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Easily accessible lithium compounds catalyzed mild and facile hydroboration and cyanosilylation of aldehydes and ketones

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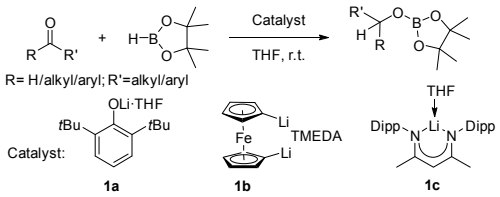
Milan Kumar Bisai,[a] Tamal Das,[b] Kumar Vanka,[b] and Sakya S. Sen*[a]

Simple and readily accessible lithium compounds such as 2,6-ditertbutyl phenolate lithium (1a), 1,1' dilithioferrocene (1b) and nacnac lithium (1c) are found to be efficient single site catalysts for hydroboration of a range of aldehydes and ketones with HBpin at room temperature. The efficacy of 1a-1c as catalysts is extended towards the cyanosilylation of aldehydes and ketones with Me_3SiCN.

While observing the hundred years of the birth of lithium chemistry,[1] the growth of *s*-block compounds is still in the early days finding its feet slowly and gradually from curiosity driven explorations to important catalytic transformations. Driven by the demand for the catalytic processes with reduced environmental impact and low cost, numerous groundbreaking results have been achieved in molecular catalysis derived from the heavier alkaline earth metals complexes.[2] Following the demonstration of hydroboration of carbonyl compounds by a magnesium alkyl complex,[3] there has been a flurry of research activity on hydroboration reactions by compounds with alkaline earth metals[4-8] as well as p-block elements.[9-16] For the heavier alkaline-earth metal catalysts, Schlenk equilibrium is an issue, which is likely to impose a severe limitation on the preparation as well as the activity of the catalyst. In this context, Group 1 complexes are advantageous over their adjacent neighbours as they are not involved in Schlenk-type equilibrium. Moreover, as catalysts involving group 2 and p-block elements are usually prepared from the corresponding lithium compounds, the direct use of lithium compounds in catalysis would reduce the need for such additional transformations. In fact, Group 1 complexes were sporadically reported for hydrosilylation of alkenes[17] or hydrogenation of aldimines,[18] but they were not very efficient compared to their corresponding group 2 complexes in terms of reactivity or selectivity or both. Hence, group 1 based complexes have remained largely unexplored in molecular catalysis. The paradigm has shifted with the two significant breakthroughs that recently came from the groups of Okuda[19,20] and Mulvey.[21] These breakthroughs have created a new avenue for the lithium compounds to be used as single component catalysts for important organic transformations.



Scheme 1. Hydroboration of aldehydes and ketones using **1a**, **1b** and **1c** as catalysts.

Okuda and coworkers noted that the success of lithium catalysts relies on the combination of the Lewis acidity of the Li atom and the hydridicity of the borate anions. The Li catalysts with $[HB(C_6F_5)_3]$ anion was reported to be inert which was attributed to the diminished hydridicity of the borate anion.[19] Thus, there remains a scope for a study of catalytic properties of lithium compounds with no hydridic hydrogen present in the counter anion. In light of our interests in developing catalytic methods for reduction of carbonyl compounds,[4,12,22,23] we attempted to use three popular and readily accessible lithium compounds with different electronegative substituents such as 2,6-ditertbutyl phenolate lithium (**1a**), nacnac lithium (**1c**) and 1,1' dilithioferrocene (**1b**) (Scheme 1) for the reduction of aldehydes and ketones with HBpin at the ambient conditions. The reason behind such selection is to examine how the Lewis acidity of the Li center influence the catalytic activity. For example, the Li atom in **1c** is purportedly more Lewis acidic than **1a** as the Li atom in **1c** is bound to two nitrogen atoms, while the Li atom in **1a** is bound to only one oxygen atom. It is also interesting to compare the catalytic competence of **1b** with others as it possesses of two active Li centres although they are bound to less electronegative carbon atoms. Consistent to our hypothesis,

