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Letter

Expanding Zirconocene Hydride Catalysis: *In Situ* Generation and Turnover of ZrH Catalysts Enabling Catalytic Carbonyl Reductions

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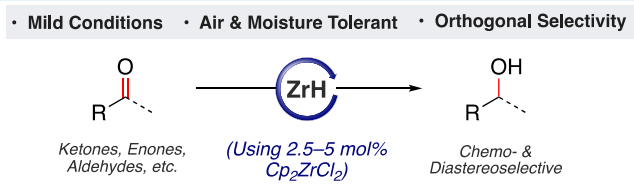
ABSTRACT: Despite the wide use and popularity of metal hydride catalysis, methods utilizing zirconium hydride catalysts remain underexplored. Here, we report the development of a mild method for the *in situ* preparation and use of zirconium hydride catalysts. This robust method requires only 2.5−5 mol % of zirconocene dichloride in combination with a hydrosilane as the stoichiometric reductant and does not require careful air- or moisture-free techniques. A key finding of this study concerns an amine-mediated ligand exchange en route to the active zirconocene hydride catalyst. A mechanistic investigation supports the intermediacy of an oxo-bridged dimer precatalyst. The application of this method to the reduction of a wide variety of carbonyl-containing substrates, including ketones, aldehydes, enones, ynones, and lactones, is demonstrated with up to 92% yield and exhibits broad functional group tolerability. These findings open up alternative avenues for the catalytic application of chlorozirconocenes, potentially serving as the foundation for broader applications of zirconium hydride catalysis.



KEYWORDS: *zirconium, zirconocene, hydride, hydrosilylation, reduction*

Metal hydrides are widely employed in chemical synthesis for the delivery of both a hydride and a functional group across various π-systems. The metal hydride chemistry of copper, ruthenium, rhodium, iron, cobalt, palladium, and nickel have seen broad application over the last two decades, providing catalytic platforms for the efficient diversification of simple chemical building blocks.[1] However, the number of catalytic applications of zirconocene hydrides are few, despite the improved toxicity, orthogonal reactivity, and lower cost of zirconium in comparison to many late-transition-metal congeners.[2−6]

Wailes and Weigold's venerable zirconocene hydrochloride **1**, more commonly referred to as Schwartz's reagent, represents the most widely employed zirconium hydride (ZrH) complex (Figure 1a).[7,8] Upon hydrozirconation, the resulting organozirconium reagents participate in a wealth of organic transformations through transmetalation or electrophilic trapping.[9] Furthermore, the attenuated nucleophilicity of organozirconium species renders these complexes comparatively mild and functional group tolerant. While Schwartz's reagent is commercially available and is frequently used to achieve a variety of fundamental synthetic transformations in organic synthesis, this reagent has an exceptionally short shelf life due to air, moisture, and light sensitivity.[10]

For these reasons, the stable and inexpensive zirconocene dichloride **2** represents an improved starting point for ZrH chemistry (Figure 1b).[11] The *in situ* conversion of dichloride **2** to the corresponding ZrH complex is most commonly achieved through the implementation of alanes, boranes, or alkyl metal reagents, providing a reliable alternative to

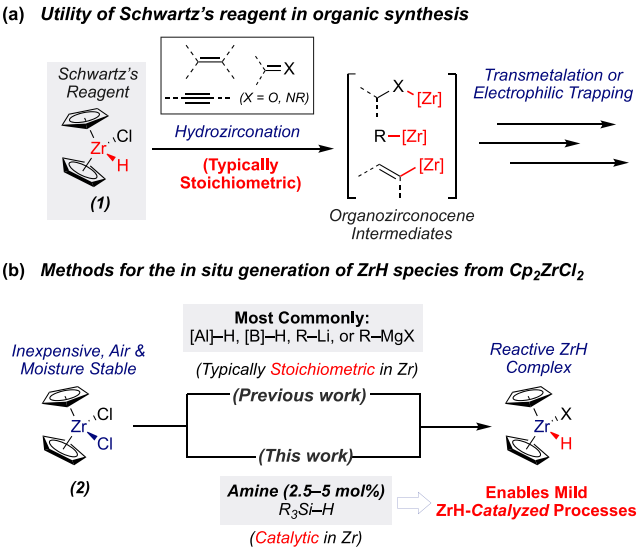


Figure 1. Utility and preparation of reactive zirconocene hydride complexes.

