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Metal-free alkene hydroboration with pinacolborane employing $C_6F_5BH_2{\cdot}SMe_2$ as a precatalyst†

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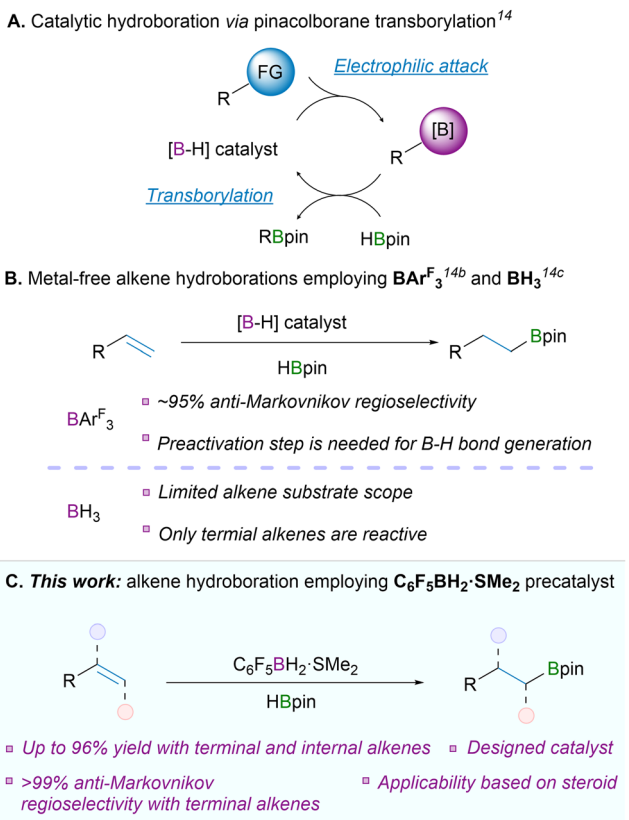
We have developed $C_6F_5BH_2{\cdot}SMe_2$ as a unique, metal-free precatalyst for alkene hydroboration. It combines high reactivity and excellent regio- and chemoselectivity. Mechanistic studies reveal that the catalyst's structure is nearly ideal: the transborylation step occurs *via* an [sp^3-C–B/B–H] transition state and the hydroborylation step goes through a low barrier ($\Delta G^{\ddagger}$ = 15.2 kcal mol^{-1}) with cyclohexene as a substrate.

Boronic esters are highly valuable compounds in both the chemical industry and scientific research. Unlike alkylboranes, they are air-stable, isolable and relatively inexpensive.[1] Boronic esters are used in a wide range of transformations[2] including Suzuki–Miyaura coupling,[3] Chan–Evans–Lam coupling,[4] Zweifel olefination[5] and Matteson homologation,[6] providing access to multiple structurally complex compounds.[7] Accordingly, boronic esters are one of the most important building blocks in the pharmaceutical industry, leading to significant and increasing demand for their synthesis.[8] There are many outstanding methods for the synthesis of boronic esters using Li- or Mg-containing catalysts[9] and transition-metal catalysis.[10] Despite its undoubted advantages, transition-metal catalysis has also shortcomings. Scarcity and high cost of metals along with the energetically expensive procedure for removing traces of metals from target molecules are relevant concerns for the modern pharmaceutical industry.[11] Metal-free catalysis is void of these disadvantages, making it a substantial augmentation of current synthetic methods.[12]

Hydroboration reaction is a crucial method for synthesizing boronic esters.[1] In general, pinacol-substituted boronic esters are highly stable allowing their easy isolation, purification, and storage,[1] as well as transformations targeted at other functional groups in their presence.[5,6,7a] Metal-free approaches for the production of pinacol boronic esters can be divided into two categories. The classical method involves an attack by a boron electrophile followed by esterification of the resulting compound with a 1,2-diol.[13] In the second method a boron electrophile reacts first and subsequent transborylation takes place with pinacolborane (HBpin) to yield the desired product (Scheme 1A).[14] The latter option is more appealing for future



Scheme 1 Metal-free synthetic routes (A–C) to pinacol boronic esters (RBpin).