[a] *Inorganic Chemistry and Catalysis Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pashan, Pune 411008, India. E-mail: ss.sen@ncl.res.in*
[b] *Physical and Material Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pashan, Pune 411008, India.*
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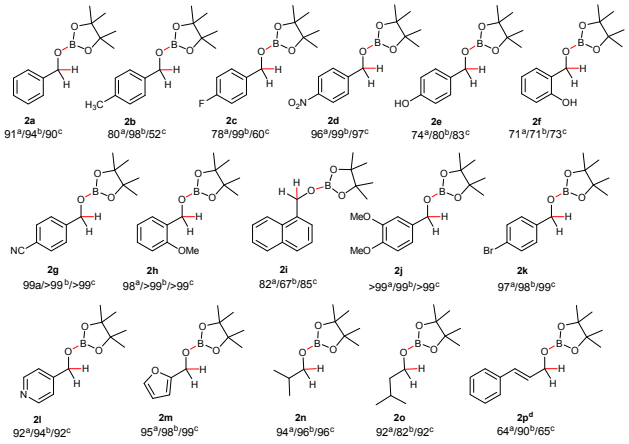
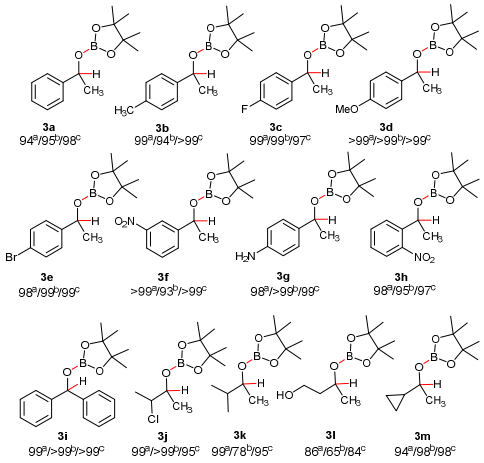
the catalytic activity (TOF) of **1c** is found to be better than **1a** or **1b**. To broaden the horizon of the lithium compounds in catalysis, we have successfully employed **1a**-**1c** for the cyanosilylation of the carbonyl compounds; a transformation thus far not known to be catalyzed by group 1 complexes.



Scheme 2. Substrates scope for the hydroboration of aldehydes. Reaction conditions: Catalyst: 0.1 mol%, room temperature in THF. Reaction time (except trans-cinnamaldehyde): **1a**: 60 min, **1b**: 40 min, **1c**: 50 min. Yields are calculated based on the integration area of product and starting material signals in the ^{1}H spectra using mesitylene as an internal standard. Superscripts a, b and c stand for the catalysts **1a**, **1b** and **1c**, respectively; [d]the reaction time for *trans*-cinnamaldehyde reduction was 5 h.



Scheme 3. Substrates scope for the hydroboration of ketones. Reaction conditions: Catalyst: 0.1 mol%, room temperature in THF. Reaction time: **1a**: 3 h, **1b**: 2 h, **1c**: 2h. Yields are calculated w.r.t. mesitylene as internal standard.

The hydroboration reactions for a variety of aldehydes (Scheme 2, **2a**-**2p**) and ketones (Scheme 3, **3a**-**3m**) have been evaluated using **1a/1b/1c** as a catalyst (For optimization, please see ESI, Table S1a-1c, S3a-3c). Both aliphatic and aromatic aldehydes underwent hydroboration within an hour with excellent TOFs (ESI, Table S2), which reflect the high efficiency of the catalysts. Similarly, a wide range of aromatic and aliphatic ketones were converted to the corresponding boronate esters within 2-3 hours keeping the mol% constant (ESI, Table S4). Acetophenone derivatives bearing both electron-withdrawing and electron-donating functionalities (**3a-3h**) gave good yields, demonstrating a negligible electronic effect. Increasing the steric demands has also a little effect on the yield as seen in case of hydroboration of benzophenone (**3i**). All the catalysts show good functional group tolerance. The nitrile (**2g**), hydroxy (**2e** and **2f**), heterocycle (**2l** and **2m**), amino (**3g**) containing substrates yielded the desired boronate esters. Even, the bromo functionality (**2k** and **3e**) does not suffer from lithium–bromide exchange. In some cases, their catalytic efficiencies vary, as **1c** gives the lowest yield for **2b** and **2c** among them. **1b** gives the quantitative yield in the most cases presumbaly due to the presence of two Li centres, except **2i** and **3l**. Excellent chemoselectivity was observed in competitive experiment of all three catalysts (ESI, Scheme S1).

