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A Case for Asymmetric Hydrozirconation

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Thirty years after the introduction of Schwartz's reagent, Cp$_2$ZrHCl (Cp = η^5-C$_5$H$_5$),[1] the hydrozirconation of alkenes and alkynes continues to grow in value to the synthetic chemist at a constant pace.[2] However, due to facile β-hydride eliminations/reinsertions that allow the bis(cyclopentadienyl)zirconium (also known as zirconocene) moiety to "chain-walk" to the least sterically hindered terminal position of an alkyl chain,[1,2a,3] the hydrozirconation of internal alkenes and the asymmetric hydrozirconation of alkenes remain unrealized, if not impossible, objectives with zirconocene-based reagents.[4] Herein, we now document, using a nonzirconocene ligand set, the first successful hydrozirconation of an unfunctionalized internal alkene that produces a kinetically stable, chiral secondary alkyl group that then undergoes stereospecific functionalization with retention of the secondary alkyl structure. With these results, a case can be made that the asymmetric hydrozirconation of alkenes is indeed a reasonable, achievable goal.

Cyclopentadienyl zirconium acetamidinates of the general formula, Cp*ZrRCl[N(R^1)C(Me)N(R^2)] (Cp* = η^5-C$_5$Me$_5$, R = alkyl) (**1**), that bear alkyl substituents with β-hydrogens, have been shown to be remarkably stable in solution at elevated temperatures.[5] As Scheme 1 shows, this stability extends to (chiral) secondary alkyl groups as confirmed by the isopropyl and *sec*-butyl derivatives, **2** and **3**, that were conveniently prepared through monoalkylation of the dichloride **4**,[5] and which ^{1}H NMR revealed do not engage in β-hydride elimination, isomerization, or epimerization of the chiral center in **3** (i.e., **3a** and **3b** are noninterconverting).[6] Further structural characterization by NMR and single-crystal X-ray analysis of **2** and diastereomerically pure **3a**, the latter of which was obtained through fractional crystallization, confirmed that each compound exists as a single diastereomer in which the alkyl group is positioned toward the Et substituent of the amidinate fragment as depicted in Scheme 1 and shown in Figure 1a.[6]

With the stability of secondary alkyl groups in **1** firmly established, attention was focused on the synthesis of an analogue of Schwartz's reagent that could be used for the hydrozirconation of internal alkenes. Unfortunately, all attempts to prepare either a hydrido chloride (i.e., R = H in **1**) or a dihydride complex from **4** using standard hydride reagents failed. Hydrogenolysis of **1**, where R = Et or *i*-Bu, further proceeded only very sluggishly, even at 60 °C, and the complex mixture of products obtained suggested that the desired hydrido chloride is not stable once formed.[7] Tilley and co-workers,[8] however, made the observation that hydrogenolysis of the zirconium–silicon bond is a more facile process than that of the zirconium–carbon bond. Accordingly, reaction of **4** with 1 equiv of LiSiMe$_2$Ph[9] was first carried out to provide the diastereomerically pure, deep-red crystalline silyl complex **5**, the molecular structure of which is presented in Figure 1b.[6] Satisfactorily, the hydrogenolysis of **5** was now observed to proceed rapidly in pentane at room temperature over the course of 4 h, although no discreet hydrido chloride species could still be identified among the final hydrogenolyzed products.[10] However, in the presence of 1-hexene, this transiently generated species could apparently be
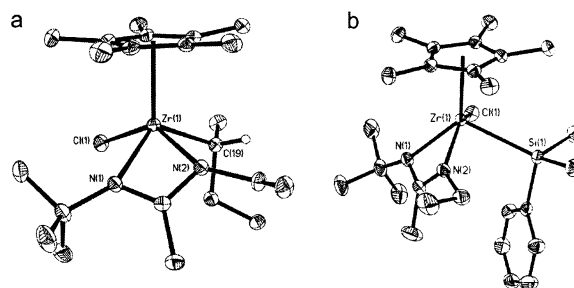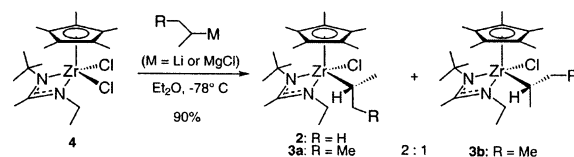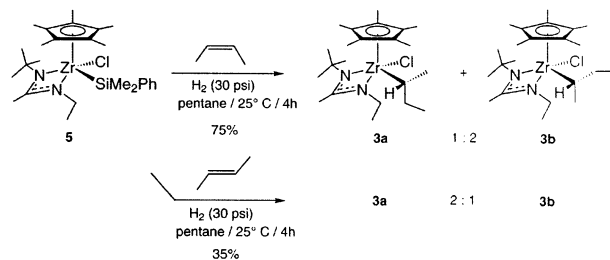

Figure 1. Molecular structure (30% thermal ellipsoids) of (a) **3a** and (b) **5**. Hydrogen atoms, except for that at C(19) in **3a**, have been removed for the sake of clarity.

