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COMMUNICATION

Expedient Hydrofunctionalisation of Carbonyls and Imines Initiated by Phosphacyclohexadienyl Anions

Matthew J. Margeson,[a] Felix Seeberger,[a] John A. Kelly,[a] Julia Leitl,[a] Peter Coburger,[a] Robert Szlosek,[a] Christian Müller*[b] and Robert Wolf*[a]

Abstract: The ability of phosphacyclohexadienyl anions [Li(1-R-$PC_5Ph_3H_2$)] [R = Me (**1a**), *n*Bu (**1b**), *t*Bu (**1c**), Ph (**1d**) and CH_2SiMe_3 (**1e**)] to initiate hydrofunctionalisation reactions was investigated and compared with simple, commercially available compounds, such as LiO*t*Bu, KO*t*Bu and *n*BuLi. All compounds are expedient catalysts for the hydroboration of a wide scope of substrates, ranging from aldehydes to imines and esters. In the hydroboration of carbon dioxide, however, only our system was observed to efficiently produce the desired methanol equivalents.

The past few decades have seen considerable strides in main group chemistry, both from a fundamental and applied point of view. One of the more attractive prospects is the utilisation of main group compounds as precious metal mimics, especially in terms of catalytic applications.[1] The main goal is the eventual replacement of rare transition metal catalysts with an effective and more abundant main group counterpart.

The hydroelementation of unsaturated organic compounds, in particular hydroboration and hydrosilylation, is a reaction that traditionally was firmly in the remit of precious metal catalysts.[2] Hydrofunctionalisation processes are highly prevalent in industry; products from these reactions are used extensively in the production of fine chemicals, pharmaceuticals, lubricants, adhesives and insulation.[3] The past decade has witnessed an influx of main group compounds capable of such transformations and in the case of hydroboration reactions, actually surpassing transition metal catalysts.[4] Beside these rather sophisticated catalysts, recent years have also seen a plethora of reports with more easily accessible and commercially available compounds, which are able to effectively catalyse hydroelementation reactions. Alkoxides,[5,6] potassium fluoride/carbonate,[7] Grignard reagents[8] as well as *n*-butyl lithium[9,10] all were able to hydroborate ketones to their respective alkoxyborane. Furthermore, *Leung* and co-workers reported the catalyst-free reduction of ketones with pinacolborane in solvent-free conditions at elevated temperatures.[11]

Compared to hydroboration, hydrosilylation reactions catalysed by main group compounds are much less common. Noteworthy examples include the highly Lewis acidic borane $B(C_6F_5)_3$,[12] and phosphemium cations[13] as well as commercially available bases, such as KO*t*Bu,[14,15] KOH,[15] and Cs_2CO_3.[16] Although promising, main groups systems still do not match the efficiency and scope of many transition metal catalysts in terms of the hydrosilylation of carbonyl compounds, thus the demand for more effective main group catalysts remains high.

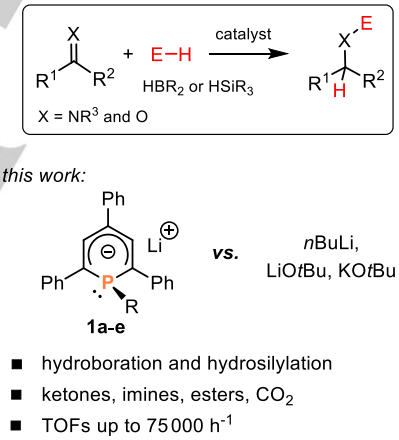

Figure 1. Catalytic hydrofunctionalisation of carbonyl compounds using phosphacyclohexadienyl salts **1a**-**e** [R = Me (**1a**), nBu (**1b**), *t*Bu (**1c**), Ph (**1d**), CH_2SiMe_3 (**1e**)] and [a] Turnover frequency – average value for complete reaction.

