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Letter

Arylboronic Acid Catalyzed *C*-Alkylation and Allylation Reactions Using Benzylic Alcohols

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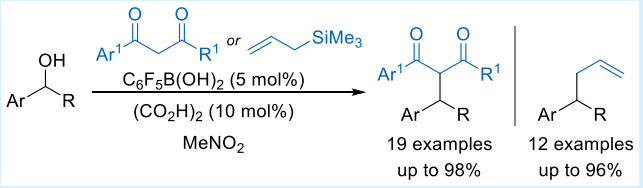
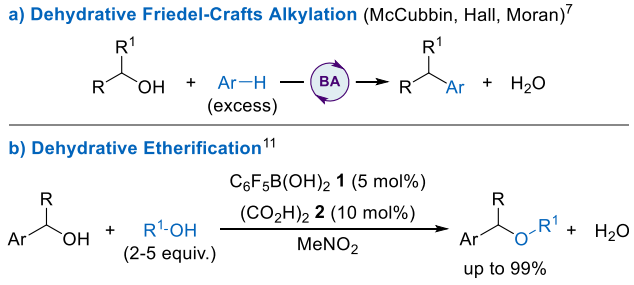
ABSTRACT: The arylboronic acid catalyzed dehydrative *C*-alkylation of 1,3-diketones and 1,3-ketoesters using secondary benzylic alcohols as the electrophile is reported, forming new C−C bonds (19 examples, up to 98% yield) with the release of water as the only byproduct. The process is also applicable to the allylation of benzylic alcohols using allyltrimethylsilane as the nucleophile (12 examples, up to 96% yield).



The formation of carbon−carbon bonds is central to the synthesis of organic molecules, with the alkylation of carbon-based pro-nucleophiles an important strategy within this area. Traditionally, alkylation reactions are performed using either alkyl halides or stoichiometrically activated alcohol derivatives as the electrophile. However, with the drive to develop more efficient and sustainable organic reactions,[1] there has been increasing interest in catalytic methods for the direct use of alcohols as electrophiles in alkylation processes, releasing water as the only byproduct.[2] Catalytic dehydrative substitutions can occur by a number of general mechanistic pathways including nucleophilic substitution, "borrowing hydrogen" via a redox reaction of primary or secondary alcohols,[3] or addition to metal π-allyl complexes formed from allylic alcohols.[4]

Recently, arylboronic acids have gained increasing attention as catalysts that can activate hydroxyl groups toward both electrophilic and nucleophilic reactivity.[5] Boronic acids are attractive as catalysts due to their wide availability, tractability, and generally low toxicity.[6] Of particular relevance is the use of arylboronic acid catalysis for the activation of alcohols toward C−C bond formations through either complete or partial ionization of the C(sp^3)−OH bond. In this regard, dehydrative Friedel−Crafts alkylation processes have been most widely explored to date (Scheme 1a).[7] Seminal work by McCubbin[7a,b] and Hall[7c] showed that electron-deficient arylboronic acids catalyze the Friedel−Crafts alkylation of electron-rich arenes and heteroarenes using either allylic or benzylic alcohols as the electrophile. The reaction scope has recently been extended to the use of electron-deficient arenes using 2,3,4,5-tetrafluorophenylboronic acid as the catalyst alongside perfluoropinacol as a cocatalyst.[7g] Arylboronic acid catalysis can also be combined with enamine catalysis for the enantioselective α-alkylation of aldehydes using tertiary allylic alcohols.[8] Other C−C bond formations promoted by the catalytic arylboronic acid activation of alcohols include dehydrative Nazarov cyclizations of divinyl alcohols,[9] and [4 + 3] cycloadditions promoted by the ionization of indolyl alcohols.[10]

Scheme 1. Boronic Acid Catalyzed Dehydrative Substitutions



We recently reported the use of catalytic pentafluorophenylboronic acid **1** alongside cocatalytic oxalic acid **2** for the activation of benzylic alcohols toward inter- and intramolecular dehydrative etherification reactions (Scheme 1b).[11] Mechanistic investigations suggest that pentafluorophenylboronic acid **1** and oxalic acid **2** condense in situ to form a Brønsted acid catalyst that promotes S_N1-type reactivity. We therefore questioned whether this system could be applied to the *C*-alkylation of 1,3-diketone derivatives and allylation reactions, which have not previously been explored using arylboronic acid catalysis. Various Brønsted acid catalysts have previously been reported for dehydrative C−C bond formations.[2,12] However, the use of a tractable arylboronic acid would avoid the direct handling of strong acids and further expand the

