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Regioselective 1,4-Hydroboration of Pyridines Catalyzed by an Acid-Initiated Boronium Cation

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The reaction of the commercially available ammonium salt NH_4BPh_4 with a pyridine-activated pinacolborane species generates a boronium cation that facilitates the 1,4-selective hydroboration of pyridines in polar solvents. This catalytic reaction is amenable to a host of reactive functional groups and provides access to sterically bulky hydroboration products, previously inaccessible by metal-free routes. Further, the regioselectivity of this reaction can be altered by reducing the polarity of the reaction solvent, resulting in greater proportions of the 1,2-hydroboration product.

Dihydropyridines (DHPs) are an important class of compounds with many pharmacological applications. First synthesized by Hantzsch in 1882,[1] the subsequent discovery of the medicinal and synthetic potential of DHPs has led to their being the subject of sustained interest since the 1950s.[2] A number of stoichiometric methods have been developed for the formation of DHPs, including the Hantzsch synthesis, reduction of pyridines by complex metal hydrides, and nucleophilic additions to pyridines.[3] However, these methods can require numerous steps for asymmetric DHP synthesis, pre-activation of the pyridines, and can result in poor reduction regioselectivity—affording both the 1,2- and 1,4-regioisomers—which can limit their utility.[2g] Many catalytic reactions have also been developed that enable regioselective reductions of a broad range of functionalized pyridines.[4] Among these, a number of catalytic 1,2- and 1,4-hydroborations have been developed that utilize boranes (R_2BH) for the reduction and *N*-functionalization of pyridines. Mg(II)-hydride complexes investigated by Hill and Harder have been shown to promote catalytic hydroboration of pyridines; however, in these systems many substrates reacted to give mixtures of the 1,2- and 1,4-hydroboration products.[5,6] Advances reported by the groups of Suginome and Marks show efficient and functional-group tolerant methods for the 1,2-hydroboration of pyridines using Rh(I) and La(III) catalysts, respectively.[7,8]

Catalytic methods for the 1,4-selective hydroboration of pyridines have also been the focus of several recent studies. In 2015, Wang and co-workers demonstrated a method for regioselective 1,4-hydroboration using a fluoro-organoborane Lewis acid catalyst that affords DHPs in high yields under mild conditions.[9] The fluoro-organoborane was demonstrated to abstract a hydride from a pyridine-activated pinacolborane (HBpin), resulting in a pyridine-stabilized boronium cation that is then reduced by the fluoro-organoborohydride to generate the hydroboration product. Additionally, the groups of Okuda and Gunanathan have used Mg(II) hydridotriphenylborate and Ru(II) catalysts, respectively, for the selective 1,4-hydroboration of pyridine.[10,11]

Here, we present an efficient and practical metal-free catalytic method for the highly regioselective 1,4-hydroboration of pyridines using only pyridines, pinacolborane, and low loadings of an inexpensive and commercially available ammonium salt initiator (NH_4BPh_4). This method relies on the formation of a boronium cation through the reaction between pyridine-activated HBpin and NH_4BPh_4, releasing H_2 and NH_3. Borocations have been well established as effective catalysts for the reduction and bor/silylation of various substrates[12] and a number of these cations have been similarly generated using Brønsted acids.[13] In addition to generating the active boronium catalyst, the pyridine-activated HBpin acts as the hydride source for pyridine reduction. This reaction provides access to 1,4-DHPs containing reactive functional groups and the active hydridic species affords 1,4-hydroboration products that are not easily accessible through other metal-free methods. Further, solvent polarity has been found to play a significant role in the regioselectivity of the reaction, whereby the use of non-polar solvents results in higher ratios of the 1,2- regioisomer.

Our initial results showed that the addition of 10 mol% of NH_4BPh_4 to a solution of HBpin (1.5 equiv.) and pyridine (1 equiv.) in dry CD_3CN results in the formation of a colourless gas

