Catalysis
Science &
Technology

ROYAL SOCIETY
OF CHEMISTRY

PAPER

View Article Online
View Journal

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Cite this: DOI: 10.1039/c7cy01088e

Received 31st May 2017,
Accepted 1st July 2017

DOI: 10.1039/c7cy01088e

rsc.li/catalysis

Catalytic carbonyl hydrosilylations *via* a titanocene borohydride–PMHS reagent system†

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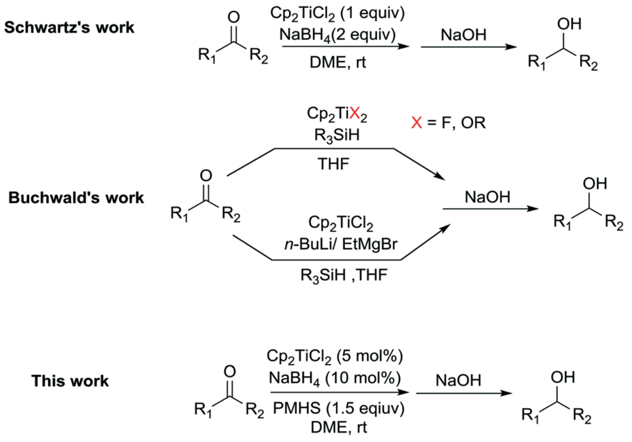
Reduction of a wide range of aldehydes and ketones with catalytic amounts of titanocene borohydride in concert with a stoichiometric poly(methylhydrosiloxane) (PMHS) reductant is reported. Preliminary mechanistic studies demonstrate that the reaction is mediated by a reactive titanocene(III) complex, whose oxidation state remains constant throughout the reaction.

Carbonyl reductions to alcohols are an important and fundamental reaction in organic chemistry. Synthetic organic chemists have routinely applied this transformation to form basic motifs in multi-step syntheses of complex organic molecules, of biological and synthetic utility.[1–5] In view of its significance, a large number of methods have been developed for carbonyl reductions to their respective alcohols. Notable methods include reductions mediated by hydride sources such as lithium aluminium hydride (LAH) and sodium borohydride ($NaBH_4$),[6] Meerwein–Ponndorf–Verley reductions,[7,8] samarium-mediated reductions,[9,10] catalytic hydrogenations[11–13] and low-valent metal-catalyzed hydroborations and hydrosilylations.[14–17]

Work described herein is primarily focused on carbonyl reductions mediated by catalytic titanocene borohydride. We were inspired by seminal work of Schwartz and coworkers whereby simple ketones were reduced to alcohols in aprotic media by titanocene borohydride: a complex that is easily generated *in situ*, by mixing titanocene dichloride and $NaBH_4$ in dimethoxyethane (DME) (Scheme 1).[18] Although this method was simple, prepared from readily available reagents, and performed under mild conditions, it required stoichiometric amounts of titanocene borohydride. To the best of our knowledge, a catalytic approach to this process has not yet been developed. Conversely, Buchwald and coworkers developed an elegant approach to carry out hydrosilylation of ketones with subsequent workup to reduce alcohols with catalytic low-valent titanocene hydride complexes and an inexpensive siloxane polymer, poly(methylhydrosiloxane) (PMHS) as the stoichiometric reductant. In this approach, the active titanocene hydride species was either synthesized from a premade titanocene precatalyst or generated *in situ* at very low temperatures with reagents that required careful handing (Scheme 1).[19–22]

Based on the aforementioned titanocene mediated reductions developed by Schwartz and Buchwald, we envisioned designing a system whereby carbonyls could be reduced to their respective alcohols with catalytic amounts of titanocene borohydride. Ideally, this complex would be generated under mild conditions, from inexpensive, readily available titanocene dichloride and a hydride source as a stoichiometric reductant. Although catalytic approaches have been reported for reducing carbonyls to alcohols in refluxing diisopropylether (DIPE) using catalytic Zn(2-ethylhexanoate)$_2$ and $NaBH_4$ with PMHS as the stoichiometric reductant,[23] a similar approach with commercially available titanocene dichloride has not been reported. Herein, we present a procedurally simple, inexpensive, and mild approach for the hydrosilylation of aldehydes and ketones and subsequent conversion to their respective alcohols at room temperature with catalytic amounts of titanocene borohydride and PMHS as the stoichiometric reductant (Scheme 1).