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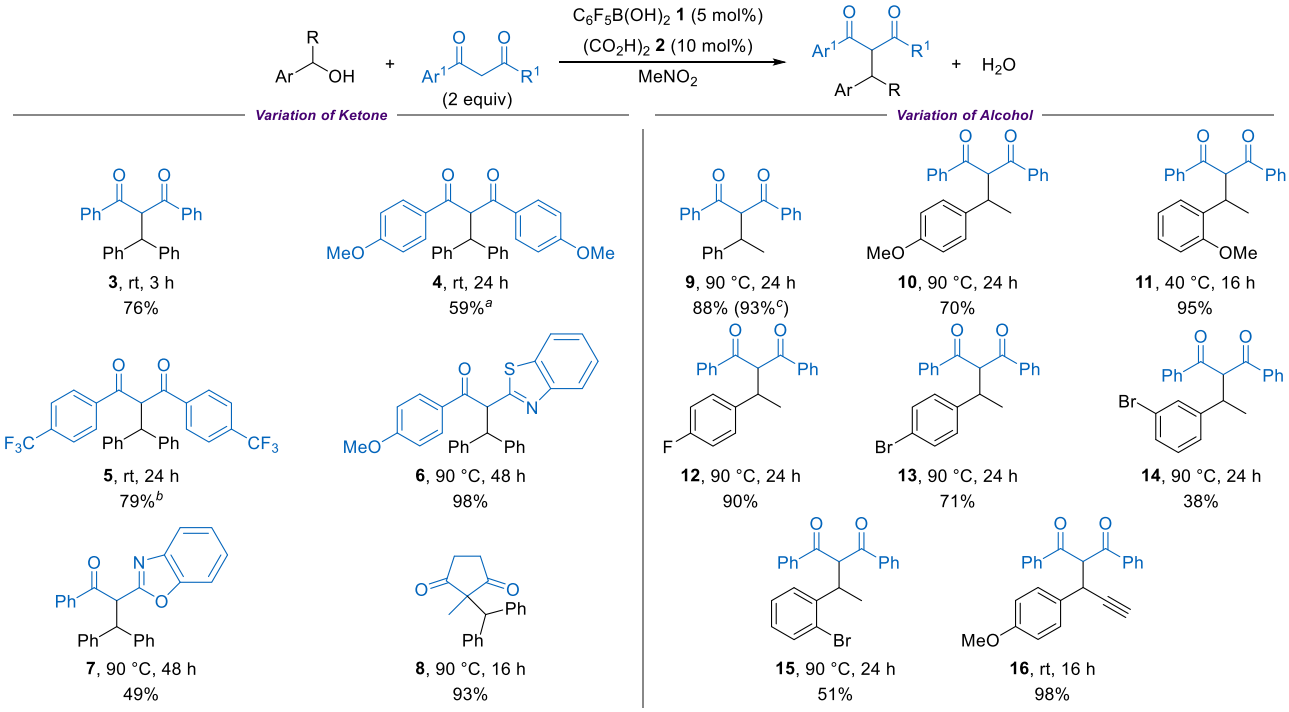
Scheme 2. Dehydrative Alkylation of 1,3-Diektone Derivatives



[a]Using 1,3-diketone (5 equiv). [b]Using benzhydrol (2 equiv) and 1,3-diketone (1 equiv). [c]Reaction performed on a 4 mmol scale.

scope of reactions promoted by these readily available catalytic systems.