Our efforts to devise new main group element based catalysts involved investigating phosphacyclohexadienyl anions **1a**-**e** (Figure 1), which are readily synthesised by treatment of 2,4,6-triphenylphosphinine with alkyl lithium reagents.[17] These species (typically referred to as λ^4-phosphinine anions) are best described as anionic tertiary phosphines, although they display distinct chemical properties. We envisioned that the highly reactive nature of these anions would lend themselves to small molecule activation/catalysis. Here we show that such anions have excellent properties for the hydrofunctionalisation of ketones, imines and esters. We also compared our findings with commercially available catalysts such an *n*BuLi, LiO*t*Bu and KO*t*Bu.

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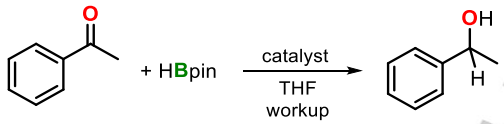
To test the catalytic potential of anions **1a**-**e**, we performed a series of hydroboration/silylation reactions. Acetophenone hydrofunctionalisation was chosen as the benchmark reaction to probe the capability of **1a**-**e**, and to compare their catalytic activity (Table 1). While all compounds displayed high efficiency, the *t*Bu derivative, **1c** performed the best (see Table 1, entry 3) and thus was chosen for further optimisation in both hydroboration and hydrosilylation reactions. Using **1c** at a loading of 0.01 mol%, acetophenone was fully converted to 1-phenylethan-1-ol in less than 8 minutes at T = 23 °C. This equates to a TOF of ≥ 75 000 h^{-1}, which is among the most rapid of any reductions employing pinacolborane to date.

The catalyst was able to readily hydroborate a wide array of substrates, including aldehydes, ketones, esters, ald- and ketimines as well as benzoic acid (see Table S1 and S2, SI for details). Besides its good functional group tolerance, **1c** also showed exceptional chemoselectivity in the presence of other reducible moieties such as nitro, nitrile, pyridyl, and alkenyl groups. In the hydrosilylation reactions, **1c** showed a similar substrate scope, excluding only esters, benzoic acid and ketimines (see SI).

Table 1. Acetophenone hydrofunctionalisation catalysed by phosphacyclohexadienyl anions in comparison to literature-known alkoxides and *n*BuLi.[a]

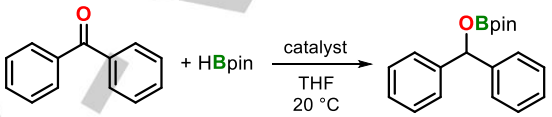


Entry	cat. [mol%]	Red. Agent [eq]	T [°C]	Time [h][b]	TOF [10^3 h^{-1}][c]
1	**1a** (0.01)	HBpin (1.0)	23	0.40	25
2	**1b** (0.01)	HBpin (1.0)	23	0.25	40
3	**1c** (0.01)	HBpin (1.0)	23	<0.13	≥75
4	**1d** (0.01)	HBpin (1.0)	23	0.17	60
5	**1e** (0.01)	HBpin (1.0)	23	0.17	60
6[d]	LiO*t*Bu (1.0)	HBpin (1.3)	rt	0.5	0.2
7[e]	NaO*t*Bu (5.0)	HBpin (1.1)	22	3	< 0.007
8[f]	*n*BuLi (0.1)	HBpin (1.1)	rt	0.17	5.8

[a] Reducing agent = 0.20 mmol, substrate = 0.20 mmol, 0.1 mL solvent. [b] Time for complete substrate conversion, detected by GC-FID using *n*-pentadecane as an internal standard. [c] Turnover frequency - average value for complete reaction. [d] See ref. 6. [e] See ref. 7. Reaction performed in toluene. [f] See ref. 12. Reaction performed without solvent.