To optimize the reaction conditions, a series of experiments were performed and the results are summarized in Table 1. As shown, 2-octanone (**1**) was successfully reduced to



Scheme 1 Low-valent titanocene catalyzed carbonyl reductions.

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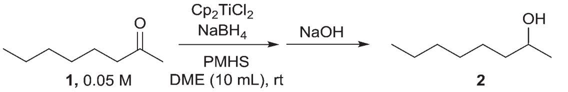
† Electronic supplementary information (ESI) available: Experimental details, IR and NMR spectra. See DOI: 10.1039/c7cy01088e

2-octanol (**2**) with 10 mol% catalyst and with $NaBH_4$ as the stoichiometric hydride source in DME (Table 1, entry 1). The reduction of **1** to **2** was ineffective in DME solvent with either only $NaBH_4$ as reductant or with the addition of 5 mol% catalyst (Table 1, entries 2 & 3). Complete reduction of **1** to **2** was achieved with 5 mol% catalyst and PMHS as stoichiometric reductant (Table 1, entry 4). Control experiments showed that the reaction was unsuccessful without the active titanocene catalyst (Table 1, entries 5 & 6).

Reductions were also performed in THF, which proceeded smoothly but relied on a very low catalyst to solvent ratio (6.25 mg (Cp_2TiCl_2) : 10 mL (THF) or 2.5 mM of catalyst). At higher catalyst to solvent ratios (25 mg (Cp_2TiCl_2) : 10 mL (THF) or 10 mM of catalyst), the active titanocene borohydride complex was not formed until after three days due to the poor solubility of $NaBH_4$ in THF, corroborating observations made by Schwartz and coworkers.[18] Attempts to form the active titanocene catalyst directly by mixing titanocene dichloride with PMHS were not successful. In addition to $NaBH_4$, attempts to form the active titanocene borohydride intermediate with milder hydride sources including sodium cyanoborohydride ($NaBH_3CN$) and sodium triacetoxyborohydride ($NaBH(OAc)_3$), were not successful and provided only recovered starting material (see ESI† for details). With these control studies in hand, further reactions were performed using DME as the solvent of choice because it provided the fastest preparation of the active catalyst.