First, the use of enolizable 1,3-diketones as potential pro-nucleophiles was investigated with the reaction of benzhydrol with dibenzoylmethane. Reaction optimization showed that a combination of pentafluorophenylboronic acid **1** (5 mol %) and oxalic acid **2** (10 mol %) in $MeNO_2$,[13] a catalytic system first reported by Moran for a dehydrative Friedel–Crafts alkylation reaction,[7f] gave the desired *C*-alkylation product **3** in 76% yield after 3 h at room temperature. In the absence of any catalyst or with pentafluorophenylboronic acid **1** alone, no reaction was observed, while using only oxalic acid **2** (10 mol %) gave 5% conversion into **3** over 3 h.[13] The reaction scope was first investigated through variation of the 1,3-diketone component (Scheme 2). Symmetrical diketones bearing both electron-donating and electron-withdrawing substituents were tolerated under the standard reaction conditions, forming products **4** and **5** in good yields. Heterocycle containing acyl benzothiazoles and acyl benzoxazoles were also competent pro-nucleophiles, forming products **6** and **7** after extended 48 h reaction times at 90 °C, although the analogous acyl benzimidazole was unreactive under these conditions. The use of a cyclic 1,3-diketone was also possible, forming product **8** bearing a new quaternary carbon center in an excellent 93% yield. In contrast, the reaction of benzhydrol with 1,3-cyclohexanedione gave selective *O*-alkylation into the corresponding *β*-keto enol ether.[13,14] Attempts to extend the scope to alternative enolizable ketones such as 2-phenylacetophenone or benzoylacetonitrile were unsuccessful, with only starting materials returned at room temperature. Using dibenzoylmethane (2 equiv) as standard, the use of various secondary benzylic alcohols as the electrophilic component was trialed. 1-Arylethanol derivatives bearing either neutral or electron-donating substituents were well tolerated, forming products **9**–**11** in excellent yields. The synthetic potential was demonstrated by performing the reaction on gram scale (4 mmol of alcohol) to give 1.25 g of **9** in 93% yield. Halogen substitution on the aryl ring was also possible with 4-fluoro- and 4-bromophenyl ethanol reacting to give **12** and **13** in 90% and 71% yield, respectively. Altering the substitution pattern affected the reactivity, with 1-(2-bromo- and 1-(3-bromophenyl)ethanol giving products **14** and **15** in slightly reduced yields. The presence of an alkyne on the reacting carbinol center was well tolerated, giving **16** in 98% yield. Limitations included the use of a sterically demanding secondary and tertiary alcohols, which are unreactive, while primary benzylic alcohols preferentially form the symmetric ether product.[13]

The use of 1,3-ketoesters as pro-nucleophiles was possible under the standard conditions (Scheme 3). For example, reacting ethyl benzoylacetate **17** with benzhydrol (2 equiv) gave product **18** in an excellent 97% yield after heating at 90 °C overnight. In this case, an excess of the alcohol was used to aid purification, with the symmetrical ether of benzhydrol formed as a side product. The use of 1-arylethanol derivatives bearing either electron-donating or halogen substituents as the electrophile gave *C*-alkylation products **19**–**22** in generally good yield as a mixture of diastereoisomers. Resubjecting an isolated sample of diastereomerically enriched product **21** (63:37 dr) to the reaction conditions led to equilibration of the diastereoisomers into the observed 53:47 dr, suggesting formation of a thermodynamic mixture. The product epimerization presumably occurs via catalyst-promoted enolization and protonation of the 1,3-ketoester stereocenter. The *C*-alkylation of 1,3-ketoesters could also be performed on gram scale (3.2 mmol of alcohol), giving 0.97 g of product **20** in 97% yield.

Furthermore, the isolated diastereomeric mixtures of products **19**–**21** could be derivatized into the corresponding