It is known that simple inorganic bases such as alkali metal *tert*-butoxides and *n*-butyllithium can also catalyse the hydroboration of acetophenone, but with comparatively higher catalyst loadings and longer reaction times.[5,6,9,10] Considering these results, we were interested in how well our catalytic system compares to such commercially available catalysts. With previously reported results in mind, we anticipated to see **1c** to be faster than these compounds. Surprisingly, initial tests using 2-methylacetophenone gave similar activity for all catalysts (see SI). In order to better compare the catalytic activities, ReactIR measurements were conducted, revealing high activities that surpassed expectations for these commercial compounds, especially for *n*-butyl lithium. Benzophenone was used as a sterically more demanding substrate to give a more manageable reaction timeframe. Both alkoxides achieved a conversion of at least 50% within 105 seconds, while **1c** and *n*-butyl lithium only required 60 and 30 seconds, respectively. These short reaction times translate into an approximate turnover frequency (TOF) of 64 800 h^{-1}, 35 000 h^{-1}, 34 300 h^{-1} and 153 500 h^{-1} for **1c**, LiO*t*Bu, KO*t*Bu and *n*BuLi, respectively. To our knowledge, the best known main group based catalyst for hydroboration reactions is Okuda's lithium triphenylborohydride complex containing tris[2-(dimethylamino)ethyl]amine, which was reported to achieve a TOF of at least 66 666 h^{-1}.[18] This TOF, however, was calculated after the reaction was completed, meaning the actual TOF could be much higher. Taken altogether, it is clear that *n*BuLi possesses great catalytic activity, rivalling even the most active main group hydroboration catalysts.

Table 2. ReactIR monitored catalyst comparison in the hydroboration of benzophenone.[a]

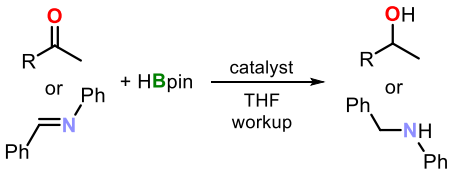


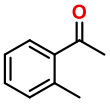
Entry	cat.	time [s][b]	conversion [%]	time$_{50\%}$ [s][c]	TOF [h^{-1}][d]
1	**1c**	480	>99	60 (54%)	64 800
2	LiO*t*Bu	1155	>99	105 (51%)	34 971
3	KO*t*Bu	2895	91	105 (50%)	34 286
4	*n*BuLi	105	>99	30 (64%)	153 600

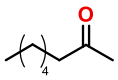
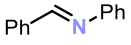
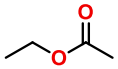
[a] Reducing agent = 0.511 mmol, benzophenone = 0.500 mmol. [b] Time until the given conversion was observed. [c] Time until a conversion of at least 50% was reached. [d] Turnover frequency – calculated at the first point when the conversion was greater than 50%.

A similar trend was also observed for the hydroboration of octan-2-one, *N*-benzylidenaniline and ethyl acetate with pinacolborane (Table 3). Low catalyst loadings are sufficient to achieve high conversions in the course of 5 – 30 min. While in most cases KO*t*Bu was observed to be slightly slower, especially in the hydroboration of the ethyl acetate, there was no major difference between **1c**, *n*BuLi and LiO*t*Bu.

Table 3. Comparison of **1c**, LiO*t*Bu, KO*t*Bu and *n*BuLi in the reduction of different substrates using pinacolborane.



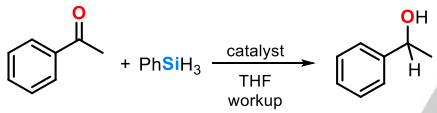
Entry	Substrate	cat. [mol-%]	Solvent [mL]	time [min]	conversion [%][b]
1		**1c** (0.05)	THF (0.5)	5	82
2		LiO*t*Bu (0.05)	THF (0.5)	5	87
3		KO*t*Bu (0.05)	THF (0.5)	5	73
4		*n*BuLi (0.05)	THF (0.5)	5	83

5		**1c** (0.05)	THF (0.5)	5	70
6		LiO*t*Bu (0.05)	THF (0.5)	5	59
7		KO*t*Bu (0.05)	THF (0.5)	5	52
8		*n*BuLi (0.05)	THF (0.5)	5	77
9		**1c** (0.5)	THF (0.2)	15	49
10		LiO*t*Bu (0.5)	THF (0.2)	15	63
11		KO*t*Bu (0.5)	THF (0.2)	15	55
12		*n*BuLi (0.5)	THF (0.2)	15	64
13[c]		**1c** (3.0)	THF (0.1)	30	49
14[c]		LiO*t*Bu (3.0)	THF (0.1)	30	44
15[c]		KO*t*Bu (3.0)	THF (0.1)	30	15
16[c]		*n*BuLi (3.0)	THF (0.1)	30	45

[a] HBpin = 0.26 mmol, substrate = 0.25 mmol. [b] Conversion detected *via* GC-FID using *n*-pentadecane as internal standard. [c] HBpin = 0.66 mmol, ethyl acetate = 0.30 mmol, conversion detected *via* ^{1}H NMR integration using mesitylene as internal standard.

