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Electrochemically Driven Deoxygenative Borylation of Alcohols and Carbonyl Compounds

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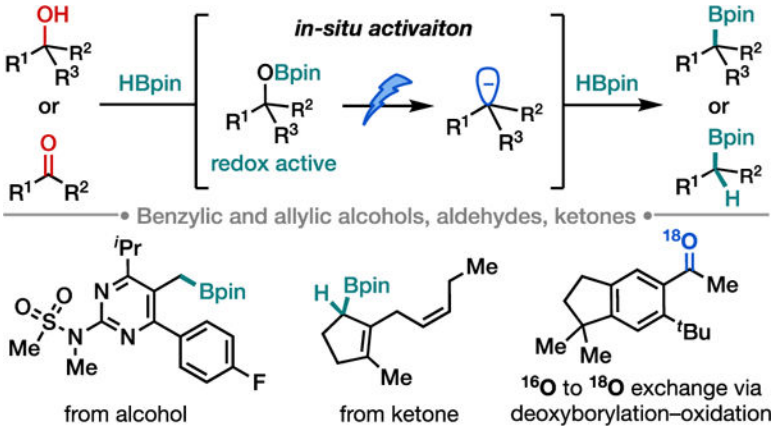
Abstract

We present a new, unified approach for the transformation of benzylic and allylic alcohols, aldehydes, and ketones into boronic esters under electroreductive conditions. Key to our strategy is the use of readily available pinacolborane, which serves both as an activator, first generating a redox-active trialkylborate species, and then as an electrophile, delivering the desired deoxygenatively borylated product. This strategy is applicable to a variety of substrates and can be employed for late-stage functionalization of complex molecules.

Graphical Abstract



Alcohols, ketones, and aldehydes are among the most prevalent functionalities found in organic molecules (Scheme 1A).[1] New efficient methodologies for the direct activation and functionalization of these oxygen-containing groups are therefore highly desirable for upgrading chemical feedstocks and late-stage modification of complex natural products and pharmaceuticals. However, deconstructive transformations of these motifs are challenging due to the strength of C–O single and double bonds.[2] In addition, because of the intrinsic reactivity differences of alcohols and carbonyl compounds, distinct reaction strategies are typically required for their activation, and currently there is no approach for the

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deoxygenative functionalization of both functional groups under the same mechanistic manifold.

Nucleophilic substitution[3] and radical-mediated bond cleavage[4] represent the most effective approaches to date for the activation of alcohols (Scheme 1B, left), converting C–OH into a carbocation or alkyl radical equivalent, respectively. These methods predominantly rely on the use of an additional stoichiometric reagent, often added in a separate synthetic step, to activate the alcohol or sequester the leaving group.[4] Indeed, notwithstanding elegant seminal contributions in catalytic alcohol functionalization,[5,6] literature examples that achieve direct or in situ activation of the native hydroxy groups remain limited. Further, methods that effectively reverse the polarity of the reactant and provide a carbanion equivalent could grant access to complementary reactivities leading to new bond disconnection strategies, but there are only two examples of such an approach to date (and only one involving direct transformation of alcohols).[7] Methods for the direct deoxygenative functionalization of aldehydes and ketones are even less common than for alcohols.[8] While elegant approaches have been advanced to transform carbonyl groups via radical,[9] electrophilic,[10] and carbene-mediated pathways[11] (Scheme 1B, right), accomplishing umpolung reactivity by means of carbanion generation from these substrates remains challenging and currently relies on substrate pre-activation to form corresponding hydrazones in a separate synthetic operation.[12]