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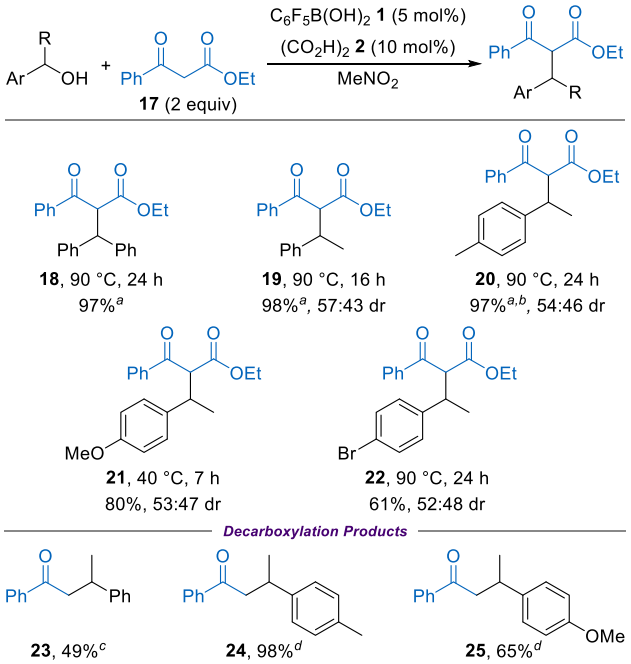
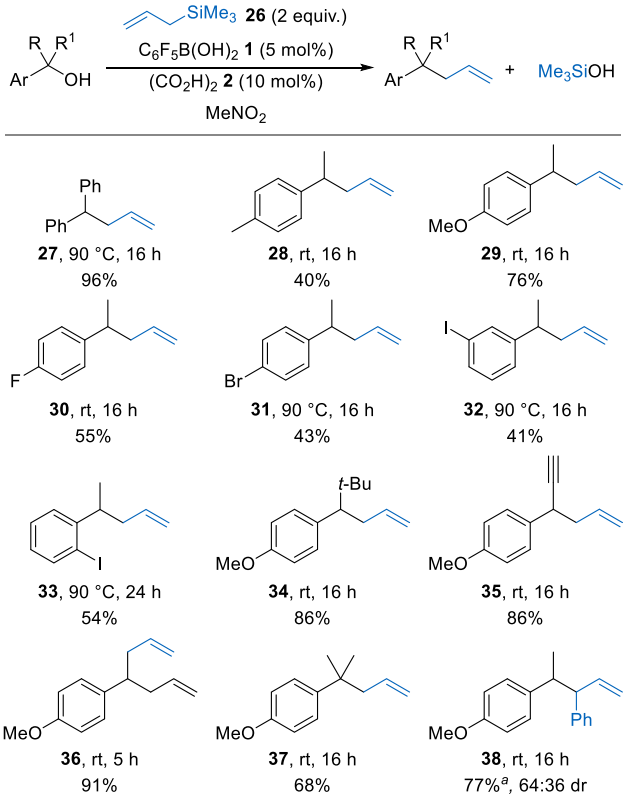
Scheme 3. Use of 1,3-Ketoesters as Pro-nucleophiles



[a]Using alcohol (2 equiv) and ethyl benzoylacetate **17** (1 equiv). [b]Reaction performed on a 3.2 mmol scale. [c]KOH, MeOH, 70 °C. [d]NaOH, EtOH, 80 °C

Scheme 4. Allylation of Benzylic Alcohols



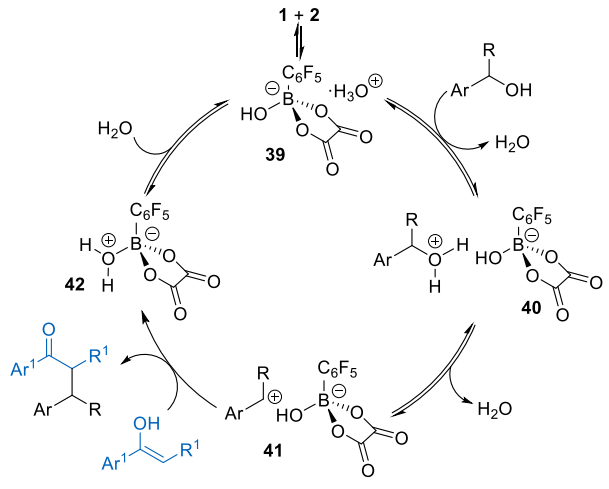
[a]Using cinnamyl trimethylsilane (2 equiv).

β-aryl ketones **23**–**25** through decarboxylation under basic conditions.