As potassium tert-butoxide has been reported as an efficient hydrosilylation catalyst,[14,15] we went on to also test **1c**, LiO*t*Bu, and *n*-butyl lithium in the hydrosilylation of acetophenone. In these reactions, however, none of the lithium salts was able to compete with potassium *tert*-butoxide hinting at a more pronounced cation effect on the activity in hydrosilylation reactions (see Table 4).

Table 4. Acetophenone hydrofunctionalisation catalysed by phosphacyclohexadienyl anions.[a]

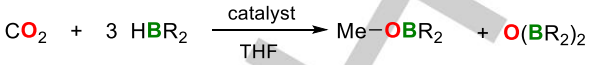


Entry	cat. [mol%]	T [°C]	Time [h][b]	TOF [h^{-1}][c]
1[d]	**1c** (0.5)	23 (40)	3 (1)	67 (200)
2	LiO*t*Bu (0.5)	23	1	200
3	KO*t*Bu (0.1)	23	<0.17	6000
4	*n*BuLi (0.5)	23	1	200

[a] Reducing agent = 0.20 mmol, substrate = 0.20 mmol, 0.1 mL solvent. [b] Time for complete substrate conversion, detected by GC-FID using *n*-pentadecane as an internal standard. [c] Turnover frequency - average value for complete reaction. [d] Solvent free.

As all tested catalysts displayed the ability to reduce very demanding substrates, we went on to test their ability to catalyse the hydroboration of CO_2. With LiO*t*Bu and KO*t*Bu, no conversion was observed even at elevated temperatures. **1c** and *n*BuLi both were able to fully consume pinacolborane, as observed in the ^{1}H and ^{11}B NMR spectra. However, in the case of *n*BuLi a mixture of products was observed. The hydroboration of CO_2 worked significantly better with **1c**, leading to the clean formation of methanol equivalent (MeOBpin). The hydrofunctionalisation of CO_2 could be further optimised by using catechol borane (HBcat), giving TOFs of 13 h^{-1}. Throughout the reaction with pinacolborane, the formate equivalent HCO_2Bpin and acetal equivalent $H_2C(OBpin)_2$ were identified by ^{1}H and ^{11}B NMR spectroscopy. These species have been previously proposed as intermediates in certain reductions mediated by main group catalytic systems.[19]

Table 5. Borane reduction of CO_2 catalysed by **1a-e**.[a]

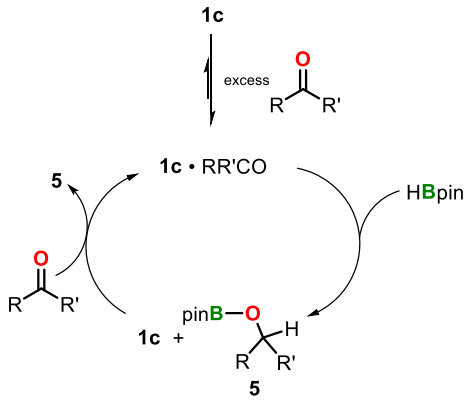


Entry	cat. [mol%]	BR_2	Time [h][b]	TOF [h^{-1}][c]
1	**1c** (2)	Bpin	16	3.1
2	LiO*t*Bu (5)	Bpin	72[d]	-
3	KO*t*Bu (5)	Bpin	72[d]	-
4	*n*BuLi (5)	Bpin	16	<0.2[e]
5	**1c** (0.5)	Bcat	16	13

[a] Borane = 0.20 mmol, ~1 bar CO_2, 0.2 mL THF-d_8, *T* = 25 °C. [b] Time for complete substrate conversion, followed by ^{1}H and ^{11}B NMR spectroscopy. [c] Turnover frequency - average value for complete reaction. [d] Reaction performed at 60 °C. [e] Yield < 15 %.

