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Letter

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Rapid, mild, and selective ketone and aldehyde hydroboration/ reduction mediated by a simple lanthanide catalyst

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ABSTRACT. Rapid, clean hydroboration of ketones and aldehydes with HBpin is achieved using the homoleptic rare earth catalyst $La[N(SiMe_3)_2]_3$ (La^{NTMS}). The reaction employs low catalyst loadings (0.01-1 mol% La^{NTMS}), proceeds rapidly (>99% in 5 min) at 25°C, and is moderately air-tolerant. Additionally, this hydroboration has good functional group compatibility, including halides, nitro groups, and nitriles, and is exclusively carbonyl-selective in the presence of alkenes and alkynes.

KEYWORDS: homogeneous catalysis, carbonyl hydroboration, ketone/aldehyde reduction, lanthanide, chemoselective hydroboration

The reduction of aldehydes and ketones serves as an efficient synthetic route to functionalized alcohols, making this transformation an invaluable tool in fine chemical production and natural product synthesis. Active hydride reagents are used ubiquitously for this transformation, but frequently show poor functional group tolerance (i.e., $LiAlH_4$ reduction of nitro groups, nitriles, amides, etc.) and/or modest reaction rates (i.e., $NaBH_4$ with hindered ketones).[1] Employing a catalyzed system with a less active reductant, such as pinacolborane (HBpin), can greatly enhance both the selectivity and the rate of carbonyl reduction. Unlike catalytic carbonyl hydrosilylation, which has a well-established literature precedent,[2-5] catalytic carbonyl hydroboration remains relatively unexplored, and as such, is currently of great interest.

The catalyst scope for carbonyl hydroboration is rapidly expanding, as detailed in a recent review.[6] Alkaline earth,[7-9] transition metal,[10-17] and main group catalysts[18-22] all mediate this transformation. While most are effective in aldehyde reduction, they typically perform poorly with ketones, requiring high catalyst loadings, long reaction times, or elevated temperatures. Additionally, many recently reported catalysts require multi-step, air-free syntheses and rigorously dried substrates and solvents. Here we report that inexpensive, commercially available homoleptic $La[N(SiMe_3)_2]_3$ (abbreviated henceforth as La^{NTMS}) catalyzes the rapid, regioselective hydroboration of diverse aldehydes and ketones with HBpin at room temperature.

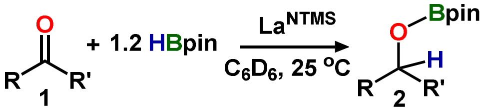
Organolanthanide catalysts were previously shown to effectively catalyze hydroelementations of olefins, allenes, and acetylenes,[23-29] however their reactivity with carbon-heteroatom multiple bonds remains relatively unexplored. After discovering that $[Cp^*_2LaH]_2$ efficiently catalyzes the hydroboration/dearomatization of pyridines,[30] we sought to investigate hydroborations of other substrates having carbon-heteroatom multiple bonds and to enhance the reaction utility by employing a more synthetically accessible/less air- and water-sensitive catalyst than $[Cp^*_2LaH]_2$. Homoleptic lanthanide amides of the type $Ln[N(SiMe_3)_2]_3$ are commercially available for most lanthanides and are less air- and moisture-sensitive than many other organolanthanides. These complexes ($Ln[N(SiMe_3)_2]_3$) effectively catalyze olefin/allene/alkyne hydroelementation,[24-25,27-29] as well as aldehyde amidation[31] and the Tishchenko reaction,[32-33] but the potentially useful hydroboration of carbonyl-containing substrates has not been investigated.

At a loading of 0.01 mol% in benzene, La^{NTMS} catalyzes benzophenone hydroboration with HBpin in up to 99% conversion in less than 5 min at 25 °C by ^1H NMR assay (see Supporting Information for details). This corresponds to a TOF >40,000 h^{-1}, which is among the most rapid pinacolborane-based reductions reported to date.[6,9] Analogous lanthanide amides (Y, Ce, Sm) were also investigated and yielded full conversion with only slightly diminished rates relative to La.[34]