Next, we sought to extend the *C*-alkylation protocol to a catalytic Hosomi–Sakurai process using allyl silanes as the nucleophile.[15] Initial investigations reacting benzhydrol as the electrophile with allyltrimethylsilane **26** (2 equiv) using pentafluorophenylboronic acid **1** (5 mol %) and oxalic acid **2** (10 mol %) exclusively gave the symmetrical ether at room temperature in nitromethane. However, increasing the temperature to 90 °C gave allylation product **27** in excellent 96% yield (Scheme 4), with no formation of the unwanted symmetrical ether. Various secondary alcohols were trialed under the standard catalytic conditions. Electron-rich and halogen substituted 1-arylethanol derivatives were suitable electrophiles, forming allylation products **28**–**33** in moderate to good yields. In all cases, complete conversion into the allylation product was observed, but the nonpolar nature of the products resulted in loss of material during purification by chromatography accounting for some of the moderate yields. Unsubstituted 1-phenylethanol derivatives were not reactive, returning either starting materials or the corresponding symmetrical ether byproduct under all conditions tested.[13] In contrast to the reactivity observed with 1,3-diketone nucleophiles, a secondary alcohol bearing a bulky *tert*-butyl substituent worked well, forming product **34** in 86% yield. Alkynyl and extended alkenyl substituents were also well tolerated, with products **35** and **36** formed in 80% and 90% yield, respectively. The catalytic allylation of an electron-rich tertiary alcohol was also possible, forming product **37** with a new quaternary carbon center in 68% yield. The electron-donating methoxy substituent on the aryl ring was essential for reactivity, with the analogous unsubstituted phenyl substrate returned unreacted under the same conditions. Cinnamyl trimethylsilane could also be used as a nucleophile, giving **38** in 77% yield as a 64:36 mixture of diastereoisomers at room temperature.

We have previously shown that pentafluorophenylboronic acid **1** and oxalic acid **2** condense in situ to form hydrated boronate ester **39**, which acts as a strong Brønsted acid to promote S_N1 type reactivity through formation of an intermediate benzylic carbocation from the secondary alcohol.[11] This is consistent with the literature on related arylboronic acid catalyzed reactions and accounts for the higher reactivity observed for electron-rich secondary benzylic alcohols in the substrate scope. A possible catalytic cycle for the dehydrative *C*-alkylation process is outlined in Scheme 5.

Scheme 5. Possible Catalytic Cycle



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In solution, pentafluorophenylboronic acid **1** and oxalic acid **2** are in dynamic equilibrium with hydrated boronate **39**,[16] which is likely to act as a Brønsted acid to protonate the secondary benzylic alcohol. This is consistent with recent work by Moran and co-workers, who found that various arylboronic acid promoted alcohol activation processes are likely to proceed via either a Brønsted acid or H-bond activation mode, as opposed to Lewis acid or covalent catalysis.[17] Dissociation of ion pair **40** forms benzylic carbocation **41**, which can undergo nucleophilic addition from the enol tautomer of either the 1,3-diketone derivatives or 1,3-ketoesters to form the *C*-alkylation products and release water as the only byproduct. An analogous mechanism is plausible using allyltrimethylsilane **26** as the nucleophile reacting with carbocation **41**, with trimethylsilanol released as the byproduct in this case.[18]

In conclusion, arylboronic acid catalysis can be used for the dehydrative *C*-alkylation of various carbon nucleophiles using secondary benzylic alcohols as the electrophile. A range of 1,3-diketones and 1,3-ketoesters can be used as pro-nucleophiles toward secondary benzylic alcohols activated by a combination of pentafluorphenylboronic acid **1** (5 mol %) and oxalic acid **2** (10 mol %) to form *C*-alkylation products in good yields, with water formed as the only byproduct. The catalytic system is also compatible with allyltrimethylsilane **26** as the nucleophile, promoting the direct allylation of various benzylic alcohols. Further studies into the applicability of arylboronic acid catalysis toward dehydrative substitution reactions are ongoing in our laboratory.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02736.

Experimental details, compound characterization, and NMR spectra for novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J. Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited. *Green Chem.* **2018**, *20*, 5082−5103.