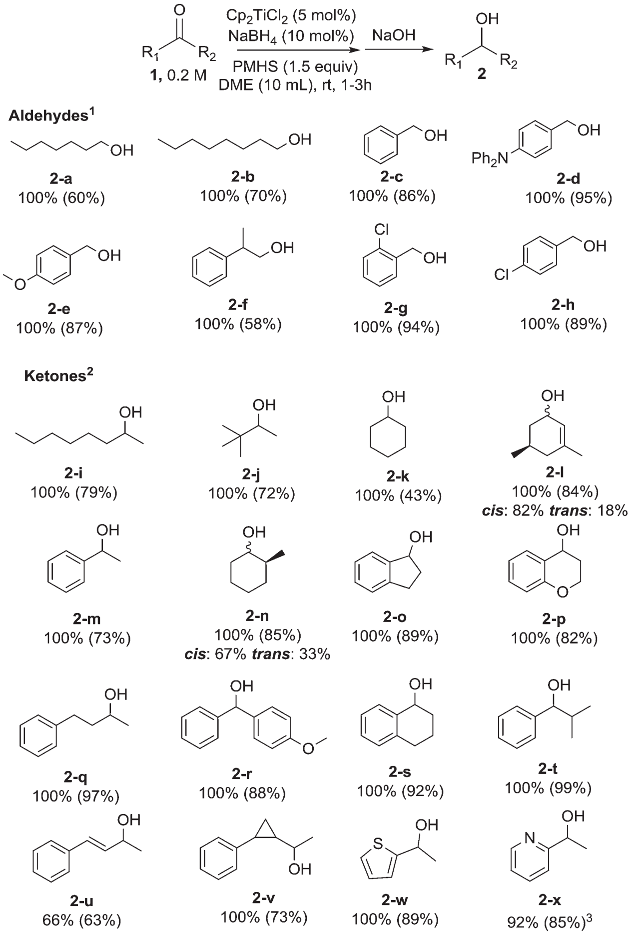
To further investigate the breadth of this approach, we probed the reduction of a variety of aldehydes and ketones with different steric and electronic properties. Our findings are summarized in Scheme 2. All of the aldehydes and ketones examined were successfully reduced to alcohols irrespective of their structural features. Under the reaction conditions, the *cis*-isomer was preferred to the *trans*-isomer for ketones **2-l** & **2-n**, suggesting that the hydride preferentially attacks the carbonyl carbon at the least sterically hindered position. Nardi and coworkers observed similar trends in their $Er(OTf)_3/NaBH_4$ catalyzed reductions of α,β-unsaturated ketones.[15] Like Luche reductions,[24,25] α,β-unsaturated ketones **2-l** and **2-u** favorably reduced *via* 1,2 addition under the reaction conditions. This approach serves as a compliment to titanocene(III) catalyzed reductions of α,β-unsaturated ketones to ketones.[26] 1-(2-Phenylcyclopropyl) ethan-1-one (**1-v**) was successfully reduced to 1-(2-phenylcyclopropyl) ethan-1-ol (**2-v**) without any evidence of ring opening. This observation suggests that this reaction proceeds *via* a hydride transfer as opposed to a hydrogen atom transfer (HAT). Heterocycles with pendant carbonyls (**1-w** & **1-x**) were also effectively reduced to their respective alcohols (**2-w** & **2-x**).

Table 1 Optimizing conditions and control experiments



Entry	Cp_2TiCl_2 (mol%)	$NaBH_4$ (mol%)	PMHS (mol%)	Time (h)	Yield[a] (%)
1	10	200	—	4	95
2	—	400	—	96	41
3	5	150	—	4	57
4	5	10	150	1	100[b]
5	—	—	150	24	—
6	—	10	150	24	13

[a] GC yields with biphenyl as internal standard. [b] Only product observed by GC.



Scheme 2 Reduction of aldehydes and ketones $Cp_2TiCl_2/NaBH_4$/PMHS in DME. Conversion to alcohol based on NMR analysis & isolated yields in parenthesis; [1] reaction time was 1 hour; [2] reaction time was 1–3 hours; [3] reaction stirred overnight.

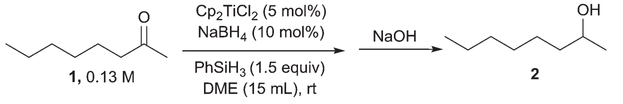
From a mechanistic standpoint, we hypothesized that the carbonyl was being reduced *via* a hydrosilylation instead of a hydrogen atom transfer (*vide supra*). To further study the process, the model reaction shown in Scheme 3 was performed and monitored by ReactIR. The C–H wag of the Cp ligand is known to be sensitive to the oxidation state of the titanocene complex as well as the nature of the ligands coordinated to the titanium metal.[27,28] Additionally, *in situ* monitoring also enabled us to follow carbonyl reduction and conversion of the Si–H bond to an Si–O bond. Since PMHS has an absorption that interferes with the C–H wag of the Cp ligand of the titanocene, we employed phenylsilane ($PhSiH_3$) as there was no interference from this terminal reductant.

The titanocene borohydride complex whose X-ray structure is known,[29] was generated by the addition of sodium borohydride to titanocene(IV) dichloride. Reduction of Ti(IV) to Ti(III) and formation of the titanocene borohydride was demonstrated by the shift of the C–H wag of the Cp ligand (Fig. 1a) from 820 cm^{-1} to 809 cm^{-1} and a change in color from red to violet was observed. Once this conversion was complete, ketone **1** was added to the solution and the C–H absorption of the Cp shifted from 809 cm^{-1} to 799 cm^{-1} (Fig. 1b) and a change in color from violet to green was observed.