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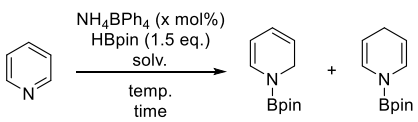
at room temperature, determined to be H_2 by ^{1}H NMR spectroscopy (δ = 4.57 ppm in CD_3CN). NH_4BPh_4 acts as both a proton source and introduces a weakly coordinating anion, precluding the formation of unwanted anion-boron interactions. Heating the above mixture to 90 °C over a 15 hour period yields the 1,4-dihydropyridine as the major product along with the 1,2-dihydropyridine as a minor product, as identified by characteristic signals in the ^{1}H NMR spectrum (Table 1, entry 1).[6] The loading of NH_4BPh_4 could be lowered to 2.5 mol% while maintaining high yields and selective hydroboration reactivity over reasonable timescales (1,2-:1,4- product ratio of 2:98; Table 1, entry 2). In the absence of NH_4BPh_4 minimal conversion to the hydroboration products was observed over a 96 hour period, verifying its role as an initiator (Table 1, entries 3). Lowering the reaction temperature only led to longer reaction times to achieve similar conversions (Table 1, entry 4). Solvent polarity was found to have a significant effect on the regioselectivity of the reaction, whereby conducting the reaction in C_6D_6 or heptane affords 1,2- and 1,4-hydroboration products in ratios of 15:85 and 22:78, respectively (Table 1, entries 5 and 7). In contrast, the use of the non-donating polar solvent 1,2-difluorobenzene (1,2-DFB) results in excellent 1,4- selectivity (6:94) and high conversion from the starting material (Table 1, entry 9).[14] The reaction can also be conducted in pure pyridine (0.5 mL) using 0.015 mmol NH_4BPh_4 and 0.89 mmol HBpin at 90 °C to produce a mixture of 1,2- and 1,4-hydroboration products in a 4:96 ratio in >95% conversion over a 12 hour period.

Table 1 Optimization of reaction conditions for the 1,4-hydroboration of pyridine.



1a **1b**

Entry	NH_4BPh_4 [mol%]	solv.	temp. [°C]	time [h]	conv. [%][a]	**1a**:**1b**
1	10	CD_3CN	90	15	87[b]	2:98
2	2.5	CD_3CN	90	20	>95(72)[c]	2:98
3	0	CD_3CN	90	96	<1	-
4	2.5	CD_3CN	70	72	93	2:98
5	2.5	C_6D_6	90	78	>95	15:85
6	0	C_6D_6	90	96	0	-
7[d]	2.5	heptane	90	96	64	22:78
8[d]	0	heptane	90	96	<1	-
9[d]	2.5	1,2-DFB	90	8	>95	6:94

NMR tube scale reactions performed in a sealed J. Young NMR tube. [a] Determined by ^{1}H NMR spectroscopy. [b] Conversion increased to 90% over a 24 hour period. [c] Isolated yield determined using 3.36 mmol pyridine in a sealed J. Young-type bomb. [d] ^{1}H NMR referenced to DMSO-d_6 in an isolated glass capillary.

Based on the work by Wang[9] and Crudden,[12d] we propose a mechanism involving a boronium cation as the active catalyst (Figure 1). In this mechanism, coordination of pyridine to HBpin in acetonitrile increases the hydridicity of the borane, allowing it to react with NH_4^+, generating H_2 and NH_3 as well as the pyridine-stabilized boronium-BPh_4 salt (Figure 1, initiation). Both H_2 and the boronium cation are observed by ^{1}H and ^{11}B NMR, respectively (the boronium species exhibits a characteristic resonance at δ = 7.1 ppm in the ^{11}B NMR spectrum).[9] The formation of the boronium cation and H_2 does not occur in the absence of pyridine, suggesting that pyridine donation is crucial for the activation of the B-H bond (Supporting information, Figures S4 and S5).† Once formed, the boronium cation activates the coordinated pyridine toward reduction by a second pyridine-HBpin adduct, regenerating the catalytic boronium species after loss of the hydride.‡ Based on this mechanism, the lower conversion obtained using 10 mol% NH_4BPh_4 compared to 2.5 mol% may be attributed to pyridine being retained in the boronium complex; however, this could not be confirmed conclusively by ^{1}H NMR spectroscopy.