We compared the catalytic activities of **1a**-**1c** for benzophenone and *trans*-cinnamaldehyde with some known catalysts. The most active one is the lithium hydridotriphenylborate, which showed a remarkable TOF of 66600 h^{-1} for benzophenone.[19] Among rare earths, Marks' La^{NTMS} has the highest TOF of ›40000 h^{-1}, while among transition metals,[24a] Mankad's copper carbene was reported to the most active (TOF of 1000 h^{-1}).[24b] Hill's magnesium alkyl complex was reported with a TOF of 500 h^{-1} for benzophenone,[3] while Stasch's magnesium catalyst $[(L)MgH]_4$ (L = $Ph_2PNDipp$; Dipp = 2,6-*i*$Pr_2C_6H_3$) was recorded with a TOF of 1760 h^{-1}.[5] We have found **1c** shows very good efficiency with a TOF of 495 h^{-1}. Although **1b** gives the best yield, the activities of **1a** and **1b** is slightly poorer (TOF: 330 h^{-1} and 247 h^{-1} respectively) than **1c**. The TOF of the *trans*-cinnamaldehyde reduction was calculated to be 130 h^{-1} for **1c**, which is only second to Okuda's lithium hydridotriphenylborate(210 h^{-1}).[19] In comparison, **1a** or **1b** was recorded with a TOF of 128 and 90 h^{-1}, respectively, but their superiority was marked over the other reported main group catalysts for *trans*-cinnamaldehyde reduction (e.g. $[Mg(thf)_6][HBPh_3]_2$: 11.2 h^{-1},[5] nacnacAl(H)OTf: 16.5 h^{-1},[14] $PhC(NtBu)_2SiHCl_2$: 63.3 h^{-1},[12] $PhC(NiPr)_2CaI$: 69 h^{-1}).[4]

We have investigated the hydroboration mechanism for **1a** and **1c**. We found that **1a** reacts with HBpin but no change in the ^{1}H NMR was detected in the reaction of **1a** and aldehyde. However, the NMR experiments indicate that no reaction takes place between **1c** and HBpin. Therefore, the catalytic pathways for **1a** and **1c** are appeared to be different. The reaction between **1a** and HBpin in toluene-d_8, shows a resonance at δ 4.7 ppm in the ^{11}B NMR, indicating a four-coordinated sp^3 boron atom.[25a] However, prolonged time led to formation of trialkoxyborane [2,6-tBu_2-C_6H_3-OBpin] and BH_4^- anion as a singlet and a quintet started to appear at δ 21.62 and –39.83 ppm after 2-3h, respectively.[25b] To obtain mechanistic insight, full quantum chemical calculations were done with density functional theory (DFT) at the dispersion and solvent corrected PBE/TZVP level of theory. The pathway is initiated with O-coordination of HBpin to the lithium atom of **1a**, resulting in the exergonic (ΔE= –11.5 kcal/mol and ΔG= –0.7 kcal/mol) formation of **Int-1** having a O···Li bond length of 1.92 Å. This binding mode is in agreement with the crystal structure of $[DippnacnacCa(H_2Bpin)]_3$ where primary bonding between the anion and the metal cation proceeds through