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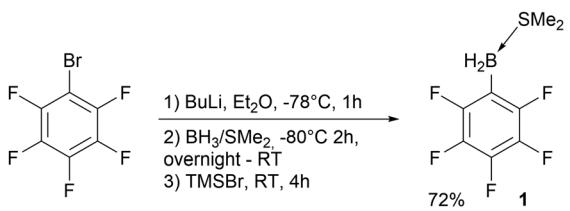
development as it can be integrated into a catalytic cycle using a B–H electrophile: during the final transborylation step, the B–H electrophile is regenerated and, thus, could be available for the next cycle. Various methods of metal-free catalytic hydroboration range from alcohols, ketones, imines, and C–C triple bonds to yield boronic esters in combination with HBpin.[12a,13d,15] However, there are only few reported studies on metal-free catalytic hydroboration of C–C double bonds using pinacolborane as a boron source.[14b,c,16] Particularly, the leading examples are B(3,5-$(CF_3)_2C_6H_3)_3$ (BAr^F_3)[14b] and BH_3.[14c] The first example, BAr^F_3, requires an additional transborylation step to generate *in situ* the catalytically active B–H species. It shows notable reactivity towards substituted styrene derivatives and terminal alkenes, achieving an average of 95% anti-Markovnikov regioselectivity (Scheme 1B). Although BH_3 represents the simplest possible catalyst candidate for hydroboration, it exhibits similar catalytic reactivity towards styrenes and terminal alkenes (Scheme 1B). Herein, we report a powerful catalytic method for hydroboration of terminal and internal olefins using $C_6F_5BH_2{\cdot}SMe_2$ as a catalyst precursor (Scheme 1C). This compound combines a boron centre with high electrophilicity and steric accessibility. Those features ensure high regioselectivity and reactivity. Notably, **1** can successfully hydroborate *R*-(+)-limonene, β-(−)-pinene, α-(+)-pinene, and a TBS-protected pregnenolone derivative, demonstrating its potential in natural product synthesis.

The borane $C_6F_5BH_2{\cdot}SMe_2$ (**1**) has traditionally been synthesized from $(C_6F_5)_3B{\cdot}OEt_2$,[17] but we pursued its preparation from more affordable reagents. A recent report introduced $C_6F_5BH_2$ as a fleeting intermediate in a one-pot reaction starting from C_6F_5Br.[18] We slightly modified this procedure and were able to isolate $C_6F_5BH_2{\cdot}SMe_2$ with an acceptable 72% yield (Scheme 2). Selective Li–Br exchange of pentafluorobromobenzene at −78 °C produces C_6F_5Li, which is capable of attacking the $BH_3{\cdot}SMe_2$ adduct to form its lithium salt ($C_6F_5BH_3Li$). Following hydride abstraction with TMSBr and recrystallization from hexane gave colourless needle-shaped crystals of $C_6F_5BH_2{\cdot}SMe_2$. Surprisingly, the dimethyl sulfide cannot be removed by applying vacuum overnight and it appears to be crucial in stabilizing the highly electrophilic boron centre.

Initial reactivity studies and catalytic performance of **1** were probed using 1-octene and cyclohexene as substrates (see ESI† for further information). For 1-octene, hydroboration in neat conditions with 5 mol% catalyst loading and 60 °C temperature gave the highest yield of the product. Furthermore, by using 3 equivalents of HBpin we were able to obtain quantitative isolated yield of the product, while using 1.5 eq. gave 92% yield. For cyclohexene, a higher temperature (80 °C) and catalyst loading of 10% with extended reaction time gave the optimal result (isolated yield of 96% for 2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, CyBpin).