Fig. 2a contains a plot of the change in absorption over time for the C–H wag for the Cp of titanocene borohydride before and after addition of ketone **1**. Upon addition of the ketone, the absorption at 1719 cm^{-1} was observed. Concurrently there was a disappearance of the C–H wag absorption for titanocene borohydride at 809 cm^{-1}, and the subsequent growth of another absorption at 799 cm^{-1} consistent with the C–H wag of a Cp_2Ti–O interaction.[27,28] The initial growth of ketone observed at 1719 cm^{-1} was followed by a minor drop in the absorption consistent with initial reduction of 2-octanone by titanocene borohydride (Fig. 2a). Furthermore, the C–H wag absorption at 799 cm^{-1} characteristic of Cp_2Ti(III) complexes indicates that the titanocene catalyst remains in the +3 oxidation state bound to the alkoxide.[18,30,31]

Once no further changes were observed, phenylsilane was added to the solution to initiate the reaction. The ketone absorption at 1719 cm^{-1} decayed over the course of approximately 100 minutes until the reaction was complete (Fig. 2b). The Si–H stretch of phenylsilane was observed at 705 cm^{-1}. The phenylsilane peak decreased with concomitant development of another absorption at 835 cm^{-1} which is attributed to the OSi–H stretch due to silylation of the Ti(III)-bound alkoxide (see ESI† for details). Interestingly, the C–H wag absorbance for titanocene at 799 cm^{-1} remains after ketone reduction, indicating the presence of either Ti(III)–O species or an active titanocene hydride intermediate. At this point, the reaction was exposed to air and worked up with 1 M NaOH, and provided a nearly quantitative yield of the carbinol product.

To verify the intermediacy of a Ti(III) hydride, a titanocene hydride complex was generated *via* the approach described by Buchwald[20–22] and monitored by ReactIR. In this experiment, titanocene difluoride was mixed with phenylsilane in refluxing THF. The formation of a titanocene(III) hydride species was demonstrated by the shift in the C–H wag of the Cp ligand of titanocene from 813 cm^{-1} to 799 cm^{-1} and a change in color from yellow to green was observed (see ESI† for experimental details). The C–H wag absorbance at 799 cm^{-1} suggests that a Ti(III) hydride complex is formed as an intermediate in the reduction process with titanocene(III) borohydride and PMHS as the stoichiometric reductant. We also observed the formation of $PhSiF_2$–H through the presence of absorbances at 876 and 858 cm^{-1} respectively.



Scheme 3 Reaction conditions for ReactIR studies.

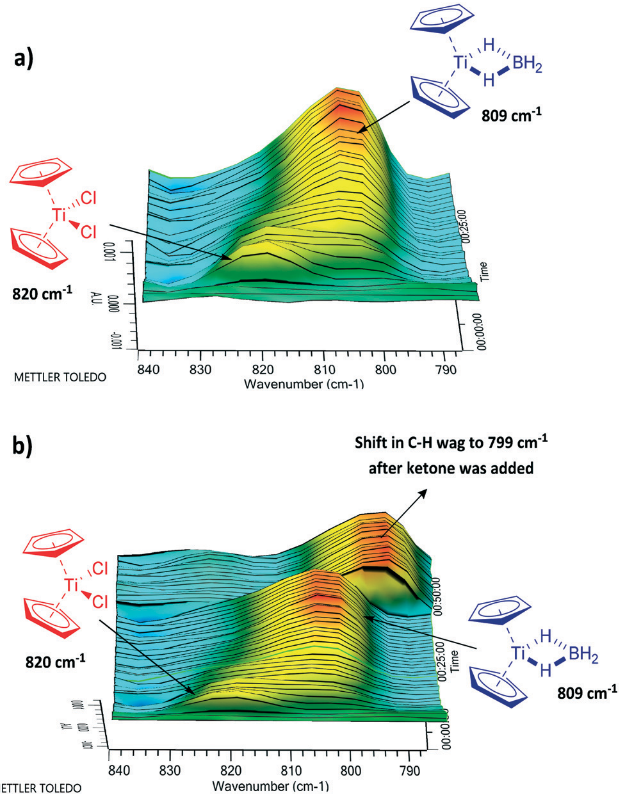


Fig. 1 a) Formation of titanocene borohydride monitored by ReactIR. b) Shift in C–H wag after ketone addition (see ESI† for details).