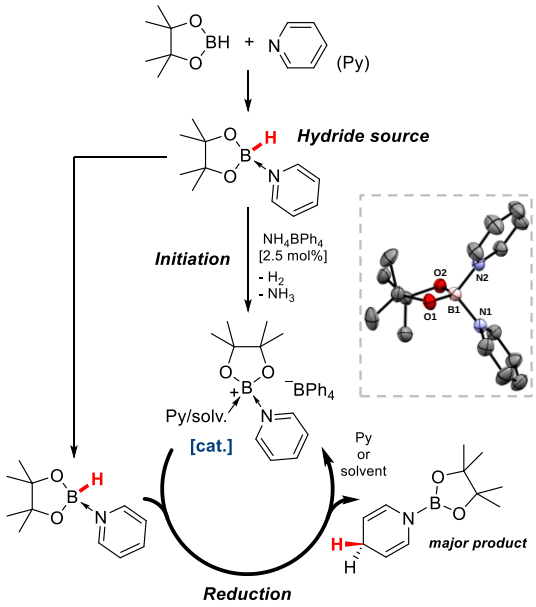


Figure 1 Proposed mechanism for the boronium-catalysed hydroboration of pyridine. Inset: cation structure of the pinBPy$_2$BPh$_4$ boronium salt. Thermal ellipsoids shown at the 50% probability level; hydrogen atoms, disorder, and ion-separated BPh_4^- omitted for clarity (B, pink; N, blue; O, red; C, grey). Selected bond lengths (Å) and angles (°): N1-B1 1.621(3), N2-B1 1.619(3), N1-B1-N2 104.8(2), O1-B1-O2 111.0(2).

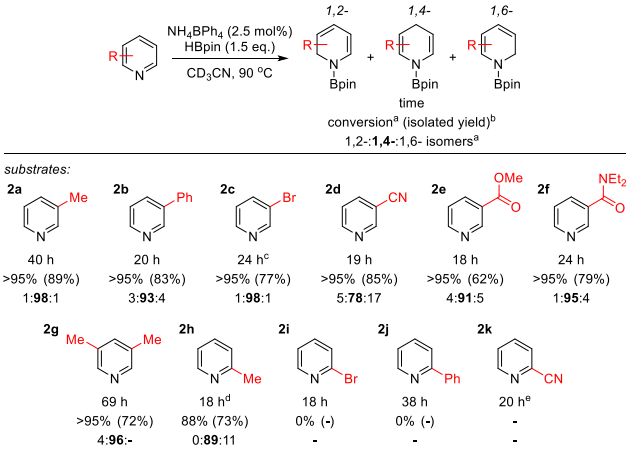
The structure of the boronium salt, pinBPy$_2$BPh$_4$, was confirmed by single crystal X-ray diffraction conducted on crystals grown from a stoichiometric reaction of HBpin, pyridine (2 equiv.), and NH_4BPh_4 in CD_3CN by layering the solution with dry $(Me_3Si)_2O$ (Figure 1). The boronium cation exhibits a tetrahedral geometry around boron and comprises two pyridine molecules and pinacolate bound to the boron centre. The ^{11}B NMR spectrum of the isolated crystals in CD_3CN exhibits resonances observed in the catalytic reactions at δ = 7.1 and -6.8 ppm, corresponding to the boronium cation and BPh_4^- anion, respectively.

Having optimised the system for pyridine, the substrate tolerance of the reaction was examined using a variety of 2- and 3-substituted pyridines (Scheme 1). The boronium-catalyzed reaction has been found to be remarkably successful in facilitating the regioselective 1,4-hydroboration of 3-substituted pyridines (Scheme 1, **2a**-**g**). The reaction is amenable to dehalogenation-prone bromide in the 3-position

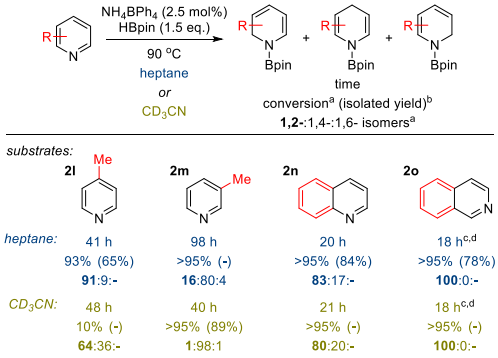
(Scheme 1, **2c**) as well as Lewis basic and reducible cyano, ester, and amide substituents in the 3-positon (Scheme 1, entries **2d**-**e**). Furthermore, the hydroboration of 3,5-lutidine, a sterically demanding substrate that failed to undergo hydroboration with Wang's bulkier fluoro-organoborane hydride, can be achieved with excellent regioselectivity (1,2-:1,4- product ratio of 4:96, Scheme 1, entry **2g**).[9]

