

Zirconocene(*iso*-butyl) Chloride: *In Situ* Generation of a Zirconocene(methyl) Chloride Equivalent for Use in Organic Synthesis

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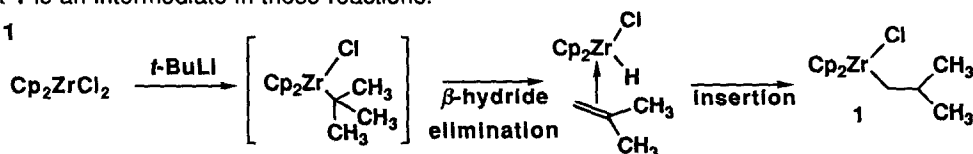
Summary: Zirconocene(*iso*-butyl) chloride, **1**, which can be generated *in situ* from commercially available, inexpensive, and air-stable zirconocene dichloride, can function as a zirconocene(methyl) chloride equivalent.

In recent years, we have devoted considerable effort towards the development of zirconocene-mediated transformations which involve the regioselective coupling of simple precursors to form molecules which are inaccessible by other means.^{1a-i} Many of these reactions proceed via a zirconocene-stabilized complex of an aryne or imine which is subsequently converted to a metallacyclic intermediate by reaction with an unsaturated molecule. The organic product is liberated when the metallacycle is treated with an electrophilic reagent, such as H⁺, I₂, or SCl₂.

The organometallic starting material for many of the transformations that we have developed is zirconocene(methyl) chloride. While this is available in reasonable quantity by a two-step route,² we reasoned that the availability of an equivalent reagent which could be generated and used in an *in situ* manner would be of some use. Herein we report that zirconocene(*iso*-butyl) chloride,³ **1**, can readily serve as such a surrogate in many of the procedures which we have previously reported.¹

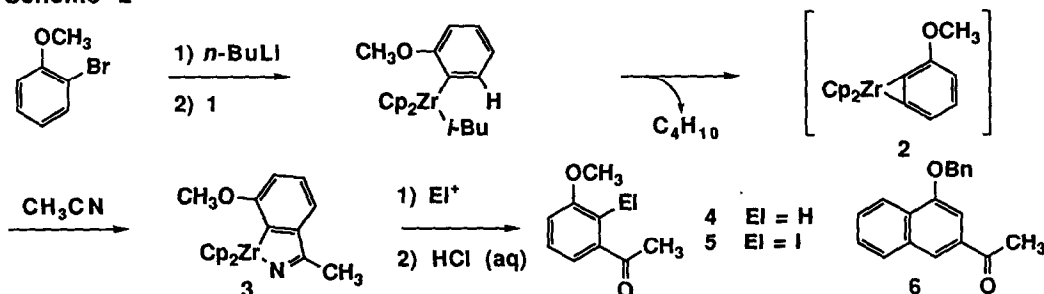
Complex **1** is generated *in situ* from zirconocene dichloride⁴ by adding *tert*-butyllithium at -78° C and allowing the reaction mixture to warm gradually to room temperature. We believe that the reaction proceeds via the β-hydride elimination/olefin insertion sequence shown in Scheme 1.⁵ We note that Negishi and coworkers have investigated the addition of *tert*-butylmagnesium chloride to zirconocene dichloride for the hydrozirconation of olefins and acetylenes.⁶ These workers have also shown that **1** is an intermediate in these reactions.

