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ON THE GENERATION OF STABILIZED LOW-VALENT METALLOCENE DERIVATIVES. THE DIRECT SYNTHESIS AND REDUCTIVE COUPLING REACTIONS OF 1-METHYLTHIOALKYNE-ZIRCONOCENE COMPLEXES

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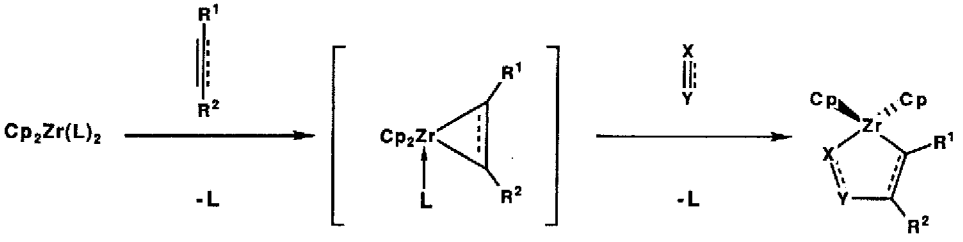
Abstract: 4-Dimethylaminopyridine has been found to be a remarkably effective ligand for the formation of stabilized zirconocene complexes. The latter species mediate efficient coupling reactions between 1-methylthioalkynes and a variety of unsaturated organic substrates.

Preformed zirconocene complexes of the type $Cp_2Zr(L)_n$ should exhibit considerable utility for promoting the direct reductive coupling of diverse organic functionality (**Scheme** I.) To date this process has been relegated to those instances which are intramolecular in nature[2-5] and to intermolecular cases which involve a sterically congested reaction partner.[3b] In this communication we report that 1-methylthioalkynes readily undergo reductive crosscoupling with representative organic substrates mediated by 4-dimethylaminopyridine-zirconocene complexes.

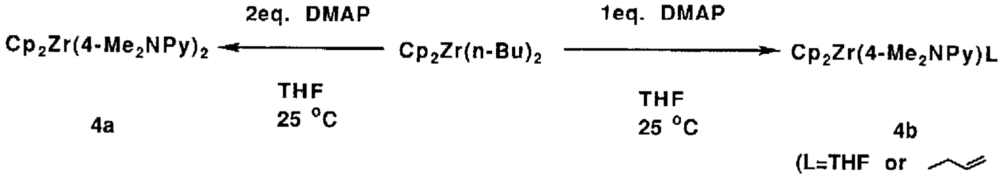


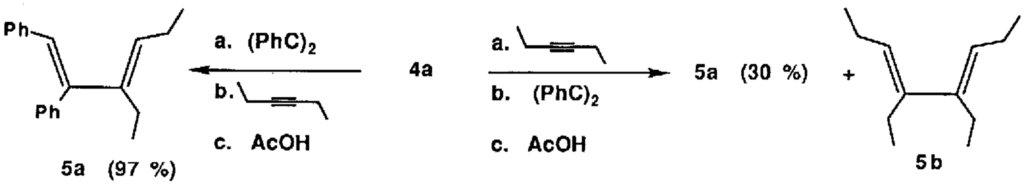
1 2 3

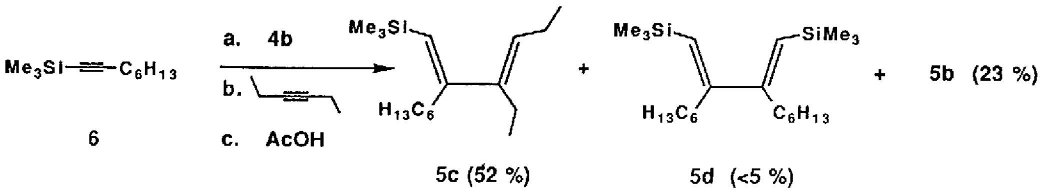
Scheme 1

At the commencement of this study the only readily exchangeable ligands which had been successfully employed for the generation of "stable" zirconocene complexes were certain phosphines[2,3,6] and bis(trimethylsilyl)acetylene.[4]