Table 1 summarizes the full scope of ketones investigated in this report (see Supporting Information for full product characterization). Electron-rich, aromatic ketones (benzophenone, 4-methylbenzophenone, and 4,4’-dimethylbenzophenone, Table 1 entries 2-4) proceed rapidly at a La^{NTMS}

loading of only 0.01 mol%, while aliphatic and less electron-rich ketones require La^{NTMS} loadings of 0.1 mol% for comparable rates. Otherwise, little variation in rate among the various ketones is noted. Note that halogenated substrates are tolerated (Table 1 entry 7) and no side-reactions with alkenes or nitro groups are observed (**Table 1**, entries **6** and **10**, respectively). Benzalacetone (**6**) undergoes hydroboration selectively at the ketone while preserving the olefin functionality, even at catalyst loadings as high as 5 mol%. This is significant since the low cost and commercial availability of the catalyst make such high loadings practical if required. Rotenone (**11**), a natural product used as a pesticide and insecticide,[35] is likewise only reduced at the ketone, exhibiting >99% selectivity over alkene hydroboration and cyclic ether ring-opening, the latter of which is common for other lanthanide Lewis acids.[36] Note also that La^{NTMS} is not deactivated by the potentially chelating catechol dimethyl ether.

Table 1. Scope of ketone hydroboration with La^{NTMS}



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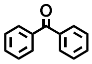
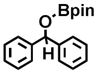
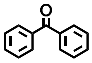
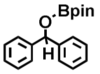
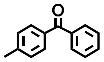
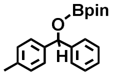
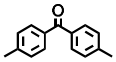
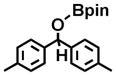
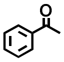
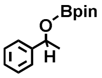
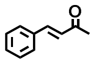
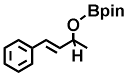
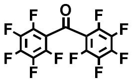
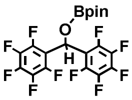
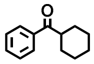
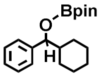
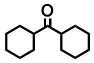
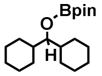
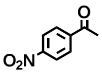
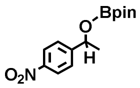
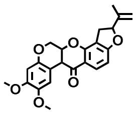
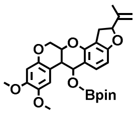
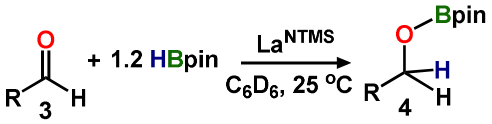
1			---	1 week	<1
2			0.01	15	>99
3			0.01	15	>99
4			0.01	15	>99
5			0.1	15	>99
6			0.1	15	>99
7			0.1	15	>99
8			0.1	15	>99
9			0.1	15 90	50 98
10			0.1	15	>99
11			1.0	15	>99

[a] NMR yield. Ketone (0.25mmol) added to 0.5 mL HBpin solution (0.30mmol) and C_6Me_6 internal standard in C_6D_6. La^{NTMS} added from a stock solution of appropriate concentration, and reaction monitored by ^{1}HNMR. Isolated alcohol yields of novel boronic esters are reported in the SI.

Benzophenone hydroboration serves as the basis for further investigation into the general applicability of this catalytic system, including scalability, ambient atmosphere tolerance, and solvent minimization for "greener" processes. Preparative scale reactions (1 g, repeated 4 times) do not show any obvious loss in reactivity from exposure to ambient atmosphere and no side reactions are observed; after hydrolysis of the product boryl ester, diphenylmethanol is obtained in 86% isolated yield. Note that this reaction was conducted entirely on the bench, foregoing the use of a Schlenk line and using unpurified benzophenone, La^{NTMS}, and benzene, taking no special precautions to exclude air or moisture. Further exploration of the catalyst's tolerance to ambient atmosphere was hindered by the moisture sensitivity of HBpin, which we found to be at least as susceptible to hydrolysis as La^{NTMS}. Other solvents can also be used (e.g., heptane, ether, THF, CH_2Cl_2), and this reaction can be run neat, with HBpin acting as the solvent (safety note: the reaction is exothermic and, without solvent to dissipate evolved heat, should be run in an ice bath). This is highly desirable from a waste-reduction perspective and further demonstrates the robustness of the catalyst. After removing volatiles *in vacuo*, benzophenoxy pinacolborane is obtained in 97% isolated yield.