(2) For reviews of catalytic dehydrative substitution reactions of alcohols, see: (a) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F. D.; Cozzi, P. G. Direct Nucleophilic S_N1-Type Reactions of Alcohols. *Eur. J. Org. Chem.* **2011**, *2011*, 647−666. (b) Kumar, R.; Van der Eycken, E. V. Recent approaches for C−C bond formation via direct dehydrative coupling strategies. *Chem. Soc. Rev.* **2013**, *42*, 1121−1146. (c) Baeza, A.; Nájera, C. Recent Advances in the Direct Nucleophilic Substitution of Allylic Alcohols through S_N1-Type Reactions. *Synthesis* **2013**, *46*, 25−34. (d) Dryzhakov, M.; Richmond, E.; Moran, J. Recent Advances in Direct Catalytic Dehydrative Substitution of Alcohols. *Synthesis* **2016**, *48*, 935−959. (e) Huy, P. H.; Hauch, T.; Filbrich, I. Lewis Base Catalyzed Nucleophilic Substitutions of Alcohols. *Synlett* **2016**, *27*, 2631−2636. (f) Ajvazi, N.; Stavber, S. Alcohols in Direct Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions: Recent Advances. *ARKIVOC* **2018**, *2018*, 288−329. (g) Beddoe, R. H.; Sneddon, H. F.; Denton, R. M. The catalytic Mitsunobu reaction: a critical analysis of the current state-of-the-art. *Org. Biomol. Chem.* **2018**, *16*, 7774−7781. (h) Huy, P. H. Lewis Base Catalysis Promoted Nucleophilic Substitutions − Recent Advances and Future Directions. *Eur. J. Org. Chem.* **2020**, *2020*, 10−27. (i) Estopiñá-Durán, S.; Taylor, J. E. Brønsted Acid-Catalysed Dehydrative Substitution Reactions of Alcohols. *Chem. - Eur. J.* **2020**, DOI: 10.1002/chem.202002106.

(3) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410−1459.

(4) Butt, N. A.; Zhang, W. Transition Metal-Catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929−7967.

(5) For reviews on boronic acid catalysis, see: (a) Dimitrijević, E.; Taylor, M. S. Organoboron Acids and Their Derivatives as Catalysts for Organic Synthesis. *ACS Catal.* **2013**, *3*, 945−962. (b) Zheng, H.; Hall, D. G. Boronic Acid Catalysis: an Atom-Economical Platform for Direct Activation and Functionalization of Carboxylic Acids and Alcohols. *Aldrichimica Acta* **2014**, *47*, 41−51. (c) Hall, D. G. Boronic Acid Catalysis. *Chem. Soc. Rev.* **2019**, *48*, 3475−3496.

(6) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2011; Vol. 2.

(7) For examples of boronic acid catalyzed Friedel−Crafts alkylation processes, see: (a) McCubbin, J. A.; Hosseini, H.; Krokhin, O. V. Boronic Acid Catalyzed Friedel−Crafts Reactions of Allylic Alcohols with Electron-Rich Arenes and Heteroarenes. *J. Org. Chem.* **2010**, *75*, 959−962. (b) McCubbin, J. A.; Krokhin, O. V. Organocatalyzed Friedel−Crafts arylation of benzylic alcohols. *Tetrahedron Lett.* **2010**, *51*, 2447−2449. (c) Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. Boronic Acid Catalysis as a Mild and Versatile Strategy for Direct Carbo- and Heterocyclizations of Free Allylic Alcohols. *Angew. Chem., Int. Ed.* **2012**, *51*, 6187−6190. (d) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. Unsymmetrical Diarylmethanes by Ferroceniumboronic Acid Catalyzed Direct Friedel−Crafts Reactions

with Deactivated Benzylic Alcohols: Enhanced Reactivity due to Ion-Pairing Effects. *J. Am. Chem. Soc.* **2015**, *137*, 9694−9703. (e) Ricardo, C. L.; Mo, X.; McCubbin, J. A.; Hall, D. G. A Surprising Substituent Effect Provides a Superior Boronic Acid Catalyst for Mild and Metal-Free Direct Friedel−Crafts Alkylations and Prenylations of Neutral Arenes. *Chem. - Eur. J.* **2015**, *21*, 4218−4223. (f) Wolf, E.; Richmond, E.; Moran, J. Identifying lead hits in catalyst discovery by screening and deconvoluting complex mixtures of catalyst components. *Chem. Sci.* **2015**, *6*, 2501−2505. (g) Ang, H. T.; Rygus, J. P. G.; Hall, D. G. Two-component boronic acid catalysis for increased reactivity in challenging Friedel−Crafts alkylations with deactivated benzylic alcohols. *Org. Biomol. Chem.* **2019**, *17*, 6007−6014.