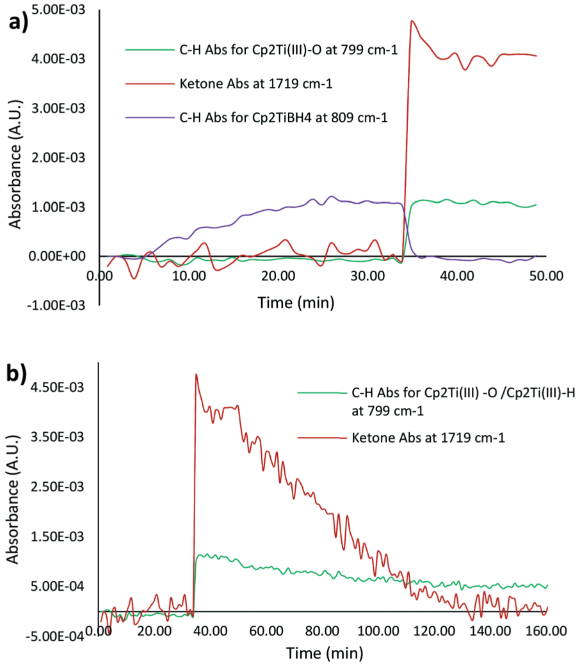


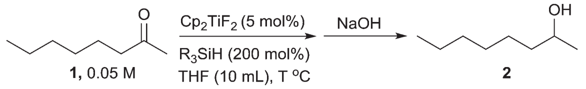
Fig. 2 a) Trend observed on ReactIR for 2-octanone and C–H wag of Cp for titanocene complex. b) Monitoring reaction after addition of phenylsilane (see ESI† for experimental details).

To determine if the titanocene hydride intermediate in our approach is the same as the one generated by Buchwald, the reduction of 2-octanone to 2-octanol was performed *via* the method described by Buchwald and coworkers[20–22] and the results are summarized in Table 2. Reactions were monitored after an hour and it was observed that reduction of 2-octanone only proceeded under refluxing conditions and product yield was improved when the active catalyst was prepared with 20 mol% $PhSiH_3$ (Table 2, entries 4 & 5). With our optimized reaction conditions however, full conversion to product was realized within an hour and at room temperature (Table 1, entry 4). These results indicate that the titanocene hydride generated *in situ* with our approach is not identical to that generated in the system developed by Buchwald and coworkers.

Attempts to isolate and crystallize the intermediate generated using our approach has not been successful thus far. Nonetheless, it is useful to examine other protocols developed in the literature for generating titanocene(III) hydride complexes. To this end, we looked at the studies on titanocene(III) hydride complexes done independently by Harrod[32] and Brintzinger.[33,34] Brintzinger studied titanocene hydride complexes generated with either hydrogen gas, organolithiums or Grignard reagents.[33,34] Harrod, however, studied titanocene(III) hydride complexes generated (Fig. 3) by reacting dimethyltitanocene with phenylsilane.[32] We therefore hypothesized that the titanocene hydride intermediate generated in our system would be similar but not necessarily identical to that generated by Harrod. Complex **b** was prepared by reacting stoichiometric amounts of dimethyltitanocene (1 : 1 mole ratio) with phenylsilane while complex **c** was prepared by reacting catalytic amounts of dimethyltitanocene with phenylsilane. They observed that **c** decomposed to **b**, which eventually decomposed to **a**. Intermediate **a** was observed by ESR spectroscopy. All the intermediates were found to be reactive in polymerizing silanes with concomitant evolution of H_2 gas.[32]

It is therefore possible that for our system, the reduction could be mediated by either one or more titanocene hydride complexes generated *in situ*, which may have varying reactivity towards carbonyl reductions. This could explain the discrepancies observed between the reductions performed *via* our titanocene borohydride–PMHS system and the approach outlined by Buchwald. It should also be noted that the presence of a Ti(III)-bound alkoxide cannot be ruled out as a possible intermediate since its Cp ligand has the same C–H wag absorption at 799 cm^{-1}.