Aldehydes are also cleanly reduced by this system, showing high selectivity towards C=O reduction over alkenes, alkynes, and nitriles, as well as exhibiting halide tolerance (**Table 2** entries **6**, **4**, **8**, and **5** resp.). However, reaction rates

Table 2. Scope of aldehyde hydroboration with La^{NTMS}.



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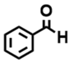
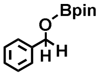
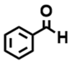
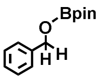
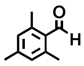
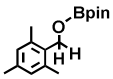
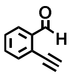
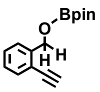
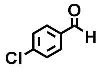
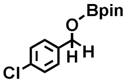
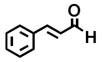
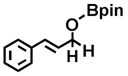
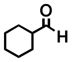
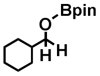
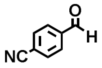
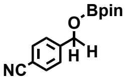
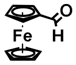
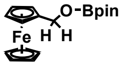
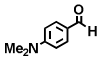
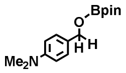
1			---	60	11%
2			0.1	15 60	50 >99
3			1.0	15	>99
4			0.1	15	>99

5			1.0	15	>99
6			1.0	15	>99
7			0.1	15	>99
8			0.1	15	>99
9			0.1	15	>99
10			0.1	15	>99

[a] NMR yield. Aldehyde (0.25mmol) added to 0.5 mL solution of HBpin (0.30 mmol) and C_6Me_6 (0.05mmol) internal standard in C_6D_6. La^{NTMS} added from stock solution of appropriate concentration, and the reaction monitored by ^1H NMR. Isolated alcohol yields of novel boronic esters are reported in the SI.

are generally slower than for ketones, and higher catalyst loadings are required for comparable reaction rates (**Table 2**). This observation is contrary to what has been observed previously, where aldehydes are more reactive than ketones.[6]

The empirical rate law for catalytic ketone hydroboration (eq. 1) was determined via ^1H NMR monitoring with reference to C_6Me_6 as internal standard (see Supporting Information for details). The most sluggish ketone examined

$$\text{Rate} = k\,[\text{La}^{\text{NTMS}}]^1\,[\text{HBpin}]^1\,[\text{Ketone}]^1 \qquad (1)$$

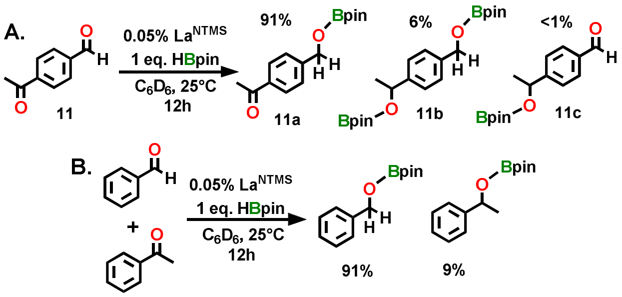
was dicyclohexylketone, which was used for kinetic analysis to enable precise rate monitoring at low conversions (< 20%). Under the present reaction conditions the rate is found to be first-order in [Ketone], [HBpin], and [La^{NTMS}], suggesting all are involved in the turnover-limiting step or in a rapid pre-equilibrium before this step. Activation parameters for the dicyclohexylketone hydroboration are $\Delta H^{\neq} = +17 \pm 1$ kcal/mol and $\Delta S^{\neq} = -15 \pm 2$ e.u. The large $\Delta H^{\neq}$ may reflect unfavorable steric repulsions in the transition state.

The rate law for catalytic aldehyde hydroboration (eq. 2) was determined in a similar manner (see Supporting Information) using cyclohexylcarboxaldehyde due to its structural similarity to dicyclohexylketone. Interestingly, the rate is *zero-order* in [HBpin] and [Aldehyde] under the same

$$\text{Rate} = k\,[\text{La}^{\text{NTMS}}]^1[\text{HBpin}]^0[\text{Aldehyde}]^0 \qquad (2)$$

conditions, and the activation parameters are markedly different as well ($\Delta H^{\neq} = +12 \pm 2$ kcal/mol and $\Delta S^{\neq} = -33 \pm 7$ e.u.), suggesting distinct mechanistic departure from the ketone hydroboration process. Further mechanistic details are currently under investigation.