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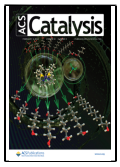

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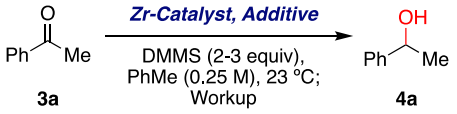
Schwartz's reagent.[10b,12] However, these methods are predominantly employed in the context of stepwise, stoichiometric preparations of ZrH reagents.

Conversely, the number of synthetic procedures for the catalytic generation and regeneration of ZrH complexes remains underdeveloped and limited in scope. The lack of mild and functional group tolerant methods for the *in situ* conversion of stable zirconocene halides to reactive hydride catalysts, in addition to the pronounced oxophilicity of zirconium, have hindered progress in this research area.[13] Herein, we report a strategy for the preparation and catalytic turnover of ZrH catalysts for the selective reduction of carbonyls.

To establish a platform for ZrH catalysis, we chose to examine the catalytic reduction of acetophenone (Table 1, **3a**).

Table 1. Optimization of the ZrH-Catalyzed Carbonyl Reduction[a]



entry	catalyst (mol %)	additive (mol %)	silane (equiv)	yield (%)[b]
1	Cp_2ZrHCl (10)		3	93
2	Cp_2ZrCl_2 (10)		3	8
3	Cp_2ZrCl_2 (10)	$HNEt_2$ (10)	3	90
4		$HNEt_2$ (10)	3	ND
5[c]	**Cp_2ZrCl_2 (2.5)**	**$HNEt_2$ (2.5)**	**2**	95 (92)[d]
6[c,e]	Cp_2ZrCl_2 (2.5)	$HNEt_2$ (2.5)	3	91

[a]Unless specified otherwise, reactions were carried out under an N_2 atmosphere at room temperature using 0.25 mmol of acetophenone in anhydrous PhMe (1 mL). Reactions were run for a duration of 13−23 h. [b]Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. ND = not detected. [c]Reaction was run on a 1 mmol scale instead. [d]Isolated yield. [e]Reaction was run in nondried glassware in an air atmosphere rather than an N_2 atmosphere.

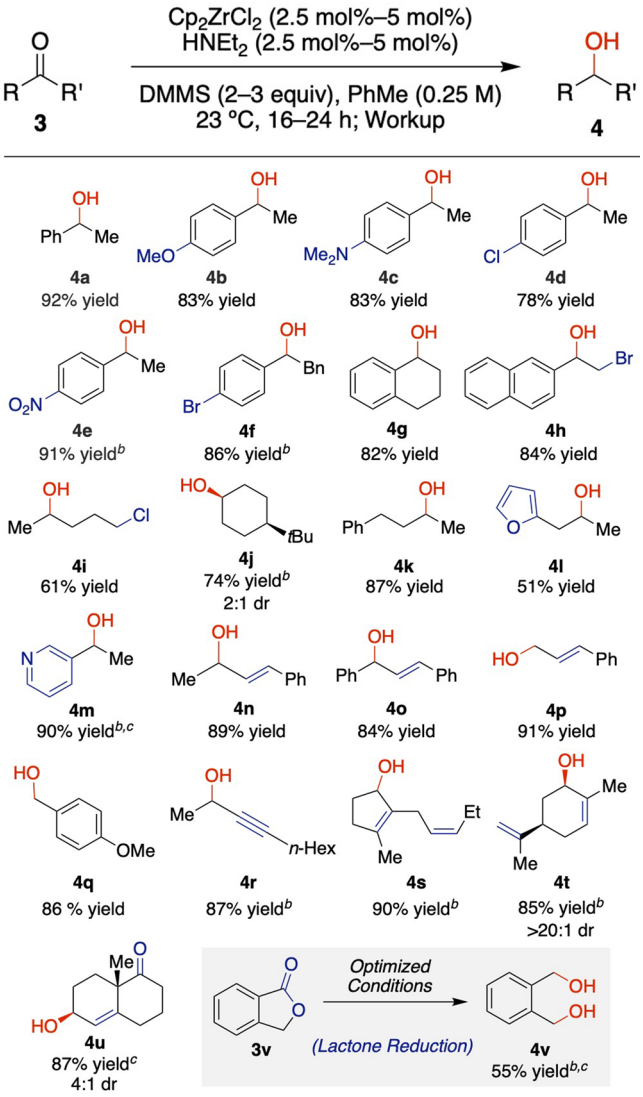
This strategy would simplify preliminary studies to three key steps: catalyst generation, hydrozirconation, and catalyst turnover.[14] Furthermore, we chose to focus our efforts on the use of hydrosilanes as the hydride source for this chemistry. These reductants are generally mild and compatible with a wide assortment of functional groups. Moreover, we postulated that the high oxophilicity of silicon would not only enable catalyst turnover, but additionally act as a traceless *in situ* protecting group for the newly formed product, thereby avoiding catalyst inhibition.