(8) Mo, X.; Hall, D. G. Dual Catalysis Using Boronic Acid and Chiral Amine: Acyclic Quaternary Carbons via Enantioselective Alkylation of Branched Aldehydes with Allylic Alcohols. *J. Am. Chem. Soc.* **2016**, *138*, 10762−10765.

(9) Zheng, H.; Lejkowski, M.; Hall, D. G. Mild boronic acid catalyzed Nazarov cyclization of divinyl alcohols in tandem with Diels−Alder cycloaddition. *Tetrahedron Lett.* **2013**, *54*, 91−94.

(10) Cao, K.-S.; Bian, H.-X.; Zheng, W.-H. Mild arylboronic acid catalyzed selective [4 + 3] cycloadditions: access to cyclohepta[*b*]-benzofurans and cyclohepta[*b*]indoles. *Org. Biomol. Chem.* **2015**, *13*, 6449−6452.

(11) Estopiñá-Durán, S.; Donnelly, L. J.; Mclean, E. B.; Hockin, B. M.; Slawin, A. M. Z.; Taylor, J. E. Aryl Boronic Acid Catalysed Dehydrative Substitution of Benzylic Alcohols for C−O Bond Formation. *Chem. - Eur. J.* **2019**, *25*, 3950−3956.

(12) For reviews on catalytic dehydration to form reactive quinone methide intermediates, see: (a) Jaworski, A. A.; Scheidt, K. A. Emerging Roles of in Situ Generated Quinone Methides in Metal-Free Catalysis. *J. Org. Chem.* **2016**, *81*, 10145−10153. (b) Mei, G.-J.; Shi, F. Indolylmethanols as Reactants in Catalytic Asymmetric Reactions. *J. Org. Chem.* **2017**, *82*, 7695−7707.

(13) See the Supporting Information for further details.

(14) Curini, M.; Epifano, F.; Genovese, S. Ytterbium triflate catalyzed synthesis of *β*-keto enol ethers. *Tetrahedron Lett.* **2006**, *47*, 4697−4700.

(15) Chaskar, A.; Murugan, K. Direct allylation of alcohols using allyltrimethylsilane: a move towards an economical and ecological protocol for C−C bond formation. *Catal. Sci. Technol.* **2014**, *4*, 1852−1868.

(16) Boronate complex **39** has been isolated and fully characterized and is a competent pre-catalyst for dehydrative etherification (ref 11). However, the exact nature of the Brønsted acid formed in solution is unknown, while formation of higher-order catalytic complexes with water and/or solvent also cannot be ruled out. For example, Moran has shown that nitromethane promotes the formation of supramolecular aggregates with $B(C_6F_5)_3{\cdot}H_2O$; see: Montalvo-Acosta, J. J.; Dryzhakov, M.; Richmond, E.; Cecchini, M.; Moran, J. A Supramolecular Model for the Co-Catalytic Role of Nitro Compounds in Brønsted Acid Catalyzed Reactions. *Chem. - Eur. J.* **2020**, *26*, 10976−10980.

(17) Zhang, S.; Lebœuf, D.; Moran, J. Brønsted Acid and H-Bond Activation in Boronic Acid Catalysis. *Chem. - Eur. J.* **2020**, *26*, 9883−9888.

(18) Hall showed that symmetric ether formation was kinetically favored for a 2,3,4,5-tetrafluorophenylboronic acid (10 mol%) and perfluoropinacol (10 mol%) catalyzed Friedel−Crafts alkylation using benzylic alcohols, with the ether subsequently converted into the product (ref 7g). The symmetric ether derived from benzhydrol was a competent precursor to both *C*-alkylation and allylation under our standard conditions. However, the symmetric ether derived from 1-(4-fluorophenyl)ethan-1-ol was unreactive in the allylation reaction, suggesting that this process is substrate specific. See the Supporting Information for details.

(19) Research data underpinning this manuscript can be found in the following: Estopiñá-Durán, S.; Mclean, E.; Donnelly, L.; Hockin, B.; Taylor, J. Data for Arylboronic Acid-Catalyzed *C*-Alkylation and Allylation Reactions Using Benzylic Alcohols. University of Bath Research Data Archive: Bath. https://doi.org/10.15125/BATH-00892.

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