The phosphine most frequently used in the above capacity, Ph_2PCH_3, gives rise to zirconocene complexes endowed with only limited stability[2] and is difficult to separate from the desired products subsequent to reductive coupling. We have found that 4-dimethylaminopyridine[7] serves as a remarkably versatile ligand for the stabilization of reduced zirconocene derivatives. The preparation of the zirconocene-DMAP complexes **4a** and **4b** in THF solution is experimentally straightforward as is illustrated below. Treatment of Cp_2ZrCl_2 (1 mmol) in 3.0 mL THF with 5M n-BuLi[8] (2 mmol) under argon at -78 °C followed by the addition of DMAP[9] (2 mmol) in 2.5 mL THF and warming to 25 °C for 1.5 h provided **4a** as a deep burgundy solution. Solutions of **4a** so obtained retained their activity for several hours. An analogous procedure employing only one equivalent of DMAP gave cherry red solutions of **4b** which were more labile and required immediate use.

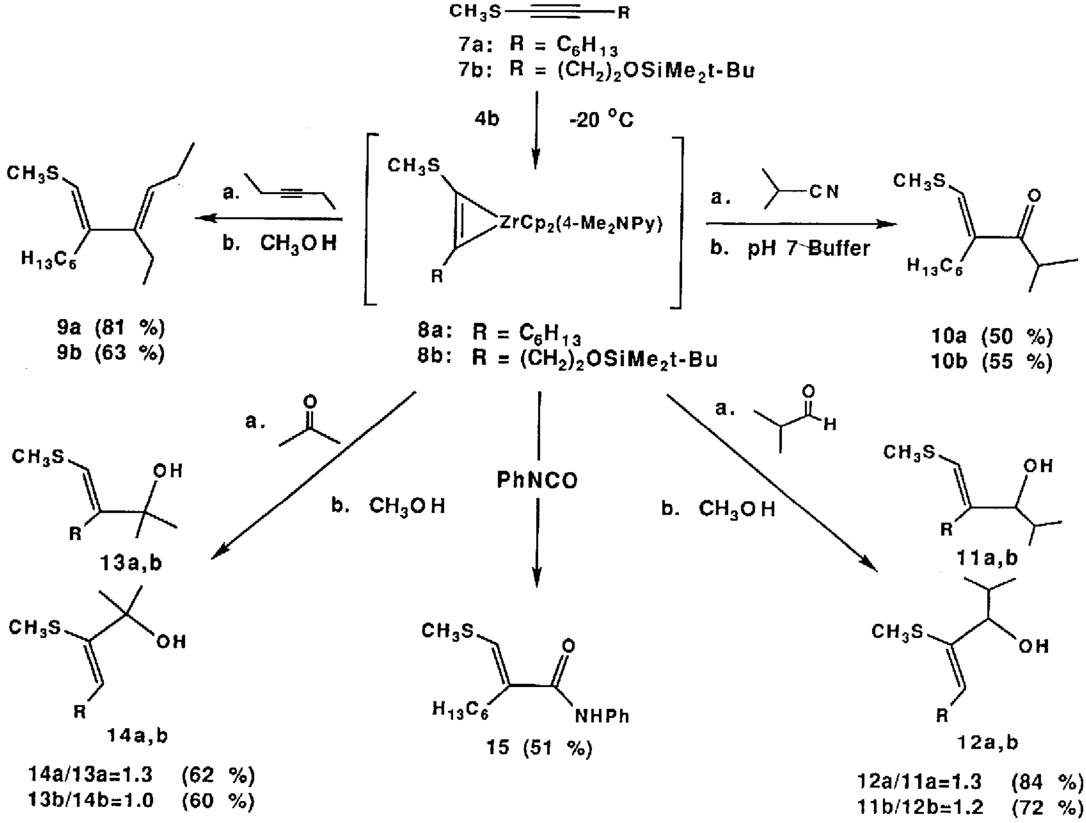






Addition of the hindered alkyne $(PhC)_2$ to **4a** (0 °C, 1.5 h) followed by the addition of 3-hexyne (0 °C → 25 °C, 1 h) and protonation (AcOH) furnished the desired unsymmetrical coupling product **5a** in 97% isolated yield. Unfortunately, repeated efforts to prepare **5a** <u>via</u> initial complexation (at 0 °C or -40 °C) of the relatively unhindered substrate 3-hexyne proceeded in low (ca., 30%) yield. In this case the symmetrical diene **5b** was the major product.