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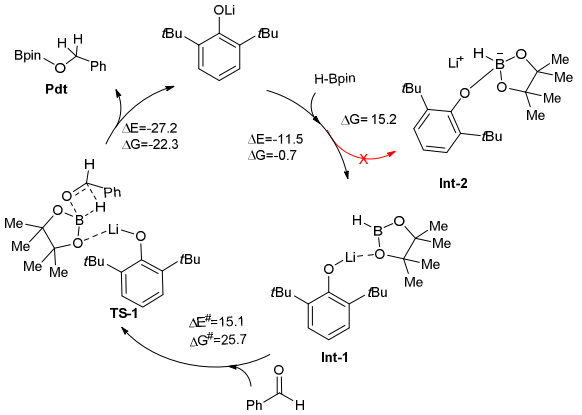
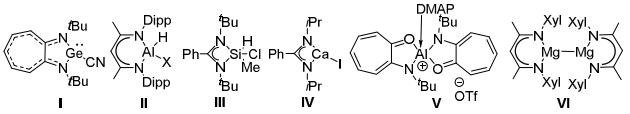
O···Ca interaction.[26] The other possibility of coordinating phenolate oxygen to boron atom of HBpin leading to a four coordinate boron complex (**Int-2**) was found to be thermodynamically unfavorable as the ΔG of reaction was 15.2 kcal/mol. In the next step, the carbonyl oxygen atom of benzaldehyde attacks the boron centre of HBpin, with the hydride being transferred from the boron centre to the carbonyl carbon. This occurs through a four-membered transition state (**TS-1**), where a significant amount of the B-H bond activation (1.29 Å) takes place which leads to the formation of hydroboration product (**Pdt**) along with the regeneration of **1a** (Scheme 4). The ΔE (-27.2 kcal/mol) and ΔG (-22.3 kcal/mol) values for this step are highly negative and the activation energy ($\Delta G^{\#}$) barrier corresponding to the transition state is calculated to be 25.7 kcal/mol.

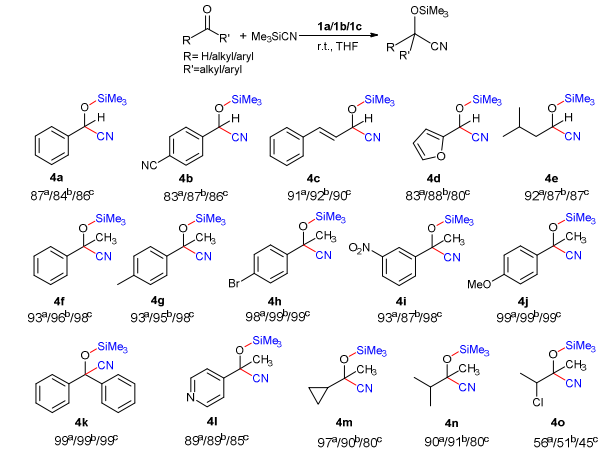


Scheme 4. The catalytic cycle and reaction mechanism for the aldehyde hydroboration by catalyst **1a**, ΔG and $\Delta G^{\#}$ represent the Gibbs free energy of reaction and the Gibbs free energy of activation respectively. All values are in kcal/mol.

In case of **1c**, a weakly bound complex (**Int-3**) is formed between **1c** and benzaldehyde, with the oxygen atom of benzaldehyde approaching towards the lithium atom of **1c** (ESI, Scheme S3). The ΔE and ΔG for this step are -19.5 and -5.5 kcal/mol, respectively. Subsequently, the nucleophilic attack by the lone pair of the N atom of **1c** in **Int-3** to the vacant p orbital of the boron centre of HBpin takes place. A four coordinated B centre is thus generated (**Int-4**). The ΔE and ΔG for this step are -5.3 kcal/mol and 7.2 kcal/mol, respectively. The activation free energy for the N···B bond formation is 24.1 kcal/mol. In the next step, the hydride is transferred from the boron centre to the electrophilic carbonyl carbon of the benzaldehyde through a three-membered transition state (**TS 3**), with a barrier of 21.6 kcal/mol. In this transition state, there is a significant amount of B-H bond activation (1.33 Å vs 1.19 Å in the intermediate complex) occurs, which allows the hydride transfer from the boron to the carbonyl carbon centre. In the last step, the oxygen centre of the aldehyde attacks the boron centre of pinacolborane and simultaneously, B···N bond cleavage occurs along with N···Li bond formation. This takes place through a four-membered transition state (**TS-4**) and leads to the formation of hydroboration product (**Pdt-1**) along with the regeneration of the catalyst. The ΔE (-14.5kcal/mol) and ΔG (-29.9 kcal/mol) values for this step are very favourable and the barrier ($\Delta G^{\#}$) corresponding to the transition state is 15.7 kcal/mol.