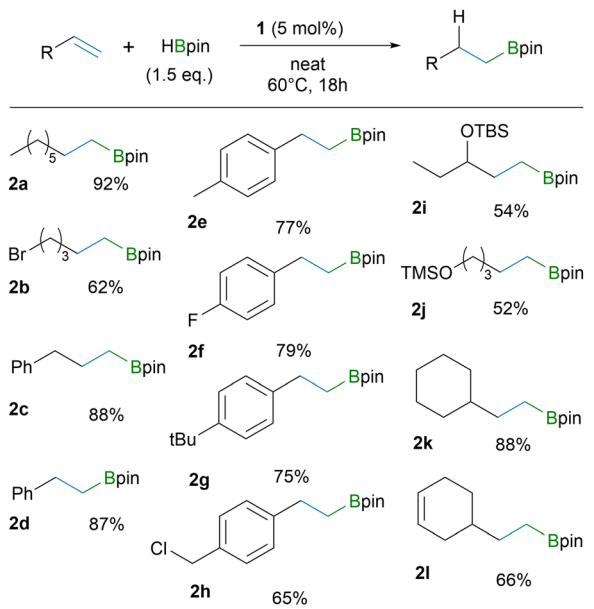
The optimized reaction conditions were then applied to a variety of terminal alkenes (Tables 1 and 2). The results clearly demonstrate functional group tolerance towards Br (**2b**), Cl (**2h**), F (**2f**), OTBS (**2i**) and OTMS (**2j**) and that the reaction is effective for styrene derivatives (**2d–h**). The hydroboration maintains exclusive regioselectivity forming only the anti-Markovnikov products (>99% based on GC-MS; see ESI†). The only outlier in the substrate series is C_6F_5-substituted styrene **3e** by giving two different regioisomers in a 5 : 2 ratio (Table 2). Presumably, the strong electron withdrawing effect of perfluoroaromatic unit makes also the Markovnikov addition feasible.

The catalyst system demonstrates noteworthy chemoselectivity towards a terminal C–C double bond instead of an internal one (Table 1, **2l**). However, when treating vinylcyclohexene with a larger excess HBpin (4 eq.), the double hydroboration product **3g** was isolated in 97% yield. Applying the optimized cyclohexene conditions to various other alkenes, it is evident that 1,1-disubstituted C–C double bonds react more compliantly compared to 1,2-disubstituted C–C double bonds (Table 2). Notwithstanding, the hydroboration occurs also for the 1,1,2-trisubstituted alkene substrate (**3f**), which is a highly challenging substrate even for transition-metal catalysts.[2b] Here, four diastereomers are seen for **3f**. It is also worth to note that chloride in an allyl position remains unaffected to yield borylated methallyl chloride (**3c**), which was isolated in an almost quantitative yield. These results above demonstrate the high reactivity of **1** towards terminal and internal olefins and its complimentary character for metal catalysed hydroboration reactions. However, the catalyst



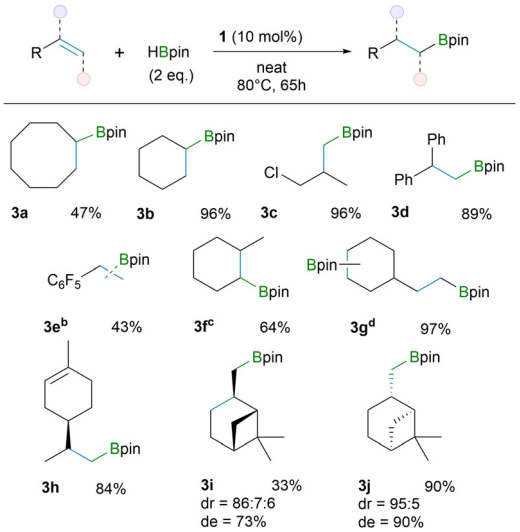
Scheme 2 Synthetic procedure for $C_6F_5BH_2{\cdot}SMe_2$ (**1**).

