to the relief of ring strain which accompanies substrate insertion. The selectivity for single olefin insertion leading to the formation of metallacycles **4–6** is notable as the acyclic complex $Cp_2Zr(Me)(THF)^+$ (**1**) polymerizes ethylene[5a] and dimerizes propene[9] under the conditions studied here. Presumably, the lack of further olefin insertion of **4–6** is due to the size and stability of the six-membered chelate ring which disfavors olefin coordination. The high Lewis acidity of the cationic Zr(IV) center in **3** promotes coordination and activation of unsaturated substrates and is responsible for the unusually high insertion reactivity relative to that of titanacyclobutenes, 1-zircona-3-silacyclobutanes, and related neutral group 4 metallacycles.[4] Additionally, the observation of **11** in the reaction of **3** with $CH_3CN$ suggests that substrate-promoted ring opening of **3** (which is not possible for the neutral group 4 metallacycles) may precede insertion in some cases. The regiochemistry observed in these insertions is similar to that observed for reactions of $Cp_2M(benzyne)$, $Cp_2M(pyridyl)^+$, and related complexes.[1,3,9]

We have demonstrated here that the cationic four-membered metallacycle **2**, which in solution exists predominantly in its THF-dissociated form **3**, exhibits high insertion reactivity with a variety of organic substrates. The combination of the C–H activation and insertion chemistry summarized in Schemes I and II constitutes a general approach to the zirconium-mediated functionalization of the methyl C–H bonds of 2,6-lutidine and other *o*-alkylpyridine derivatives.[9,10] We are currently exploring the development of catalytic[3a] and stereoselective[5f] versions of this chemistry.

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**Supplementary Material Available:** Details of experimental procedures and spectroscopic and analytical data for complexes **4–13** (7 pages). Ordering information is given on any current masthead page.

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[7] Key $^1H$ NMR data for **11** ($CD_2Cl_2$, 300 MHz): $\delta$ 2.40 (s, 3 H, Me), 1.95 (s, 6 H, MeCN), 1.85 (s, 2 H, $CH_2$-py). Key FTIR data for **11** (KBr pellet): $\nu_{CN}$ 2279, 2250 $cm^{-1}$. Key $^1H$ NMR data for **12** (from a mixture of **11**, **12**, and **13**) ($CD_2Cl_2$, 300 MHz): $\delta$ 6.06 (s, 10 H, Cp), 3.58 (br s, 2 H, py-$CH_2$), 2.53 (s, 3 H, py-*Me*), 1.78 (br s, 3 H, MeCN). Key FTIR data for **12** (from a mixture of **11** and **12**) (KBr pellet): $\nu_{CN}$ 2308, 2279, $\nu_{C=N}$ 1685 $cm^{-1}$.

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[10] Ortho-substituted pyridines are of interest as intermediates in organic synthesis and as ligands in organometallic chemistry. Functionalization of methyl groups of 2,6-lutidine is possible via reaction of 2-(lithiomethyl)-6-methylpyridine with appropriate electrophiles. (a) Goldberg, N. N.; Levine, R. *J. Am. Chem. Soc.* **1952**, *74*, 5217. (b) Mathew, J. *J. Org. Chem.* **1990**, *55*, 5294. (c) Wolfe, J. F.; Portlock, D. E.; Feuerbach, D. J. *J. Org. Chem.* **1974**, *39*, 2006. (d) Cassity, R. P.; Taylor, L. T.; Wolfe, J. F. *J. Org. Chem.* **1978**, 43, 2286. (e) Danishefsky, S.; Cain, P. *J. Org. Chem.* **1974**, *39*, 2925.

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# Direct Nuclear Magnetic Resonance Spectroscopic Determination of Organolithium Ion Pair Structures in THF/HMPA Solution[1]

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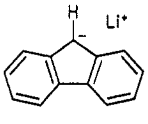
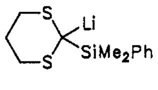
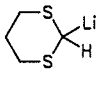
The reactivity of organolithium reagents depends in a profound way on the fine details of association among the anionic carbon, the lithium cation, and the solvent.[2] We have reported that lithium cations coordinated by HMPA (hexamethylphosphoric triamide) often undergo sufficiently slow dynamic exchange on the NMR time scale at low temperatures to allow the direct observation of distinct cation–HMPA complexes.[1a] It is frequently possible to detect $^2J_{Li-P}$ scalar coupling, and hence the number of HMPA molecules coordinated to $Li^+$ can be measured.[3] We now report the application of this NMR procedure for the direct and unambiguous determination of important features of lithium–carbanion and other ion pair structures.



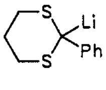
**1⁻//Li⁺**



**2-Li**



**3-Li**



**4-Li**

Figures 1 and 2 illustrate the contrasting behavior of a separated ion pair (SIP), fluorenyllithium ($\mathbf{1}^-//Li^+$),[4] and a contact ion pair (CIP), [2-(phenyldimethylsilyl)-1,3-dithian-2-yl]lithium (**2**-Li),[5] on treatment with HMPA. Fluorenyllithium has been exhaustively studied by a variety of techniques and is known to be a SIP in THF at low temperature,[4b] and largely SIP even at 25 °C.[4c] Indeed, the $^7Li$ signal at −120 °C is sharp ($\nu_{1/2}$ = 1.1 Hz), as expected for a symmetrically coordinated ion. Addition of HMPA to fluorenyllithium in THF produced first a doublet in the $^7Li$ spectra, then a triplet, a quartet, and finally a quintet corresponding to $Lih_n^+$ with $n$ = 1–4 (we will abbreviate: $Li(HMPA)_n^+$ = $Lih_n^+$). The concentration of the separated $Lih_n^+$ species throughout the HMPA titration and the $^7Li$ and $^{31}P$ NMR properties were virtually identical in all other SIPs we have examined.[1a] Thus the nature of the anion has little effect on the NMR properties or on the formation constants of the various $Lih_n^+$ species. Fluorenyllithium differs from other SIPs in that small

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[2] (a) SIPs can be orders of magnitude more reactive than CIPs: Hogen-Esch, T. E. *Adv. Phys. Org. Chem.* **1977**, *15*, 153. (b) Ion pair structure has been proposed as a key feature controlling 1,2- vis 1,4-addition to enones: Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923.

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