Reductive electrochemistry has emerged in recent years as a powerful tool for the activation of strong bonds.[13] In previous work (Scheme 2A, upper), we showed that at a sufficiently reducing potential, an alkyl halide (**A**) can undergo a sequence of electron transfer-chemical reaction-electron transfer (ECE) processes that results in cleavage of the C–X bond to form a carbanion intermediate (**F**).[14] Reaction of **F** with another alkyl halide (**G**) results in the formation of a new C–C bond and furnishes cross-electrophile-coupling (XEC) product **H**. We were interested in developing an analogous electrochemical strategy for the deoxygenative functionalization of alcohols,[15] aldehydes, and ketones, in which substrates with their native functional groups can be directly employed in the reaction via in-situ activation. Here we present such an approach using pinacolborane (HBpin) as both an activator and a reactant (Scheme 1C). This reaction proceeds through a radical-polar crossover mechanism that effectively converts the alcohol or carbonyl group into a carbanion equivalent, and ultimately gives rise to alkylboronic esters that are versatile intermediates in organic synthesis.[16]

Towards developing the electrochemical deoxygenation of alcohols, we envisioned a strategy involving in-situ activation of alcohol **B** to form a leaving group, which would then be reductively cleaved at a relatively mild potential to generate alkyl radical **E** (Scheme 2A, lower). In the presence of an anion-stabilizing substituent (e.g., aryl or vinyl), **E** would undergo further reduction to afford carbanion **F**, which would be captured by an electrophile to provide the desired deoxygenatively functionalized product. Through initial screening, we identified the pinacol boronic ester (Bpin) group as a promising candidate for alcohol activation. The installation of Bpin can be readily achieved through reaction of the alcohol substrate with a XBpin reagent (X = H,[17] halide, alkoxy, or other leaving groups), yielding intermediate **D** with a lowered reduction potential (E_{red} = −2.5 V; see SI Section 5 for cyclic

voltammetry data) that is comparable to that of alkyl halides. Thus, the reduction of **D** is expected to occur via an ECE pathway to generate carbanion **F**, which would then react with an additional equivalent of XBpin[18] to produce borylated compound **I**. An attractive feature of this approach is that the boron reagent serves as both an activator and a reactant, thus allowing the full transformation to take place in a single operation, alleviating the need for a pre-activation step using an additional reagent.

Following this working hypothesis, we selected HBpin and MeOBpin as candidate electrophilic borylation reagents and benzyl alcohol (BnOH, **1**) as the model substrate to explore the reaction. Upon optimization, we found that using HBpin (2.5 equiv) with a sacrificial Mg anode, a graphite cathode, tetrabutylammonium tetrafluoroborate ($TBABF_4$) as electrolyte, and THF as solvent in an undivided cell, the desired borylated product (**2**) was isolated in 88% yield (Scheme 2B, entry 1). The reaction likely produces a borohydride intermediate ($BnBpinH^-$),[18a] which is converted to **2** upon exposure to H^+ during workup. Using 2.5 equiv of MeOBpin in lieu of HBpin under the same conditions afforded **2** in only trace amounts (7%, entry 2), with protonated product (toluene) identified as the major product (80%). Here, the reaction with MeOBpin likely generates MeOH and intermediate BnOBPin, and the benzyl anion subsequently formed upon electroreduction then reacts with MeOH to give the undesired protodeoxygenation product. Interestingly, a reaction using one equiv of HBpin and 1.5 equiv of MeOBpin afforded **2** in 80% yield (entry 3). The latter two findings indicate that HBpin is required for substrate activation, while the electrophilic boron source can be varied.

In the reaction system using HBpin as the sole borylating agent, the trialkylborate species (**D**, Scheme 2A) is generated from a rapid reaction between **1** and Hbpin,[17] as evidenced by visible vigorous evolution of H_2 during the beginning of electrolysis. Advantageously, the depletion of H^+ in the reaction medium prevents competing proton reduction that is common for alcohols under cathodic conditions while also precluding undesired protodeoxygenation via protonation of intermediate **F**. Importantly, although HBpin is an excellent electrophile,[18] it does not show any reduction peak at potentials below −3.0 V on the cyclic voltammogram (see SI Section 5), which thus does not compete with intermediate **D** in the electroreduction.