Table 2 Reduction of **1** to **2** with Cp_2TiF_2



Entry	R_3SiH	*T* (°C)	Yield[a] (%)
1	$PhSiH_3$	r.t.	—
2	PMHS	r.t.	—
3	PMHS[2]	r.t.	—
4	PMHS	60	45
5	PMHS[b]	60	91

[a] GC yields after 1 h with biphenyl as internal standard. [b] Active catalyst formed with 20 mol% $PhSiH_3$ under reflux.

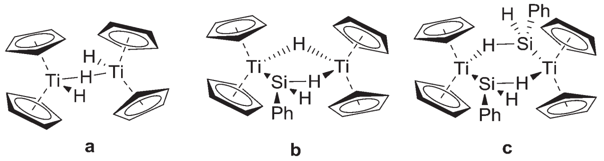
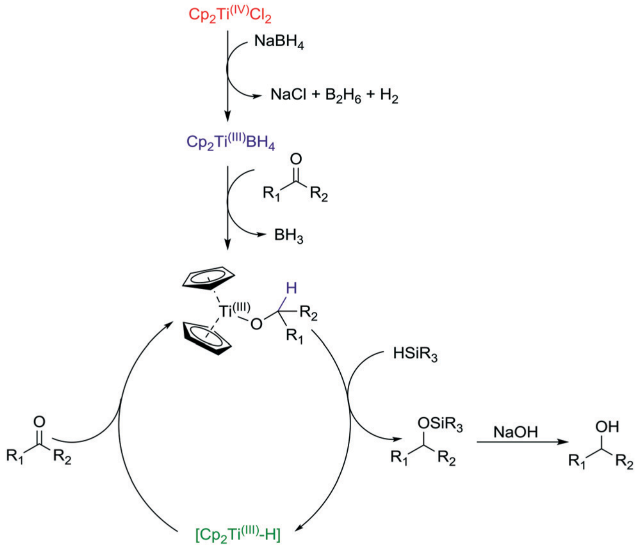


Fig. 3 Titanocene(III) hydride complexes proposed by Harrod.[32]



Scheme 4 Proposed catalytic cycle for carbonyl reduction.

Based on the results obtained from monitoring this process *via in situ* IR spectroscopy, a catalytic cycle was proposed as shown in Scheme 4. In the proposed cycle, the titanocene borohydride, formed *via* the method described in the literature,[18,35] reduces the carbonyl to form the titanium(III) alkoxide.[18,30,31] It is then posited that the titanium alkoxide reacts with the silane, *via* a method similar to that proposed by Buchwald and coworkers,[20,21,36] leading to the formation of silylated product and a titanocene(III) hydride intermediate, whose structural identity at the moment is unknown. This intermediate presumably reacts with another carbonyl to complete the cycle.

In conclusion, a procedurally straightforward, inexpensive, and mild approach to the reduction of aldehydes and ketones with a titanocene borohydride–PMHS system has been demonstrated. This method was used to successfully reduce a wide range of aldehydes and ketones. Preliminary mechanistic studies suggest that the reaction is mediated by a reactive titanocene hydride complex. Results from our studies also demonstrate that the titanocene complex remains in the +3-oxidation state throughout the reaction. Future endeavours will focus on asymmetric carbonyl reductions[11,12,20,37] catalyzed by titanocene borohydride. We are optimistic that this potentially has direct application to the synthesis of complex organic compounds. Work is also currently underway to extend this system to reduce other related functional groups including esters, amides, imines and nitriles. Initial results from these studies are promising and will be reported in future publications.

Acknowledgements

We thank the U.S. National Science Foundation (CHE-1123815) and a Faculty Innovation Grant from Lehigh University for the support of this work. We also thank Dr. Sandeepan Maity for insightful discussions.

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