Scheme 5. Examples of the reported main-group catalysts for the cyanosilylation of carbonyl compounds. This is the first report of group 1 catalyst for cyanosilylation of aldehydes and ketones.



Scheme 6. The scope of cyanosilylation with aldehyde and ketone substrates. Reaction conditions: Catalyst: 0.1 mol%, room temperature in THF. Reaction time for aldehydes: 1h and for ketones: 2h. Yields are calculated w.r.t. mesitylene as internal standard.

In contrast to a large number of publications on main group compound catalyzed hydroboration, only a few studies on the main group compound catalyzed cyanosilylation have been reported (Scheme 5).[12,22,23,27-32] A majority of them were reported to catalyze only aldehydes.[22,27-30] The use of alkaline earth metal complexes in catalytic cyanosilylation is an emerging area. Recently, we and Ma et al. independently reported the cyanosilylation of aldehydes and ketones with a calcium complex, PhC(N*i*Pr)$_2$CaI[23] and a magnesium(I) complex, {(Xylnacnac)Mg}$_2$ (Xyl=2,6-Me$_2$-C$_6$H$_3$),[32] respectively. Nevertheless, to our knowledge, the use of lithium compounds as catalysts in cyanosilylation has not been reported so far. An initial screening of the catalytic effect of **1a**-**1c** revealed good conversion in most cases at room temperature in a reasonable amount of time (for aldehyde: 1h & for ketone: 2h) with 0.1 mol% catalyst loading (Scheme 6). The catalytic efficiencies and selectivity of **1a**-**1c** were found to be very similar. Benzaldehyde, acetophenone, and benzophenone (entries **4a, 4f** and **4k**) were smoothly converted into the corresponding cyanohydrins. For the reduction of benzophenone, these lithium catalysts are superior to the **IV** (3 mol%, 2 h, 82% yield). No other main group catalyst is reported for cyanosilylation of benzeophenone so far. In the case of *α,β*-unsaturated cinnamaldehyde, the 1,2 addition of TMSCN selectively took place, no Michael addition product was formed (entry **4c**). Cyanation of aliphatic aldehyde and ketone (entries **4e**, **4m**, **4n** and **4o**) was found to proceed efficiently.

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Unlike other main group catalysts which were reported to catalyze acetophenone substrates with either electron-withdrawing (**IV**[23] and **V**[31]) or electron donating group (**II**[12] and **VI**[32]), it was observed that **1a**-**1c** can include both electron withdrawing as well as donating substituents (**4g-4j**) for cyanosilylation. Heteroarenes (**4d** and **4l**) were tolerated under reaction conditions to other substituents. ~30% chloride to cyanide exchange product along with the desired cyanohydrin formation was observed for **4o**.