Table 1 Substrate scope I: hydroboration of terminal alkenes[a]



[a] Reported yields are isolated.

Table 2 Substrate scope II: hydroboration of other alkenes[a,b,c,d]

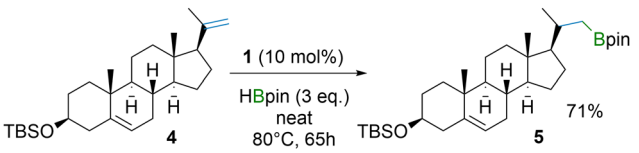


[a] Reported yields are isolated. [b] 2 different regioisomers observed in GC-MS. [c] 4 different diastereoisomers observed in GC-MS. [d] 4 eq. HBpin were used. 4 different diastereoisomers observed in GC-MS.

system **1** has also its inherent limitations. Substrates containing ketone or unprotected alcohol groups prohibit the catalytic reactivity.[19] And, unexpectedly, neither *trans*- nor *cis*-stilbene yielded any product, even though $B(3,5\text{-}(CF_3)_2C_6H_3)_3$ was amenable in hydroboration with *cis*-stilbene.[14b] We assume that breaking the conjugation between the two aromatic cores has a moderately high energy barrier that cannot be overcome under these reaction conditions.

To explore the potential of the hydroboration further, we focused on different enantiomerically pure terpenes to investigate whether stereoselectivity is attained. *R*-(+)-limonene (**3h**) and β-(−)-pinene (**3j**) gave 84% and 90% yields, respectively (Table 2). NMR analysis revealed the presence of two diastereomers for the product of *R*-(+)-limonene, whereas β-(−)-pinene product was found as one main diastereomer (dr = 95 : 5) in both NMR and GC-MS (see ESI†). Applicability of the catalytic method was further evaluated by hydroboration of a natural product derivative, pregnenolone (Scheme 3). Despite the presence of an OTBS-substituent and an internal C–C π-bond, the product **5** was isolated with a 71% yield, in line with the catalyst's high functional group tolerance and chemoselectivity.

The mechanism of the hydroboration catalysis is likely to involve two stages: addition of the $C_6F_5BH_2{\cdot}SMe_2$ to the C–C double bond and subsequent transborylation reaction with HBpin. This would be in agreeance with previously reported



Scheme 3 Hydroboration of a pregnenolone derivative with HBpin.

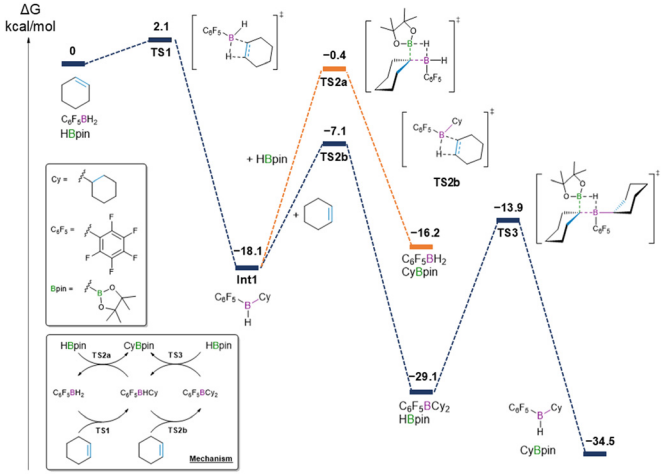


Fig. 1 Gibbs free energy diagram of the calculated reaction mechanism based on cyclohexene. The energies are given in kcal mol^{-1} in the gas phase at 298 K. The effect of SMe_2 was omitted.

mechanistic studies.[14b,20] An alternative mechanism, including an *in situ* generation of BH_3 through nucleophilic attack on HBpin, has been proposed.[21] We conducted mechanistic investigations which ruled out the involvement of BH_3 (see ESI†). However, these studies revealed minor decomposition of HBpin at elevated temperatures, therefore its slight excess is preferable to ensure high yields.