Studies of 2'-methylacetophenone hydroboration in THF and benzene using [K(1-*t*Bu-$PC_5Ph_3H_2$)] (**3**) and [N(*n*Bu)$_4$][1-*t*Bu-$PC_5Ph_3H_2$] (**4**) revealed similar catalytic activities as observed for **1c** (Table S5, SI). This was also observed for the alkoxides MOMe and MO*t*Bu (M = Li, Na, K). Therefore, it can be inferred that the cation only has a minor influence on the reactivity. Similar conversions of 73-89% were observed for all alkoxides with the exception of NaOMe, which gave a conversion of only 30% (see SI).

In order to shed light onto the mechanism, further ReactIR kinetic measurements were conducted. The reaction order was determined using the method of initial rates and the time normalisation approach (see SI for details).[20] The results clearly suggest a zero-order dependence on ketone concentration and a first order dependence on **1c** and HBpin. Furthermore, a stoichiometric reaction between **1c**, ketone and HBpin was performed. The full consumption of HBpin was observed and upon comparing the integrals of the methyl signals of the ketone (δ = 2.26 ppm) with the signals of the product (δ = 2.30 ppm) the yield of the desired borolane can be estimated to be >95%. The ^{11}B{^{1}H} NMR spectrum has a major signal (δ = 22.2 pm) that can be assigned to the borolane (**5**) with two minor signals (<10%) at δ = 6.3 and 5.8 ppm that could not be identified. The ^{31}P{^{1}H} NMR shows **1c** to be the main component (86%) with the formation of a new signal at δ = -24.3 ppm (11%). The signal at δ = -24.3 ppm was also observed, when reacting **1c** with the ketone in the absence of borane. Therefore, we propose this to be an adduct of the ketone with **1c**. Although we can isolate the presumed adduct (**2**), we were unable as of yet to crystallographically characterise it. Upon testing **2** in the hydroboration of 2'-methylacetophenone, only a slight decrease in catalytic activity was observed when compared to **1c** (Table S5, SI). When stoichiometric amounts of HBpin were added to **2**, the desired product (**5**) as well as the released catalyst **1c** could be observed as the main products. Altogether, these experiments suggest the mechanism starts with the formation of an adduct between the ketone and **1c**, which then reacts with the reducing agent. The catalytic cycle is subsequently closed by the release **5** and the reformation of **1c**.



Scheme 1. Proposed Mechanistic pathway of the hydroboration of ketones initiated by **1c**.

When comparing the effectiveness of phosphacyclohexadienyl anions in hydroboration and hydrosilylation catalysis of polar substrates with those for commercially available bases LiO*t*Bu, KO*t*Bu and *n*BuLi, we have found that these catalysts also show a remarkable efficiency, rivalling the most active catalysts available to date. All of these catalysts can reduce very challenging substrates, such as imines and esters. However, LiO*t*Bu, KO*t*Bu and *n*BuLi were ineffective in the hydroboration of CO_2. This is in contrast to compounds **1a-e** which were able to efficiently reduce CO_2 to the corresponding methanol equivalent under ambient conditions with HBpin and HBcat. On-going work in our group concerns the utilisation of this methodology and the development of asymmetric hydrofunctionalization reactions.

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Keywords: phosphinine • main group catalysis • hydrofunctionalisation • carbon dioxide reduction • phosphorus

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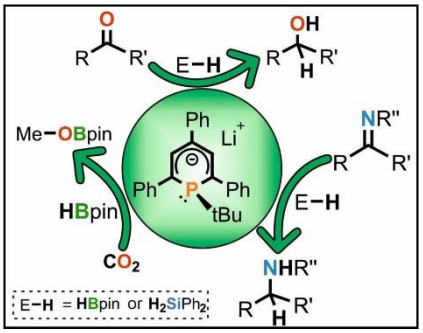

Hydrofunctionalisations of various substrates, including, imines, esters and CO_2 are effectively initiated by lithium phosphacyclohexadienyl compounds. High selectivities and excellent TOFs were found, rivalling those of previously reported organyl and alkoxide anions.