These surprising ketone vs aldehyde rate and mechanistic differences prompted competition experiments to directly probe hydroboration selectivity. In a reaction of 4-acetylbenzaldehyde (**11**, Scheme 1a) with 1.0 equiv. HBpin at 97% conversion, the aldehyde-only hydroboration product (**11a**) is obtained in 91% yield (by NMR), with only 6% of the di-hydroborated product (**11b**) and <1% of the ketone-only hydroboration product (**11c**). Subsequent addition of a second equivalent of HBpin gives **11b** in >99% yield by ^1H NMR. Similar intramolecular selectivity was reported using a metal-free diazaphospholene catalyst[19] and an aluminum monohydride catalyst.[22] However in those cases ketones are much less reactive than aldehydes in isolated reactions, requiring longer reaction times, higher temperatures, or higher catalyst loadings. In a competition study, where equimolar acetophenone and benzaldehyde are allowed to compete for 1.0 equiv. HBpin (Scheme 1b), preference for aldehyde hydro-boration is again observed, reaching 91% conversion of benzaldehyde and only 9% conversion of acetophenone. When a second equiv. of HBpin is introduced, both borylated products are obtained in >99% yield. Such selectivity for aldehyde vs ketone hydroboration with pinacolborane is also noteworthy and has only been reported twice before using either $[Ru(p\text{-cymene})Cl_2]_2$[13] or an aluminum monohydride catalyst.[22] Again, these systems exhibit lowered activity with ketones vs aldehydes in independent systems, requiring longer reaction times and/or higher temperatures for ketone reduction. The present system, which displays selectivity that is contrary to what would be expected based on kinetic data, is highly unusual and, to our knowledge, has not been reported previously for pinacolborane-based reductions.



Scheme 1. Competitive Aldehyde/Ketone Hydroboration Selectivity Study. **A.** 4-Acetylbenzaldehyde. **B.** Benzaldehyde and acetophenone.

In conclusion, we report the rapid catalytic hydroboration of ketones and aldehydes with HBpin using a simple lanthanum amido catalyst. High selectivity for aldehyde hydroboration over ketones and C-C unsaturation is observed, along with good functional group tolerance for many other groups. Further investigations of scope and mechanism are in progress.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information.

The supporting information is available free of charge at acs.org. Experimental details, kinetic analysis, ^{1}H, ^{11}B, and ^{13}C NMR characterization of products.

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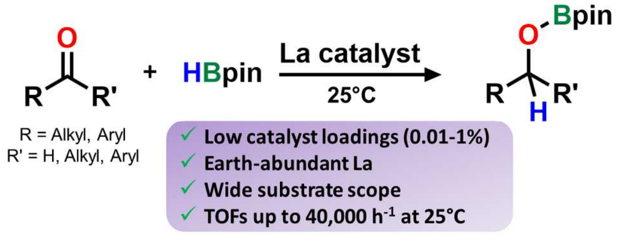

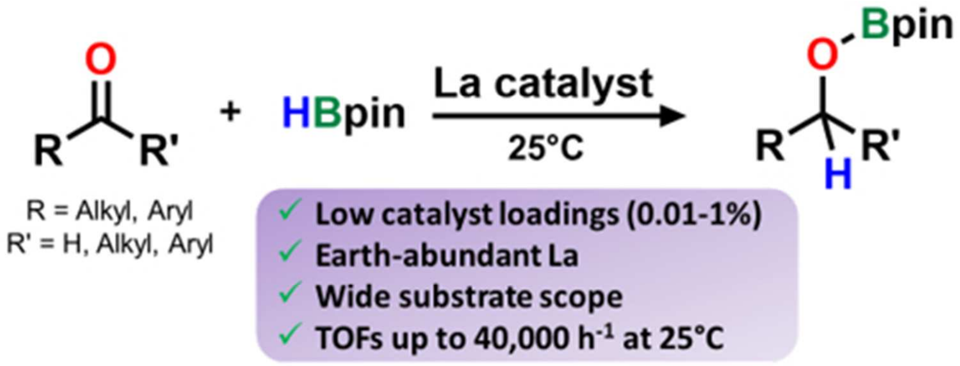

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