We also performed control experiments to probe the reaction mechanism (Scheme 2B, entries 4–9). No product was observed in the absence of an electric current (entry 4), which suggests that the observed reactivity is not alone promoted by chemical reduction at the Mg electrode. Indeed, running the reaction using magnesium powder (entry 5) or NaH (entry 6) as the terminal reductant in the absence of an electric current did not yield any product. Additionally, electrolysis carried out in the cathodic chamber of a divided cell afforded **2** in 49% yield (entry 7). Replacing Mg anode with graphite using $^{i}Pr_2EtN$ as a homogeneous sacrificial reductant also provide **2** in 40% yield (entry 8). These two findings indicated that the Mg anode or Mg^{2+} generated from anodic oxidation do not play crucial roles in the reaction mechanism.[19] Lastly, a reaction performed using BnOBpin (**3**) in lieu of BnOH as the substrate afforded **2** in 80% yield (entry 9), suggesting that under standard conditions (entry 1), the trialkyl borate (**D**) formed in situ is the key reactive intermediate.

The use of HBpin as an activating agent allowed us to further expand the reaction strategy to the deoxyborylation of aldehydes and ketones (Scheme 2A, lower). Indeed, HBpin readily reacts with carbonyl compounds (**C**) through hydroboration to form common intermediate **D**,[20] which can then undergo electrochemical activation. Using similar conditions as described above for the reaction with BnOH, benzyl aldehyde **4** was transformed to **2** in 84% yield (Scheme 2C, entry 1). Control experiments without electricity or using Mg powder as a chemical reductant in lieu of electroreduction did not afford any desired product (entries 2 and 3). We note that elegant deoxyborylation methods have recently been reported by Li and Liu, independently, under non-electrochemical conditions using bis(catecholato)diboron or bis(pinacolato)diboron reagents.[21] However, our reaction is also appliable to alcohol deoxyborylation, which is not currently the case for the other routes.

We next explored the substrate scope of our methodology (Scheme 3). A suite of primary, secondary, and tertiary alcohols were efficiently transformed into boronic esters (**5**–**15**), and various functional groups were tolerated, including aryl fluoride (**6**), boronic ester (**7**), and thioether (**8**). Of note, with *p*-F-benzyl alcohol, defluorination was initially observed under standard conditions, likely as a result of direct reduction of the fluoroarene in the starting alcohol. This issue was resolved via pre-mixing HBpin with *p*-F-benzyl alcohol in the presence of Et_3N or K_2CO_3 before starting electrolysis, which ensured complete conversion of the substrate to ROBpin and suppressed the side reaction. Strained cyclobutanol substrates were tolerated, yielding products **15** and **16** without evidence of ring-opening. Substrates featuring reductively sensitive functionalities such as secondary amides were compatible (**12**) under modified reaction conditions using a mixture of HBpin/MeOBpin and LiOTf in DME as the electrolyte medium.[22] Importantly, a diverse range of heterocyclic substrates such as piperazine (**17**), pyrazole (**18**), indazole (**19**), and pyridine (**20**–**22**) were also compatible with this reaction.

A panel of benzylic aldehydes and ketones with diverse functionalities such as silylether, *m*-chlorine, and aniline proved to be suitable substrates, yielding borylated compounds **24**, **25**, and **30**, respectively (Scheme 3B). In particular, myriad heterocyclic substituents including triazole (**31**), pyrrole (**32**), morpholine (**33**), carbazole (**34**), *N*-Boc piperazine (**35**), benzothiophene (**36**), benzofuran (**37**), pyrazole (**38**), and indole (**39**) were well-tolerated, indicating that this method may be of interest for the preparation of medicinally active compounds.