We initiated our studies utilizing 10 mol % of Schwartz's reagent, **1**, in combination with various silanes. Silanes previously employed in Zr-catalyzed alkene hydrosilylation chemistry failed to promote the catalytic reduction of ketone **3a** (see Table S1 for details).[5] However, when dimethoxy(methyl)silane (DMMS) was utilized as the stoichiometric reductant (Table 1, entry 1), alcohol **4a** was produced in 93% overall yield, signifying that catalyst turnover using hydrosilanes is feasible, even at room temperature.

Unsurprisingly, when dichloride **2** was used in lieu of hydrochloride **1**, the reaction failed to yield a significant amount of the desired product (Table 1, entry 2). Attempts to utilize various lithium, sodium, and potassium salts as additives to activate **2** resulted in background reactivity, yielding **4a** in the absence of the zirconium catalyst (see Table S1 for details).[15] Curiously, when 10 mol % of diethylamine was added in conjunction with catalyst **2**, reactivity comparable to that of **1** was observed (entry 3 versus entry 1). When the amine additive was employed in the absence of **2**, no reactivity was seen (entry 4). The quantity of catalyst and amine additive could be reduced to 2.5 mol %, affording a 92% isolated yield of alcohol **4a** (entry 5).[16] Gratifyingly, when the reaction was carried out using nondried glassware in ambient air, the desired product was still obtained in comparable yield (entry 6), demonstrating that this process is not especially air or moisture sensitive.[17]

With the optimal conditions in hand, we then surveyed the generality of the novel ZrH-catalyzed reduction (Table 2). Aryl ethers, amines, nitro groups, and halides were tolerated under these conditions, furnishing the corresponding alcohols in good to excellent yields (**4a**−**f**). However, reactions of

Table 2. Substrate Scope of the ZrH-Catalyzed Carbonyl Reduction[a]



[a]Unless specified otherwise, reactions were carried out under N_2 atmosphere at room temperature using 1 or 2 mmol of substrate in anhydrous toluene (0.25 M). [b]Reaction was run at 35 °C instead. [c]4 equiv of DMMS was used instead.

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electron-deficient arenes required longer reaction times and/or heating. Fused bicyclic ketone **3g** and α-bromoketone **3h** reacted smoothly to yield alcohols **4g**,**h** in 82% and 84% yields, respectively. Notably, hydrodehalogenation was not observed with bromide **3h**. Aliphatic and heteroaromatic ketone substrates were also readily transformed under these conditions (**4i**−**m**).

Next, we turned our attention to other classes of carbonyl substrates. Enones reacted to selectively afford the 1,2-reduction products **4n**,**o**. As expected, this catalytic reduction also accommodated aldehydes **3p**,**q**. A series of competitive reductions were also carried out with conjugated ynone **3r** and the polyene natural products *cis*-jasmone (**3s**) and (−)-carvone (**3t**). In all cases, ketone reduction took place exclusively without any detection of alkyne reduction or alkene isomerization. Furthermore, the catalytic reduction of (−)-carvone proceeded in a highly diastereoselective fashion, yielding (−)-*cis*-carveol (**4t**) with a >20:1 diastereomeric ratio. Additionally, the chemo- and diastereoselective reduction of Wieland−Miescher dione **3u** was accomplished with selective reduction of the enone moiety. This result highlights the orthogonal and mild nature of this protocol, as standard reductive procedures yield the opposite chemoselectivity or over-reduction to the corresponding diol.[18] Finally, we demonstrated the reduction of a lactone under the ZrH-catalyzed procedure, cleanly affording symmetric diol **4v** in moderate yield.