Scheme 1



Addition of 2-lithioanisole to **1** followed by heating the reaction mixture to 60° C generates nascent methoxybenzynes complex **2**, which in the presence of acetonitrile regioselectively yields the

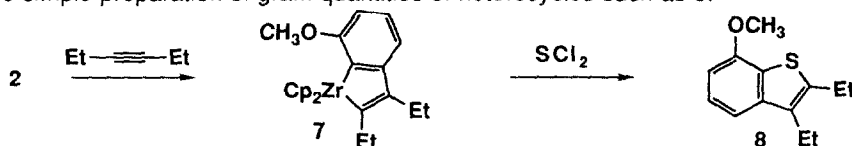
Scheme 2



metallacycle **3** (Scheme 2) Hydrolysis of **3** provides 3-methoxyacetophenone in 72% yield (0.1 mole scale) ^{1c} In a separate experiment, iodolytic cleavage of the **3** followed by acidic workup provides iodoketone **5** in 73% yield (10 mmol scale). Naphthalene **6** can be prepared, via a naphthalene complex, by a similar reaction sequence as that which leads to **4** ¹ⁱ Thus, this route provides access to reasonable quantities of a variety of substituted aromatic compounds ⁷

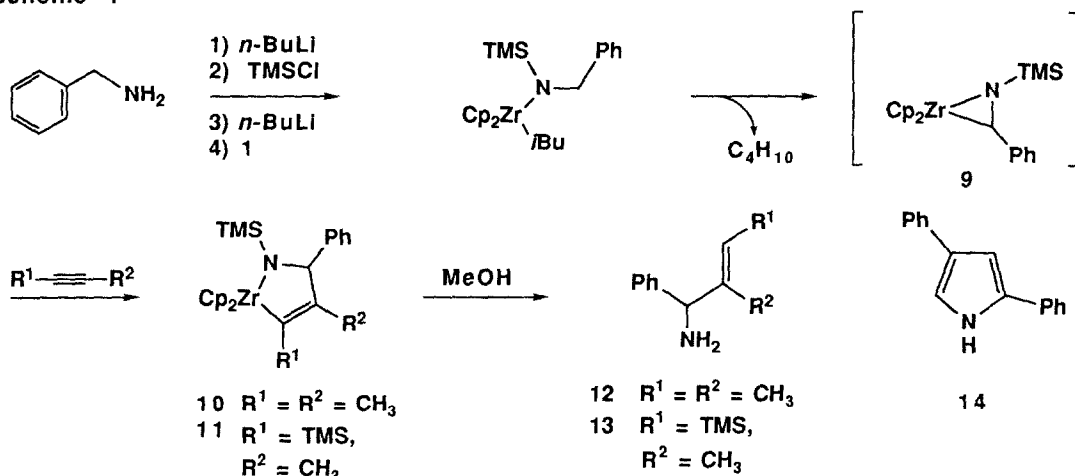
As we have previously shown, if **2** is generated in the presence of 3-hexyne, intermediate **7** is produced. This metallacycle, upon treatment with sulfur dichloride, provides benzothiophene **8**.^{1e} Use of **1** allows for the simple preparation of gram quantities of heterocycles such as **8**.

Scheme 3



Complex **1** can also be used for the synthesis of zirconocene complexes of imines. Generation of *N*-lithio-*N*-trimethylsilylbenzylamine,^{1h} followed by addition to **1** and warming the reaction mixture to 45° C, yields benzaldimine complex **9**. In the presence of an alkyne (e.g., 2-butyne or 1-trimethylsilylpropyne), **9** provides the corresponding azazirconacyclopentenes (Scheme 4).

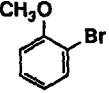
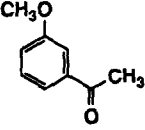
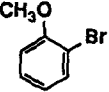
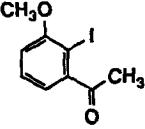
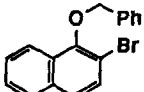
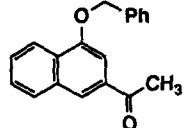
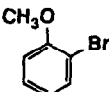
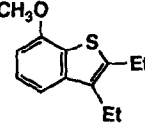
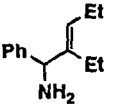
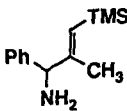
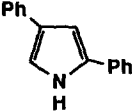
Scheme 4



Methanolysis of these metallacycles yields geometrically pure allylic amines. In accord with what we have shown previously, pyrroles may be formed by the carbonylation^{1h,f} of these azazirconacyclopentenes, as exemplified by the formation of 2,4-diphenylpyrrole, **14**, from **9**.