The above success prompted us to further expand the scope of this methodology to allylic alcohols and conjugate enones/enals, which are abundant in natural products and feedstock chemicals, and which could also form stabilized carbanion nucleophiles upon electroreduction. When our originally optimized conditions (Scheme 2B) were initially applied to allylic substrates, the desired borylated products were only detected in small amounts, along with products from decomposition of the tetrabutylammonium ion (via the Hofmann elimination).[23] To circumvent this side reaction, a series of alkali metal-based electrolytes were surveyed, and LiOTf proved optimal.[24] Using these modified conditions, a range of natural products bearing linear and cyclic allylic C–O moieties were converted to desired allylic boronic esters in good yields (Scheme 4, **40**–**47**). Linalool, (–)-verbenone, and (1R)(−)-myrtenal afforded a mixture of regioisomers as a result of allylic anion

delocalization, with moderate selectivity favoring borylation at the sterically more accessible site (**45**–**47**, respectively).[25]

Lastly, to further demonstrate the synthetic utility of our methodology, a suite of natural products, medicinal agents, and their analogs were examined (Scheme 5A, **48**–**53**). Desoxyanisoin and celestolide underwent borylation to afford **48** and **49** in excellent yields. Borylation of desoxyanisoin on a gram scale (5 mmol) was also successful, affording **49** in 58% yield (1.06 g). The methyl esters of common anti-inflammatory drugs zaltoprofen yielded boronate products **50**. Further, the alcohol precursor of cholesterol medication rosuvastatin, skin medication podophyllotoxin, and Alzheimer's drug donepezil were all found to undergo deoxyborylation in good yields (products **51**, **52**, and **53**, respectively). Furthermore, this methodology exhibits excellent chemoselectivity towards the functionalization of benzylic or allylic alcohols over unactivated alcohols (Scheme 5B, **54**–**57**).[26] For example, a zaltoprofen derivative and sclareol were selectively functionalized at the benzylic and allylic positions, respectively, to give products **56** and **57**. Lastly, employing a recent method on aerobic oxidation of boronic esters,[27] we developed a two-step, one-pot procedure to achieve the formal oxygen isotope exchange. Treament of the crude reaction mixture containing **48** derived from celestolide with a Cu catalyst in presence of $^{18}O_2$ provided ^{18}O-labeled celestolide (**58**) in 86% yield with 82% ^{18}O incoporation.[28]

In summary, we have developed an electrochemical methodology that converts alcohols, aldehydes, and ketones into value-added boronic esters leveraging the redox activity of in-situ generated trialkyl borate intermediates. We anticipate this operationally simple protocol will provide a new avenue for the upgrading of feedstock chemicals and late-stage derivatization of complex targets containing alcohols and carbonyl compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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22. The major product was identified as ^{n}BuBpin, likely resulting from hydroborylation of 1-butene, a side product of Hofmann elimination of tetrabutylammonium salts. The base in the Hofmann elimination is likely the carbanion intermediate generated from the reduction of alcohol–Bpin complexes.^{n}
23. Under the LiOTf/DME electrolyte system, the graphite electrode was severely degraded after the reaction for reasons we currently do not understand. Fe was chosen because it provided similar reactivity while being more physically robust

24. Under original optimal conditions with an excess of HBpin, reduction of amide was observed, and using LiOTf suppressed formation of protonated product.

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26. In these cases, addition of excess HBpin is necessary as both activated and unactivated hydroxy groups react to form R–OBpin; upon electrolysis, the R–OBpin group from the unactivated alcohol remains intact and can be rapidly deprotected to reveal the native −OH on silica gel. For silica deprotection of alkyl–OBpin groups to form alkyl alcohols, see:McIntosh ML; Moore CM; Clark TB Copper-catalyzed diboration of ketones: facile synthesis of tertiary α-hydroxyboronate esters. Org. Lett, 2010, 12, 1996–1999. [PubMed: 20392113]