Regioselective hydroboration of 2-substituted pyridines was found to be less successful than those substituted in the 3-positon. The hydroboration of 2-methylpyridine can be achieved with good selectivity for the 4-position using two equivalents of HBpin to ensure complete reactivity (Scheme 1, **2h**). However, 2-phenylpyridine and 2-bromopyridine were found not to undergo hydroboration under the optimized reaction conditions (Scheme 1, **2i**-**j**). The steric profile of 2-phenylpyridine and the reduced donor ability of 2-bromopyridine likely limit coordination of pyridine to HBpin, preventing these substrates from activating the B-H bond sufficiently.[9] Additionally, the use of 2-cyanopyridine resulted in a red precipitate along with a complex mixture of nitrile and pyridine reduction products that could not be fully assigned by ^{1}H NMR spectroscopy (Scheme 1, **2k**).

The results listed in Table 1 show that the regioselectivity of this reaction exhibits a significant solvent dependence; conducting the hydroboration reaction in non-polar solvents (i.e. heptane and benzene) affords a greater proportion of the 1,2-hydroboration product (Table 1, entries 5 and 7). This solvent-dependent regioselectivity can also be observed for the hydroboration of substituted pyridines. Comparing the regioselectivity of the hydroboration of 4-methylpyridine conducted in heptane and acetonitrile, the reaction conducted in heptane shows a dramatic increase in conversion from starting material as well as in selectivity for the 1,2-isomer (Scheme 2, **2l**). Very little conversion is observed in CD_3CN when the 4-position is 'blocked' with a methyl group suggesting that for the catalytic reduction of pyridine, the 1,4-product is produced directly and that regioselectivity is not exclusively the result of thermodynamic interconversion from the 1,2-product. The hydroboration of 3-methylpyridine, a substrate that exhibits a strong preference for reduction in the 4-position in acetonitrile, shows a significant increase in the 1,2-hydroboration product when the reaction is conducted in heptane (Scheme 2, **2m**). This solvent effect is less pronounced for the hydroboration of quinoline, where reactions conducted in heptane and acetonitrile afford nearly identical 1,2- : 1,4-regioisomer ratios (Scheme, **2n**). The similar reactivity of quinoline observed in CD_3CN and heptane presumably results from greater charge delocalization causing 1,2- and 1,4-hydroboration to be less energetically distinct. The same reduction of isoquinoline results exclusively in the 1,2-hydroboration product in both heptane and acetonitrile as the 4-position is inaccessible (Scheme 2, **2o**). Further, we note the presence of a minor product formed during the hydroboration of isoquinoline (ca. 6% and 11% in heptane and acetonitrile, respectively) that exhibits signals in the ^{1}H NMR spectrum consistent with a 1,2,3,4-tetrahydroisoquinoline species.



Scheme 1 Catalytic 1,4-regioselective hydroboration of substituted pyridines. NMR tube scale reactions performed in a sealed J. Young NMR tube using 0.015 mmol NH_4BPh_4. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield using 3.36 mmol pyridine in a sealed J. Young-type bomb. [c] Performed at 60 °C. [d] Conducted using 2 equivalents of HBpin. [e] Complex mixture of pyridine and nitrile reduction products.



Scheme 2 Catalytic 1,2-regioselective hydroboration of pyridines and quinolines. NMR tube scale reactions performed in a sealed J. Young NMR tube using 0.015 mmol NH_4BPh_4. ^{1}H NMR of heptane reactions referenced to DMSO-d_6 in an isolated glass capillary. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield using 3.36 mmol pyridine in a sealed J. Young-type bomb. [c] Reactions conducted at 60 °C. [d] Unknown by-product formed during the reaction (6-11%).

While reactions in heptane afford a greater proportion of the 1,2-regioisomer, 1,4-hydroboration is observed in most cases. Even 4-methylpyridine forms the 1,4-DHP as a minor product in heptane despite steric hindrance in the 4-position. It has been established that, in general, formation of a 1,4-dihydropyridine is more thermodynamically favourable than formation of a 1,2-dihydropyridine and several reports have noted superior regioselectivity for the 1,4-DHP as the reaction temperature is increased.[6,15] In our system, hydroboration of 4-methylpyridine results in a 91:9 ratio of 1,2-:1,4- isomers when heated to 90 °C in heptane (Scheme 2, **2l**). Further heating of the resulting mixture of DHPs at 110 °C for 72 hours results in a 1,2-:1,4- ratio of 24:76, giving the 1,4-isomer as the major product.