In an effort to obviate problems associated with alkyne autodimerization, the complexation and coupling reactions of 1-trimethylsilylacetylenes (e.g., **6**) were examined. Accordingly, complexation of **6** with either **4a** or **4b** (0 °C, 1.5 h) followed by the addition of 3-hexyne and protonation gave the desired unsymmetrical adduct **5c** in improved (52%) yield. In this instance less than 5% of the dimer **5d** was formed along with 23% of **5b**. The unexpected formation of **5b** in this reaction is consistent with the competitive displacement[4] of the bulky silylalkyne ligand prior to coupling. It was ultimately determined that complexation of the more strongly ligating 1-methylthioalkynes (e.g., **7a** and **b**)[10] to **4b** (-20 °C, 60 min) led to the generation of zirconacyclopropenes of the type **8a,b** with a minimum (ca. < 3%) of dimer formation. Interception of **8a** or **b** with representative organic addends (added at -20 °C followed by warming to 25 °C over 12 h) and subsequent protonation gave rise to the corresponding coupling products **9-15** in good to excellent yield.[11,12] It is of particular note that the use of displaceable ligands other than DMAP (e.g., bistrimethylsilylacetylene) in these reactions led to poor yields of the desired adducts.



The foregoing results are significant in that they constitute the first examples of unsymmetrical coupling reactions involving acetylenes bearing sterically comparable but electronically dissimilar end substituents (e.g. CH_3S- vs. n-C_6H_{13}). It is of particular interest in this regard that the regiochemistry of coupling leading to the adducts **9a,b**, **10a,b** and **15** is consistent with a transition state involving internal $CH_3S \rightarrow Zr$ ligation. The utilization of $Cp_2Zr(4\text{-}Me_2NPy)$ complexes for effecting intramolecular carbon-carbon carbon-heteroatom bond forming reactions as well as the application of these to problems of synthetic interest will be reported in due course.

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Literature Cited and Footnotes

1. Fellow of the Alfred P. Sloan Foundation 1989-1991.
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3. a) Negishi, E-i.; Swanson, D.R.; Cederbaum, F.E.; Takahashi, T. Tetrahedron Lett. **1987**, 28, 917 and references therein. b) Takahashi, T.; Swanson, D.R.; Negishi, E-i. Chemistry Lett. **1987**, 623.
4. Fagan, P.J.; Nugent, W.A. J. Am. Chem. Soc. **1988**, 110, 2310.
5. Jensen, M.; Livinghouse, T. J. Am. Chem. Soc. **1989**, in press.
6. Buchwald, S.L.; Watson, B.T. J. Am. Chem. Soc. **1987**, 109, 2544.
7. Many alternative ligands were examined and found inferior to DMAP. A partial list of these includes HMPT, HMPA, tetrahydrothiophene, trimethylphosphite, and tetramethylthiourea.
8. It is imperative that "alkoxide free" n-BuLi be used for the preparation of the complexes **4a** and **b**. For optimum results, commercial 10 M n-BuLi (Aldrich Chemical Co. Inc.) was diluted to ~5 M with heptane (distilled from Na°) and then used over a period of less than one month.
9. Commercial 4-dimethylaminopyridine was recrystallized from hot heptane prior to use.
10. 1-Methylthioalkynes are readily prepared in excellent (ca. 90%) yield by the sulfenylation of 1-lithioalkynes with CH_3SCN; Brandsma, L., Preparative Acetylene Chemistry, p. 91. Elsevier, Amsterdam (**1971**).
11. All yields correspond to chromatographically purified products. All new compounds have been fully characterized by 300 MHz ^1H NMR, IR, and possessed satisfactory elemental analyses or exact mass.
12. Ratios of regioisomeric adducts were determined by 300 MHz ^1H NMR spectroscopy.

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