Herein, we have demonstrated that the reduction of a variety of carbonyl compounds with HBpin and Me_3SiCN can be catalyzed rapidly by very simple lithium compounds (**1a**-**1c**) under mild and facile conditions with excellent functional group tolerance and TOFs. We have investigated the hydroboration mechanism for **1a** and **1c** and the mechanistic studies for cyanosilylation are currently ongoing. The methodologies described have clearly opened up new avenues for the catalytic application of lithium compounds encouraged by the very economic and almost non-toxicity of these reagents.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 W. Schlenk and J. Holtz, Ber. *Dtsch. Chem. Ges.*, 1917, **50**, 262–274.
2 (*a*) S. Harder, *Chem. Rev.*, 2010**, 110**, 3852–3876; (*b*) T. E. Stennett and S. Harder, *Chem. Soc. Rev.*, 2016, **45**, 1112-1128; (*c*) M. S. Hill, D. J. Liptrot and C. Weetman, *Chem. Soc. Rev.*, 2016, **45**, 972-988; (*d*) K. Revunova and G. I. Nikonov, *Dalton Trans.*, 2015, **44**, 840–866.
3 M. Arrowsmith, T. J. Hadlington, M. S. Hill and G. Kociok-Köhn, *Chem. Commun.,* 2012, **48**, 4567–4569.
4 S. Yadav, S. Pahar and S. S. Sen, *Chem. Commun.*, 2017, **53**, 4562–4564.
5 L. Fohlmeister and A. Stasch, *Chem. Eur. J.,* 2016, **22**, 10235-10246.
6 D. Mukherjee, S. Shirase, T. P. Spaniol, K. Mashima and J. Okuda, *Chem. Commun.,* 2016, **52,** 13155–13158.
7 D. Mukherjee, A. Ellern and A. D. Sadow, *Chem. Sci.,* 2014, **5**, 959–965.
8 K. Manna, P. Ji, F. X. Greene and W. Lin, *J. Am. Chem. Soc.,* 2016, **138**, 7488−7491.
9 (*a*) T. J. Hadlington, M. Hermann, G. Frenking and C. Jones, *J. Am. Chem. Soc.*, 2014, **136**, 3028–3031; (*b*) J. Schneider, C. P. Sindlinger, S. M. Freitag, H. Schubert and L. Wesemann, *Angew. Chem., Int. Ed.,* 2017, **56**, 333–337; (c) Y. Wu, C. Shan, Y. Sun, P. Chen, J. Ying, J. Zhu, L. L. Liu and Y. Zhao, *Chem. Commun.,* 2016, **52**, 13799−13802.
10 C.-C. Chong, H. Hirao and R. Kinjo, *Angew. Chem., Int. Ed.,* 2015, **54**, 190−194.
11 M. K. Bisai, S. Pahar, T. Das, K. Vanka and S. S. Sen, *Dalton Trans.,* 2017, **46**, 2420–2424.
12 Z. Yang, M. Zhong, X. Ma, S. De, C. Anusha, P. Parameswaran and H. W. Roesky, *Angew. Chem., Int. Ed.,* 2015, **54**, 10225–10229.
13 (*a*) V. K. Jakhar, M. K. Barman and S. Nembenna, *Org. Lett.,* 2016, **18**, 4710−4713; (b) J. R. Lawson, L. C. Wilkins and R. L. Melen, *Chem. Eur. J.*, 2017, **23**, 10997–11000.
14 (*a*) C. Weetman, M. D. Anker, M. Arrowsmith, M. S. Hill, G. Kociok-Köhn, D. J. Liptrot and M. F. Mahon, *Chem. Sci.,* 2016, **7**, 628–641; (*b*) C. Weetman, M. S. Hill and M. F. Mahon, *Chem. Commun.,* 2015, **51**, 14477–14480;