Scheme 1

Scheme 2

competitively trapped by the alkene to provide a final 87% yield of the expected terminal *n*-hexyl hydrozirconated product. As Scheme 2 shows, it was next determined that when hydrogenolysis of **5** was conducted using *cis*-2-butene, a similarly high yield of the internal hydrozirconated product **3** could be obtained, with ^{1}H NMR revealing that the ratio of the two diastereomers, **3a** and **3b**, was 1:2 in favor of **3b**. Resubjecting a pure sample of **3** to further hydrogenolysis for the same period of time did not change the ratio of **3a** and **3b**, thereby suggesting that this diastereomeric ratio is indeed a product of alkene face selectivity which occurs during hydrozirconation. A small amount (<10%) of the *n*-butyl product (R = *n*-Bu in **1**) is also produced in the hydrozirconation of *cis*-2-butene, but it is unlikely that it derives from the isomerization of **3** as this process has been shown not to occur in solution even at elevated temperatures. We speculate, therefore, that this isomerized product might arise from another hydride species,[10] the hydrozirconated product of which is capable of engaging in reversible β-hydride elimination of the alkyl group. Interestingly, hydrozirconation of *trans*-2-butene using the same hydrozirconation protocol now provided a 2:1 ratio of **3a** and **3b** as a result of a reversal in face selectivity that was coupled with a substantially
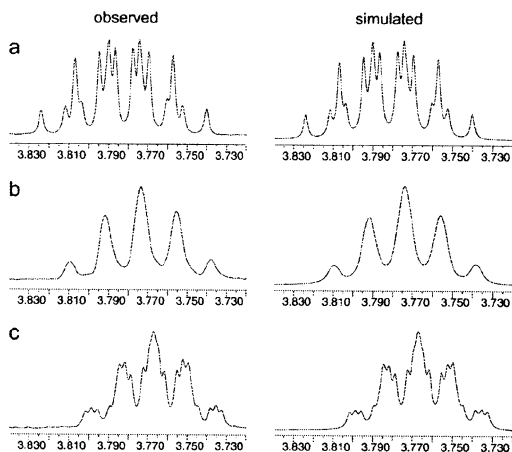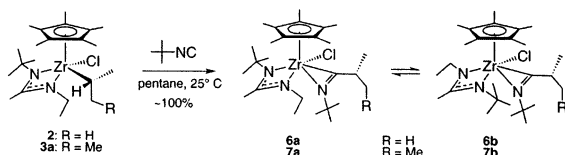
Figure 2. Partial ^{1}H NMR spectra for the H2 resonance of (a) 2-iodobutane, (b) *threo*-3-*d*-2-iodobutane obtained from *trans*-2-butene, and (c) *erythro*-3-*d*-2-iodobutane obtained from *cis*-2-butene.[6]

Scheme 3

poorer yield of product (see Scheme 2). The significant amount of **4** observed in the crude material would seem to indicate that hydrozirconation of this *trans*-alkene cannot compete with disproportionation of the unstable hydrido chloride intermediate. Taken together, these observations implicate the important involvement of steric interactions in the transition states for hydrozirconation by this species in terms of directing both reactivity and face selectivity, and, accordingly, through careful ligand design, it might be possible to achieve higher alkene face selectivities and greater cis/trans discriminations.[11] Finally, carrying out the hydrozirconation of *cis*- and *trans*-2-butene using D$_2$ in place of H$_2$ provided the corresponding monodeuterated products which were subsequently treated with iodine to cleave the zirconium–carbon bonds.[12] As Figure 2 reveals, ^{1}H NMR spectroscopy was then used to conclusively show that hydrozirconation occurs with stereospecific syn addition to the alkene and iodinative bond cleavage occurs with retention of configuration at the α-carbon[12] to produce *erythro*-3-*d*-2-iodobutane from *cis*-2-butene, and *threo*-3-*d*-2-iodobutane from *trans*-2-butene.

As a further example of potential synthetic utility, insertion of *tert*-butylisocyanide into the zirconium–carbon bond of **2** and **3a** was shown to occur in high yield to produce the corresponding η^2-iminoacyl complexes **6** and **7** in which the secondary alkyl group structure has been preserved as shown in Scheme 3 and Figure 3. Such isocyanide insertions are routinely used in place of CO insertion to produce aldehyde products with extension of the carbon framework using Schwartz's reagent.[2] However, to the best of our knowledge, these reactions represent the first example of insertion into a secondary alkyl group of an early transition metal that is not stabilized by secondary bonding interactions.[13]

In conclusion, the present results provide a critical platform upon which continued efforts for the development of reagents for the
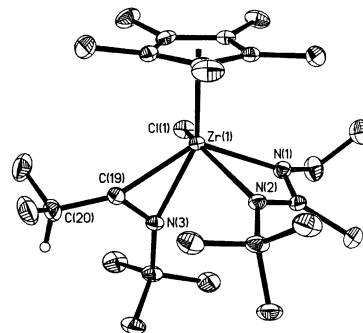

Figure 3. Molecular structure of **6b** (30% thermal ellipsoids). Hydrogen atoms, except for that at C(20), have been removed for the sake of clarity.

asymmetric hydrozirconation of alkenes can be founded. In this regard, the cyclopentadienyl/amidinate ligand set appears to potentially offer many of the same benefits of zirconocenes in terms of cost and ease of preparation, the range of achiral and chiral derivatives that are available through short synthetic manipulations, and a highly discriminating chiral environment about the metal that can form the basis of efficient stoichiometric, catalytic, and asymmetric transformations.[14]

Supporting Information Available: Experimental details, including crystallographic analyses of **2**, **3a**, **5**, and **6b** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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