To gain a more detailed understanding of the hydroboration mechanism, we performed quantum chemical calculations using density functional theory (DFT) at the PBE0-GD3BJ/Def2-TZVP level. We excluded the effect of SMe_2 in our calculations as it is not present in any of the product NMR spectra and used the hydroboration of cyclohexene as our model reaction (Fig. 1). The first step in the calculated mechanism includes the addition of $C_6F_5BH_2$ to cyclohexene, which proceeds in an almost barrierless fashion (**TS1**, $\Delta G^{\ddagger}$ = 2.1 kcal mol^{-1}) to produce an intermediate C_6F_5BHCy (**Int1**). In the next step, the transborylation between **Int1** and HBpin can happen directly *via* a barrier of 17.7 kcal mol^{-1} (**TS2a**), but interestingly, the addition of a second cyclohexene to **Int1** is more facile and requires only 11 kcal mol^{-1} of energy (**TS2b**). This difference in barrier heights can be related to the degree of polarization of the B–H bonds in **TS2a** and **TS2b**. The higher polarization of the bond in **TS2b** (the difference of calculated Mulliken charges is 0.54 in **TS2b** and 0.40 in **TS2a**) is in agreement with a lower transition state energy compared to **TS2a**. Subsequently, the activation barrier for the transborylation of $C_6F_5BCy_2$ was calculated to be 15.2 kcal mol^{-1} (**TS3**), which is 2.5 kcal mol^{-1} lower than the transborylation of C_6F_5BHCy (**TS2a**). The overall reaction is exergonic in nature (ΔG = −37.3 kcal mol^{-1}), and furthermore, the relatively modest energy barrier for **TS3** indicates that the sp^3-C–B fragment is feasible to undergo transborylation in the presence of a C_6F_5–B bond.

In conclusion, we have developed a highly efficient metal-free hydroboration reaction for olefinic C–C double bonds using easy-to-synthesize $C_6F_5BH_2{\cdot}SMe_2$ as a catalyst precursor.

Noteworthy are high regioselectivity of the reaction with terminal alkenes and catalyst's good tolerance toward halides and silicon-protected alcohols. Our approach is also effective not only with terminal alkenes but also with internal ones. Computational analysis together with experimental data unfolds that B–C_6F_5 motif of the catalyst is averse to undesired decomposition, providing a pathway for selective transborylation of an alkyl sp^3-C–B bond. This method proves to be effective with a model steroid and terpenes, providing stereoselectivity with the latter. We believe that this approach can serve as a straightforward and inexpensive way to convert alkenes to pinacol boronic esters, which are essential for various synthetic applications.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