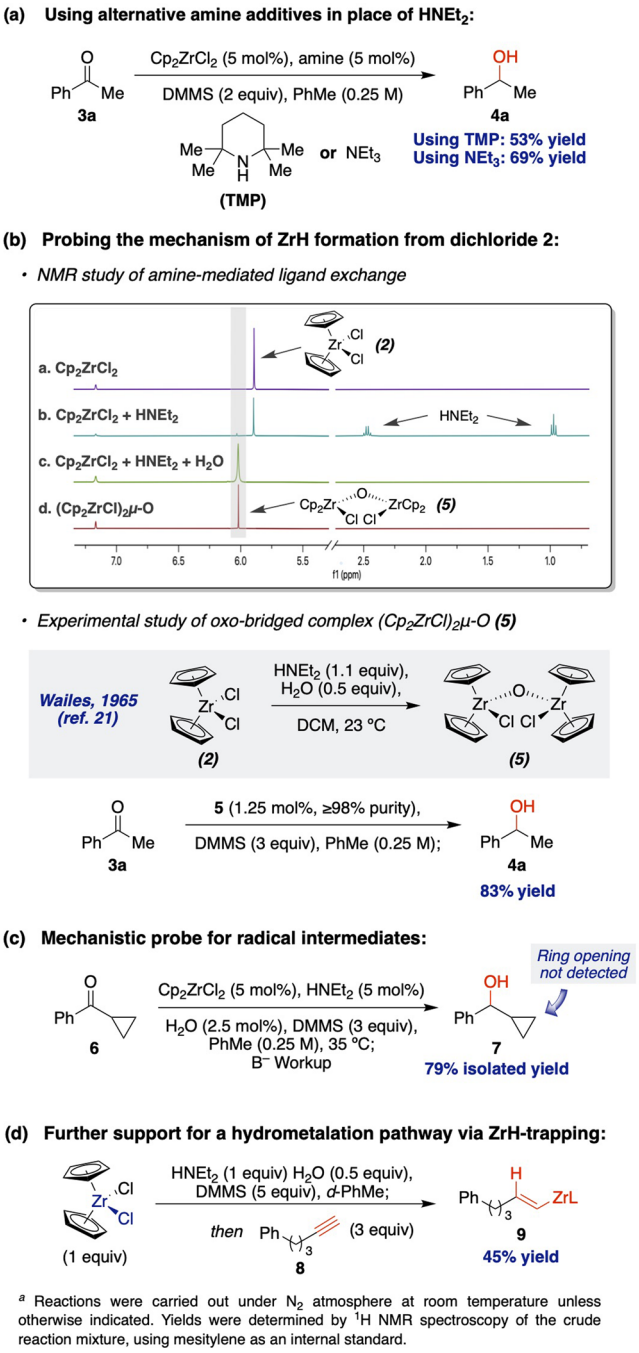
A series of experiments were carried out in order to gain further insight into the mechanism of the zirconium-catalyzed reduction (Scheme 1). To better understand the role of the amine additive, alternative N-containing additives were assayed under the denoted reaction conditions. Notably, when diethylamine was replaced with 2,2,6,6-tetramethylpiperidine (TMP) in the reduction of acetophenone, phenylethanol **4a** was still obtained, albeit in diminished yield (Scheme 1a). This reaction was likewise facilitated by catalytic quantities of triethylamine. These findings indicate that neither an α-proton on the amine nor an amine-ligated zirconocene complex is necessary for the catalytic ketone reduction.[19]

Throughout the course of our studies, it became apparent that trace quantities of water were necessary for the catalytic reduction on starting from precatalyst **2**.[20] When **2** was studied by ^{1}H NMR in the presence of diethylamine under rigorously anhydrous conditions, no apparent change was evident for the chemical shifts attributed to the Cp-region of **2** or the amine (Scheme 1b, NMR lines a and b). Upon the addition of 0.5 equiv of water, **2** undergoes rapid and clean conversion to the previously reported μ-oxo dimer **5**, as evidenced by the downfield shift of the Cp signal (NMR lines c and d). Likewise, the multiplets associated with diethylamine disappear entirely, which is consistent with the salting out of an HCl adduct.