Based on the observations in polar and non-polar solvents, it is likely that conditions favouring the thermodynamic 1,4-product are reached at lower temperatures in polar solvents. Thus, larger proportions of the 1,2-product are observed at 90 °C in benzene or heptane compared to reactions conducted in

acetonitrile, 1,2-DFB, or pyridine. As the reaction occurs more quickly in 1,2-DFB than acetonitrile or pyridine, it is possible that polar donor solvents inhibit the reaction through coordination to boron during the reaction cycle. Further investigations into the solvent-dependent regioselectivity of this reaction using computational methods, as well as the possibility of alternative reaction pathways in non-polar solvents, are underway.

In conclusion, we have demonstrated a practical methodology for the regioselective 1,4-hydroboration of pyridines based on a boronium-catalyzed reaction, initiated by the readily available ammonium salt, NH_4BPH_4. Additionally, the proposed active boronium species in this reaction, $pinBPy_2BPh_4$, could be isolated and characterized in the solid state. This reaction is tolerant to a variety of substituents in the 3-position and exhibits high conversions to the hydroboration products. The regioselectivity of this transformation can be altered by changing solvent polarity, where polar solvents (acetonitrile, 1,2-DFB, pyridine) favour selective 1,4-hydroboration and non-polar solvents (benzene, heptane) result in poor regioselectivity or favour the generation of the 1,2-regioisomer for certain substituted pyridine substrates. Beyond the hydroboration of pyridines, we are currently working to extend this methodology to use of other pinacol boranes and the hydroboration of carbonyls as well as enantioselective hydroborations using chiral BINOL-derived phosphoric acid initiators.

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Note and references

† ^{1}H and ^{11}B NMR spectroscopy of the reaction mixture containing only HBpin and NH_4BPh_4 in acetonitrile show decomposition of the system at 90 °C over a 24 hour period, giving moderate amounts of C_6H_6, NH_3, and possibly B_2pin_3. Decomposition is not observed in the presence of pyridine.

‡ On a few occasions minor amounts of pyridine-BH_3 adduct is observed by ^{11}B NMR spectroscopy in the solvents tested, possibly formed through the decomposition of HBpin. This species may be active in the reduction of pyridine but does not appear to affect the regioselectivity of the reaction (no differences observed in CH_3CN with or without BH_3).

1 A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1–82.

2 (a) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1–42; (b) D. M. Stout and a I. Meyers, *Chem. Rev.*, 1982, **82**, 223–243; (c) R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1141–1156; (d) S. G. Ouellet, A. M. Walji and D. W. C. Macmillan, *Acc. Chem. Res.*, 2007, **40**, 1327–1339; (e) N. Satoh, T. Akiba, S. Yokoshima and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2007, **46**, 5734–5736; (f) N. Edraki, A. R. Mehdipour, M. Khoshneviszadeh and R. Miri, *Drug Discov. Today*, 2009, **14**, 1058–1066; (g) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642–2713; (h) C. Zheng and S.-L. You, *Chem. Soc. Rev.*, 2012, **41**, 2498; (i) G. W. Zamponi, *Nat. Rev. Drug Discov.*, 2016, **15**, 19–34.

3 (a) F. W. Fowler, *J. Org. Chem.*, 1972, **37**, 1321–1323; (b) T. Chennat and U. Eisner, *J. Chem. Soc., Perkin Trans. 1*, 1975, 926–929; (c) E. Booker and U. Eisner, *J. Chem. Soc., Perkin Trans. 1*, 1975, 929–931; (d) J. Pabel, C. E. Hösl, M. Maurus, M. Ege and K. T. Wanner, *J. Org. Chem.*, 2000, **65**, 9272–9275; (e) C. E. Hoesl, M. Maurus, J. Pabel, K. Polborn and K. T. Wanner, *Tetrahedron*, 2002, **58**, 6757–6770.