References

1 A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412–443.
2 (*a*) J. F. Hartwig, *Acc. Chem. Res.*, 2012, **45**, 864–873; (*b*) S. J. Geier, C. M. Vogels, J. A. Melanson and S. A. Westcott, *Chem. Soc. Rev.*, 2022, **51**, 8877–8922; (*c*) S. Nandy, S. Paul, K. K. Das, P. Kumar, D. Ghorai and S. Panda, *Org. Biomol. Chem.*, 2021, **19**, 7276–7297.
3 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*b*) J. Xu, O. P. Bercher and M. P. Watson, *J. Am. Chem. Soc.*, 2021, **143**, 8608–8613; (*c*) J. Li, X. Zhang, Y. Yao, Y. Gao, W. Yang and W. Zhao, *J. Org. Chem.*, 2022, **87**, 6951–6959; (*d*) M. Zhang, P. S. Lee, C. Allais, R. A. Singer and J. P. Morken, *J. Am. Chem. Soc.*, 2023, **145**, 8308–8313.
4 (*a*) J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769–4779; (*b*) J. D. Grayson, F. M. Dennis, C. C. Robertson and B. M. Partridge, *J. Org. Chem.*, 2021, **86**, 9883–9897.
5 (*a*) G. Zweifel, H. Arzoumanian and C. C. Whitney, *J. Am. Chem. Soc.*, 1967, **89**, 3652–3653; (*b*) R. Armstrong and V. Aggarwal, *Synthesis*, 2017, 3323–3336.
6 (*a*) D. S. Matteson and D. Majumdar, *J. Am. Chem. Soc.*, 1980, **102**, 7588–7590; (*b*) J. L. Stymiest, G. Dutheuil, A. Mahmood and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2007, **46**, 7491–7494.
7 (*a*) R. E. Shade, A. M. Hyde, J.-C. Olsen and C. A. Merlic, *J. Am. Chem. Soc.*, 2010, **132**, 1202–1203; (*b*) T. Bootwicha, J. M. Feilner, E. L. Myers and V. K. Aggarwal, *Nat. Chem.*, 2017, **9**, 896–902; (*c*) A. Fawcett, T. Biberger and V. K. Aggarwal, *Nat. Chem.*, 2019, **11**, 117–122.
8 Y. Wang, I. Haight, R. Gupta and A. Vasudevan, *J. Med. Chem.*, 2021, **64**, 17115–17122.
9 (*a*) M. K. Bisai, S. Yadav, T. Das, K. Vanka and S. S. Sen, *Chem. Commun.*, 2019, **55**, 11711–11714; (*b*) R. Kumar, S. Dutta, V. Sharma, P. P. Singh, R. G. Gonnade, D. Koley and S. S. Sen, *Chem. – Eur. J.*, 2022, **28**, e202201896.
10 (*a*) S. A. Westcott, H. P. Blom, T. B. Marder and R. T. Baker, *J. Am. Chem. Soc.*, 1992, **114**, 8863–8869; (*b*) D. A. Evans, G. C. Fu and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1992, **114**, 6671–6679; (*c*) Y. Yamamoto, R. Fujikawa, T. Umemoto and N. Miyaura, *Tetrahedron*, 2004, **60**, 10695–10700; (*d*) L. Zhang, Z. Zuo, X. Leng and Z. Huang, *Angew. Chem., Int. Ed.*, 2014, **53**, 2696–2700; (*e*) W. N. Palmer, T. Diao, I. Pappas and P. J. Chirik, *ACS Catal.*, 2015, **5**, 622–626; (*f*) Y. Xi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 6703–6706; (*g*) S. Kisan, V. Krishnakumar and C. Gunanathan, *ACS Catal.*, 2017, **7**, 5950–5954; (*h*) W. Zhao, K.-Z. Chen, A.-Z. Li and B.-J. Li, *J. Am. Chem. Soc.*, 2022, **144**, 13071–13078.
11 (*a*) A. J. Hunt, T. J. Farmer and J. H. Clark, *Elemental Sustainability and the Importance of Scarce Element Recovery*, The Royal Society of Chemistry, 2013, p. 1; (*b*) J. D. Hayler, D. K. Leahy and E. M. Simmons, *Organometallics*, 2019, **38**, 36–46.