15 (*a*) M.-A. Courtemanche, M.-A. Légaré, L. Maron and F.-G. Fontaine, *J. Am. Chem. Soc.*, 2013, **135**, 9326−9329; (*b*) D. Franz, L. Sirtl, A. Pöthig and S. Inoue, *Z. Anorg. Allg. Chem.,* 2016, **642**, 1245-1250; (*c*) J. L. Lortie, T. Dudding, B. M. Gabidullin and G. I. Nikonov, *ACS Catal.*, 2017, 7, 8454–8459.
16 For selected reviews on main group compound catalyzed hydroboration, please see: (*a*) C. C. Chong and R. Kinjo, *ACS Catal.,* 2015, **5**, 3238−3259; (*b*) G. I. Nikonov, *ACS Catal.,* 2017, **7**, 7257-7266; (*c*) D. Mukherjee and J. Okuda, *Angew. Chem., Int. Ed.*, 2018, **57**, 1458-1473; (*d*) S. Dagorne and R. Wehmschulte, *ChemCatChem*, 2018, (doi.org/10.1002/cctc.201800045).
17 (*a*) F. Buch, J. Brettar and S. Harder, *Angew. Chem., Int. Ed.*, 2006, **45**, 2741–2745. (b) V. Leich, T. P. Spaniol and J. Okuda, *Organometallics* 2016, **35**, 1179−1182.
18 H. Bauer, M. Alonso, C. Färber, H. Elsen, J. Pahl, A. Causero, G. Ballmann, F. De Proft and S. Harder, *Nature Catalysis*, 2018, **1**, 40–47.
19 D. Mukherjee, H. Osseili, T. P. Spaniol and J. Okuda, *J. Am. Chem. Soc.,* 2016, **138**, 10790–10793.
20 (*a*) H. Osseili, D. Mukherjee, K. Beckerle, T. P. Spaniol and J. Okuda, *Organometallics*, 2017, **36**, 3029–3034. (*b*) H. Osseili, D. Mukherjee, T. P. Spaniol and J. Okuda, *Chem. Eur. J.*, 2017, **23**, 14292–14298.
21 (a) R. McLellan, A. R. Kennedy, R. E. Mulvey, S. A. Orr and S. D. Robertson, *Chem. Eur. J.*, 2017, **23**, 16853–16861; (*b*) V. A. Pollard, S. A. Orr, R. McLellan, A. R. Kennedy, E. Hevia and R. E. Mulvey, *Chem. Commun.,* 2018, **54**, 1233-1236.
22 V. S. V. S. N. Swamy, M. K. Bisai, T. Das and S. S. Sen, *Chem. Commun.,* 2017, **53**, 6910–6913.
23 S. Yadav, R. Dixit, K. Vanka and S. S. Sen, *Chem. Eur. J.*, 2018, **24**, 1269-1273.
24 (a) V. L. Weidner, C. J. Barger, M. Delferro, T. L. Lohr and T. J. Marks, *ACS Catal.*, 2017, **7**, 1244–1247; (b) S. Bagherzadeh and N. P. Mankad, *Chem. Commun.,* 2016, **52**, 3844-3846.
25 (a) A. Bonet, H. Gulyás and E. Fernández, *Angew. Chem., Int. Ed.*, 2010, **49**, 5130–5134; (b) I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley and T. B. Clark, *J. Org. Chem.*, 2011, **76**, 6452–6456.
26 S. Harder and J. Spielmann, *J. Organometal. Chem.,* 2012, **698**, 7–14
27 Y. Li, J. Wang, Y. Wu, H. Zhu, P. P. Samuel and H. W. Roesky, *Dalton Trans.*, 2013, **42**, 13715–13722.
28 R. K. Sitwatch and S. Nagendran, *Chem. Eur. J.,* 2014, **20**, 13551–13556.
29 A. L. Liberman-Martin, R. G. Bergman and T. D. Tilley, *J. Am. Chem. Soc.,* 2015, **137**, 5328–5331.
30 Z. Yang, Y. Yi, M. Zhong, S. De, T. Mondal, D. Koley, X. Ma, D. Zhang and H. W. Roesky, *Chem. Eur. J.,* 2016, **22**, 6932–6938.
31 M. K. Sharma, S. Sinhababu, G. Mukherjee, G. Rajaraman and S. Nagendran, *Dalton Trans.*, 2017, **46**, 7672-7676.
32 W. Wang, M. Luo, J. Li, S. A. Pullarkat and M. Ma, *Chem. Commun.*, 2018, **54**, 3042-3044.