Interestingly, prior reports by Wailes and co-workers detailed the formation of dimer **5** directly from **2** in the presence of diethylamine and water (Scheme 1b, bottom).[21] This prompted us to prepare **5** and employ it as a precatalyst under the indicated reaction conditions. Reduction product **4a** was obtained in 83% yield, demonstrating that the oxo-bridged dimer itself is competent as a precatalyst for the carbonyl reduction.

When cyclopropyl phenyl ketone (**6**) was subjected to the optimized reaction conditions, alcohol **7** was isolated after employing a mild basic workup (Scheme 1c). Notably, no ring-opened byproducts were observed, supporting a hydride

Scheme 1. Experimental Mechanistic Studies[a]



[a]Reactions were carried out under N_2 atmosphere at room temperature unless otherwise indicated. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard.

transfer mechanism rather than a radical pathway as a principal contributor to the mechanism of C−O reduction.[22,23]

To further substantiate the formation of a discrete metal hydride species from the dichloride precursor, a ZrH trap was employed (Scheme 1d). Zirconocene dichloride was sequentially treated with diethylamine, water, silane, and excess 5-phenyl-1-pentyne (**8**), resulting in the formation of vinyl zirconocene **9** in 45% yield. The observed *trans*-alkene geometry of **9** is in accordance with a concerted four-center hydrometalation mechanism.[8a]

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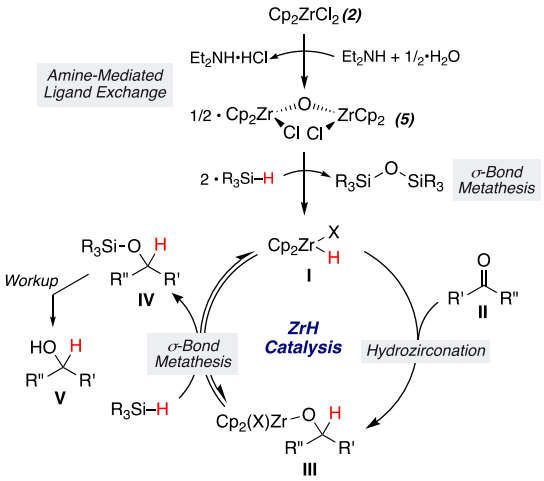
On the basis of these findings, we propose the following mechanism for the catalytic reduction of carbonyls (Scheme 2). First, oxo-bridged zirconocene dimer **5** could be formed via

Scheme 2. Proposed Mechanism for the Reduction of Carbonyls Using Cp_2ZrCl_2



an amine-mediated ligand exchange of the chlorides belonging to **2** with the oxygen of water in a 2:1 ratio. We postulate that the amine merely acts as an HCl acceptor. On the basis of spectroscopic observations, this process appears to be rapid and irreversible. Precatalyst **5** may be transferred directly to the active zirconocene hydride species **I**, presumably via a σ-bond metathesis with silane.[24]

Subsequently, ketone reduction is proposed to take place through sequential hydrozirconation and σ-bond metathesis to yield silyl ether **III**, which is desilylated upon workup to yield alcohol **V**.[25] The reaction generating **III** from hydride **I** is energetically highly favorable and likely fast. Conversely, the σ-bond metathesis to yield **IV** and regenerate **I** is anticipated to be rate limiting on the basis of enthalpic considerations and may be mechanistically more complex than what is currently proposed. At this time, further experimental mechanistic studies are underway.

In conclusion, we have developed a general method for the ZrH-catalyzed reduction of carbonyls using 2.5−5 mol % of zirconocene dichloride. This method features a mild and functional-group-tolerant method for the *in situ* preparation of the metal hydride species via an amine-mediated ligand exchange followed by reaction with DMMS. This reaction accommodates a wide assortment of carbonyl-containing substrates and does not require rigorous exclusion of air or moisture. We believe that these findings set the stage for an alternative area of metal hydride catalysis that is likely to offer selectivity orthogonal to that of other late-transition-metal hydrides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c00079.

General procedural information, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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