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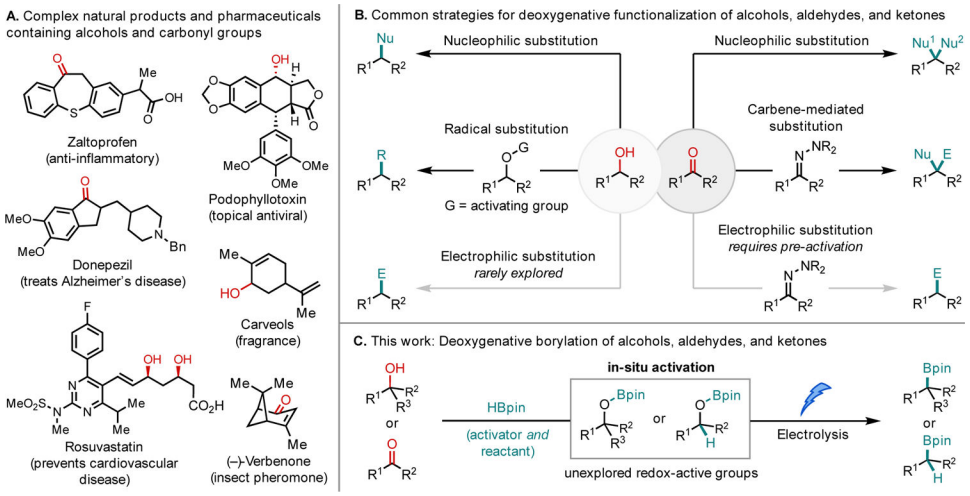
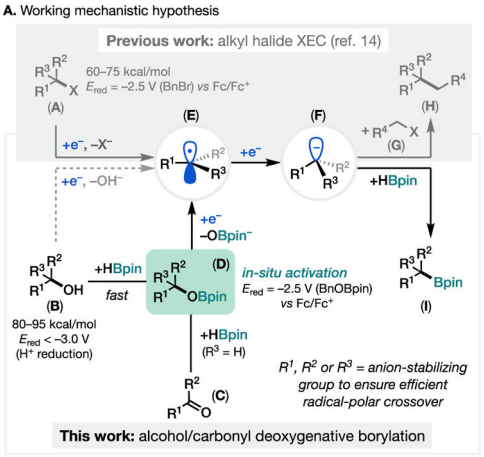
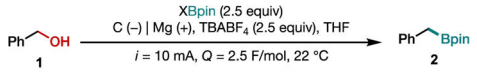


Scheme 1.

Background and introduction

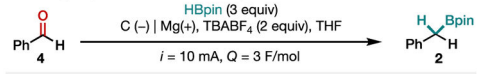


B. Reaction discovery and control experiments



Entry	Conditions: Identity of XBpin	Yield (%)
1	HBpin	88
2	MeOBpin	7
3	HBpin (1 equiv) + MeOBpin (1.5 equiv)	80
	Variations from optimal conditions (entry 1)	
4	No electricity[a]	0
5	Mg powder (2 equiv), no electricity[b]	0
6	NaH (2 equiv), no electricity[b]	0
7	C (–) ‖ Mg(+), divided cell	49
8	C (–) | C (+), with 2 equiv $^{i}Pr_2EtN$	40
9	Bn(OBpin) (**3**) instead of **1**	80