4 (a) O. Abril and G. M. Whitesides, *J. Am. Chem. Soc.*, 1982, **104**, 1552–1554; (b) L. Hao, J. F. Harrod, A. M. Lebuis, Y. Mu, R. Shu, E. Samuel and H. G. Woo, *Angew. Chem. Int. Ed.*, 1998, **37**, 3126–3129; (c) J. F. Harrod, R. Shu, H.-G. Woo and E. Samuel, *Can. J. Chem.*, 2001, **79**, 1075–1085; (d) P. S. Wagenknecht, J. M. Penney and R. T. Hembre, *Organometallics*, 2003, **22**, 1180–1182; (e) F. Glorius, N. Spielkamp, S. Holle, R. Goddard and C. W. Lehmann, *Angew. Chem. Int. Ed.*, 2004, **43**, 2850–2852; (f) A. P. Shaw, B. L. Ryland, M. J. Franklin, J. R. Norton, J. Y. C. Chen and M. L. Hall, *J. Org. Chem.*, 2008, **73**, 9668–9674; (g) Q. A. Chen, M. W. Chen, C. Bin Yu, L. Shi, D. S. Wang, Y. Yang and Y. G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432–16435; (h) D. V. Gutsulyak, A. Van Der Est and G. I. Nikonov, *Angew. Chem. Int. Ed.*, 2011, **50**, 1384–1387; (i) K. Osakada, *Angew. Chem. Int. Ed.*, 2011, **50**, 3845–3846; (j) Y. Maenaka, T. Suenobu and S. Fukuzumi, *J. Am. Chem. Soc.*, 2012, **134**, 367–374; (k) C. D. F. Königs, H. F. T. Klare and M. Oestreich, *Angew. Chem. Int. Ed.*, 2013, **52**, 10076–10079.

5 M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Köhn and C. Weetman, *Organometallics*, 2011, **30**, 5556–5559.

6 J. Intemann, M. Lutz and S. Harder, *Organometallics*, 2014, **33**, 5722–5729.

7 K. Oshima, T. Ohmura and M. Suginome, *J. Am. Chem. Soc.*, 2012, **134**, 3699–3702.

8 A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro and T. J. Marks, *Nat. Chem.*, 2014, **6**, 1100–1107.

9 X. Fan, J. Zheng, Z. H. Li and H. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 4916–4919.

10 D. Mukherjee, S. Shirase, T. P. Spaniol, K. Mashima and J. Okuda, *Chem. Commun.*, 2016, **52**, 13155-13158.

11 A. Kaithal, B. Chatterjee and C. Gunanathan, *Org. Lett.*, 2016, **18**, 3402–3405.

12 (a) P. Eisenberger and C. M. Crudden, *Dalt. Trans.*, 2017, **46**, 4874–4887; (b) Z. Zhang, P. Jain and J. C. Antilla, *Angew. Chem. Int. Ed.*, 2011, **50**, 10961–10964; (c) J. M. Farrell, J. A. Hatnean and D. W. Stephan, *J. Am. Chem. Soc.*, 2012, **134**, 15728–15731; (d) P. Eisenberger, A. M. Bailey and C. M. Crudden, *J. Am. Chem. Soc.*, 2012, **134**, 17384–17387; (e) E. R. Clark, A. Del Grosso and M. J. Ingleson, *Chem. - Eur. J.*, 2013, **19**, 2462–2466; (f) S. E. Denmark, Y. Ueki, *Organometallics*, 2013, **32**, 6631–6634.

13 (a) D. McArthur, C. P. Butts and D. M. Lindsay, *Chem. Commun.*, 2011, **47**, 6650–6652; (b) A. Prokofjevs, A. Boussonnič Re, L. Li, H. Ne Bonin, E. Lacô, D. P. Curran and E. Vedejs, *J. Am. Chem. Soc.*, 2012, **134**, 12281–12288; (c) K. Chernichenko, M. Lindqvist, B. Koai, M. Nieger, K. Sorochkina, I. Paai and T. Repo, *J. Am. Chem. Soc.*, 2016, **138**, 4860–4868.

14 S. D. Pike, M. R. Crimmin and A. B. Chaplin, *Chem. Commun.*, 2017, **53**, 3615–3633.

15 (a) N. Bodor and R. Pearlman, *J. Am. Chem. Soc.*, 1978, **100**, 4946–4953; (b) E. C. Ashby and a. B. Goel, *J. Organomet. Chem.*, 1981, **204**, 139–145; (c) W. Clegg, L. Dunbar, L. Horsburgh and R. E. Mulvey, *Angew. Chem. Int. Ed.*, 1996, **35**, 753–755.