In conclusion, as is summarized in Table 1, zirconocene(*iso*-butyl) chloride, **1**, functions as a convenient surrogate for zirconocene(methyl) chloride in many of the procedures which we have recently developed. In most cases, yields observed with *in situ* generated **1** are comparable to those realized employing zirconocene(methyl) chloride.

Table 1. Comparison of previously obtained isolated yields of organic products using $\text{Cp}_2\text{Zr}(\text{Me})\text{Cl}^1$ with newly obtained isolated yields using $\text{Cp}_2\text{Zr}(\text{iso-Bu})\text{Cl}$.

Substrate	Nitrile/ Alkyne	Product ^a	Scale (mmol)	Isolated Yield (Y = Me)	Isolated Yield (Y = <i>iso</i> -Bu)
	CH_3CN		100	86 ^{1d}	72
	CH_3CN		10	61 ^{1d}	73
	CH_3CN		10	—	40
	$\text{Et}\equiv\text{Et}$		10	71 ^{1e}	82
PhCH_2NH_2	$\text{Et}\equiv\text{Et}$		85	77 ^{1h}	66
PhCH_2NH_2	$\text{TMS}\equiv\text{CH}_3$		10	75 ^{1h}	58
PhCH_2NH_2	$\text{Ph}\equiv\text{H}$		10	69 ^{1f}	48

^a All products, excluding entry 3, were previously known and were identified by ^1H NMR. Entry 3 has been characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy as well as elemental analysis.

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- Zirconocene dichloride is commercially available from Boulder Scientific Company, Mead, CO. It is slightly hygroscopic and should be stored in the absence of moisture.
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- For leading references on the synthesis of polysubstituted aromatic compounds, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 8789.
- In situ formation of zirconocene(*iso*-butyl) chloride (10 mmol scale).** To a dry 500 mL Schlenk flask under an argon atmosphere containing Cp_2ZrCl_2 (3.508 g, 12 mmol, 1.2 eq) was added THF (70 mL), and the resulting solution was cooled to -78°C and treated with *tert*-butyllithium (6.5 mL, 11 mmol, 1.1 eq). The reaction mixture was stirred at -78°C for 15 min and then removed from the cooling bath and allowed to warm to room temperature. As warming occurred, a large amount of precipitation was observed (presumably LiCl), but the precipitate redissolved before room temperature was reached. After stirring at room temperature for 1 h, the solution was again cooled to -78°C and used immediately.
- 2-Iodo-3-methoxyacetophenone (Table 1, entry 2).** To a 100 mL Schlenk flask under an argon atmosphere was added THF (20 mL) and *n*-bromoanisole (1.54 mL, 12 mmol). After cooling to -78°C , the resulting solution was treated with *n*-butyllithium (5.8 mL, 12 mmol) and stirred for 15 min before being transferred via cannula in a dropwise fashion to a 500 mL Schlenk flask at -78°C containing freshly generated zirconocene(*iso*-butyl) chloride in THF (70 mL). The temperature was raised to -50°C , and the solution stirred for 1 h before acetonitrile (0.522 mL, 10 mmol) was added. The reaction mixture was then warmed to room temperature followed by heating at 65°C for 18 h. A dry 100 mL Schlenk equipped with magnetic stir bar was charged with I_2 (6.355 g, 25 mmol) and THF (40 mL). The I_2 solution was then transferred via cannula to the reaction mixture, which had been cooled to room temperature, and the resulting reaction mixture was stirred for 7 h. At this point, 1N HCl (20 mL, 20 mmol) was added, and the solution was stirred for 5 h and was then diluted with ether (200 mL), washed with sat'd Na_2SO_3 (6 x 50 mL), water (2 x 50 mL), and brine (50 mL), and dried over MgSO_4 . Flash chromatography (hexane:ethyl acetate = 92:8 - 80:20) afforded 2.02 g (73% yield) of a golden oil.^{1d}