12 (*a*) M.-A. Légaré, M.-A. Courtemanche, É. Rochette and F.-G. Fontaine, *Science*, 2015, **349**, 513–516; (*b*) Z.-H. Shang, J. Pan, Z. Wang, Z.-X. Zhang and J. Wu, *Eur. J. Org. Chem.*, 2023, e202201379; (*c*) C. Guo, P. Li, S. Wang, N. Liu, Q. Bu, Y. Wang and Y. Qiu, *J. Org. Chem.*, 2023, **88**, 4569–4580; (*d*) N. Slesarchuk, E. Ma, J. Miranda-Pizarro, S. Heikkinen, D. Schollmeyer, M. Nieger, P. Vasko and T. Repo, *Dalton Trans.*, 2024, **53**, 9590–9595.
13 (*a*) A. G. Karatjas and E. Vedejs, *J. Org. Chem.*, 2008, **73**, 9508–9510; (*b*) S. Li, C. Hu, X. Cui, J. Zhang, L. L. Liu and L. Wu, *Angew. Chem., Int. Ed.*, 2021, **60**, 26238; (*c*) C. Shu, A. Noble and V. K. Aggarwal, *Nature*, 2020, **586**, 714–719; (*d*) S. Rej and N. Chatani, *J. Am. Chem. Soc.*, 2021, **143**, 2920–2929; (*e*) M. Huang, J. Hu, S. Shi, A. Friedrich, J. Krebs, S. A. Westcott, U. Radius and T. B. Marder, *Chem. – Eur. J.*, 2022, **28**, e202200480; (*f*) X. Tan, X. Wang, Z. H. Li and H. Wang, *J. Am. Chem. Soc.*, 2022, **144**, 23286–23291.
14 (*a*) A. Arase, M. Hoshi, A. Mijin and K. Nishi, *Synth. Commun.*, 1995, **25**, 1957–1962; (*b*) Q. Yin, S. Kemper, H. F. T. Klare and M. Oestreich, *Chem. – Eur. J.*, 2016, **22**, 13840; (*c*) N. Ang, C. Buettner, S. Docherty, A. Bismuto, J. Carney, J. Docherty, M. Cowley and S. Thomas, *Synthesis*, 2018, 803–808; (*d*) A. D. Bage, K. Nicholson, T. A. Hunt, T. Langer and S. P. Thomas, *ACS Catal.*, 2020, **10**, 13479–13486; (*e*) A. D. Bage, K. Nicholson, T. A. Hunt, T. Langer and S. P. Thomas, *Synthesis*, 2023, 62–74; (*f*) F. Wech, N. Koch, T. Müller and U. Gellrich, *Org. Chem. Front.*, 2024, **11**, 5921–5927; (*g*) J. H. Docherty, K. Nicholson, A. P. Dominey and S. P. Thomas, *ACS Catal.*, 2020, **10**, 4686–4691.
15 A. Das and T. K. Panda, *ChemCatChem*, 2023, **15**, e202201011.
16 (*a*) C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482–3485; (*b*) N. N. H. Ton, B. K. Mai and T. V. Nguyen, *J. Org. Chem.*, 2021, **86**, 9117–9133; (*c*) P. Huninik, J. Szyling, A. Czapik and J. Walkowiak, *Green Chem.*, 2023, **25**, 3715–3722.
17 A.-M. Fuller, D. L. Hughes, S. J. Lancaster and C. M. White, *Organometallics*, 2010, **29**, 2194–2197.
18 R. J. Blagg and G. G. Wildgoose, *RSC Adv.*, 2016, **6**, 42421–42427.
19 K. Nicholson, J. Dunne, P. DaBell, A. B. Garcia, A. D. Bage, J. H. Docherty, T. A. Hunt, T. Langer and S. P. Thomas, *ACS Catal.*, 2021, **11**, 2034–2040.
20 (*a*) R. Köster, *Ann. N. Y. Acad. Sci.*, 1969, **159**, 73–88; (*b*) P. Vasko, I. A. Zulkifly, M. Á. Fuentes, Z. Mo, J. Hicks, P. C. J. Kamer and S. Aldridge, *Chem. – Eur. J.*, 2018, **24**, 10531; (*c*) E. Nieto-Sepulveda, A. D. Bage, L. A. Evans, T. A. Hunt, A. G. Leach, S. P. Thomas and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2019, **141**, 18600–18611; (*d*) A. D. Bage, K. Nicholson, T. A. Hunt, T. Langer and S. P. Thomas, *Synthesis*, 2023, 62–74.
21 A. D. Bage, T. A. Hunt and S. P. Thomas, *Org. Lett.*, 2020, **22**, 4107–4112.