C. Strategy expansion to aldehyde borylation

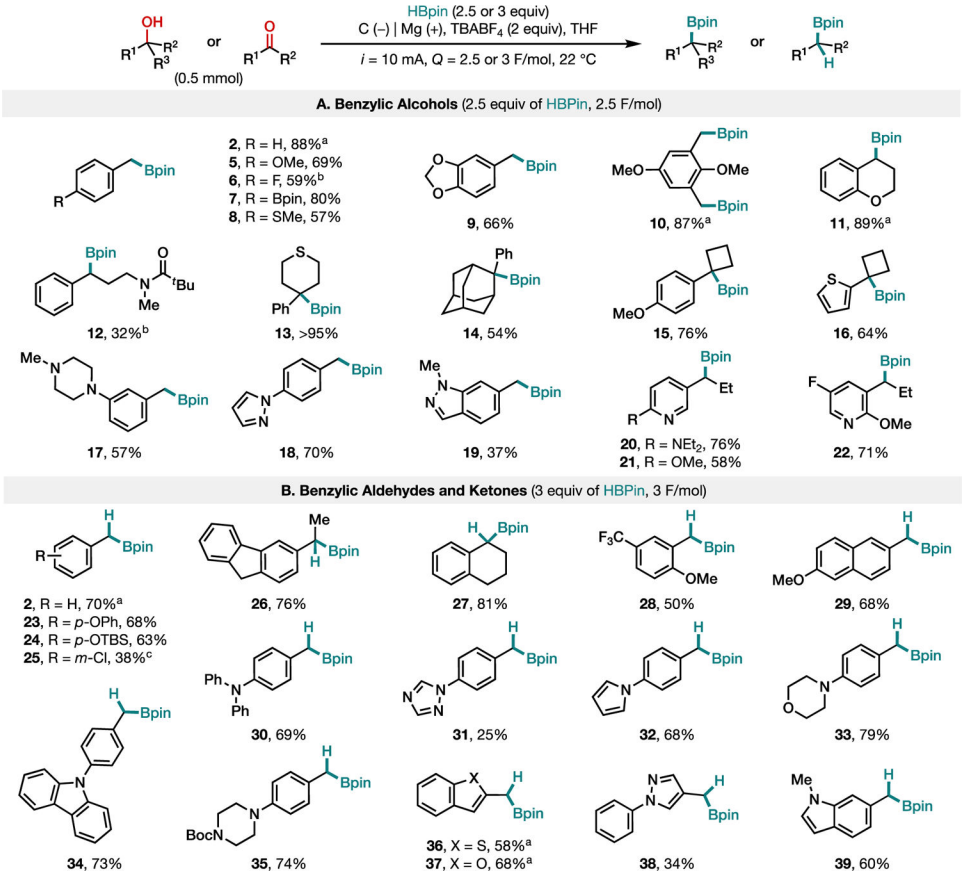


Entry	Variations from optimal conditions	Yield (%)
1	None	84
2	No electricity[a]	0
3	Mg powder (2 equiv), no electricity[b]	0

Scheme 2.

Design principle and control experiments

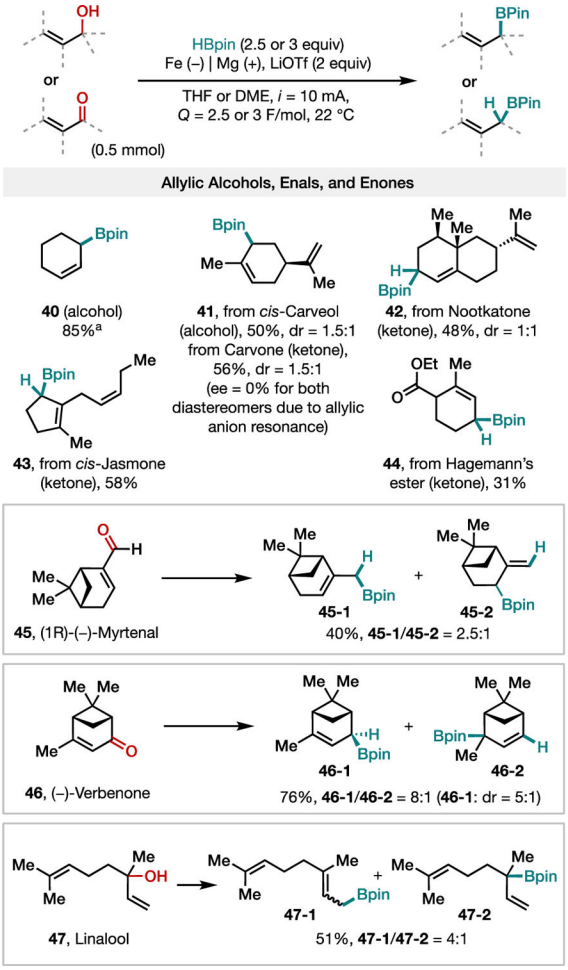
Yields were determined by ^{1}H NMR spectroscopy. [a]Reaction was set up as usual with electrodes but without applying an electric current. [b]Reactions were set up without electrodes and without applying an electric current.



Scheme 3.

Reaction scope for benzylic alcohols, aldehydes, and ketones

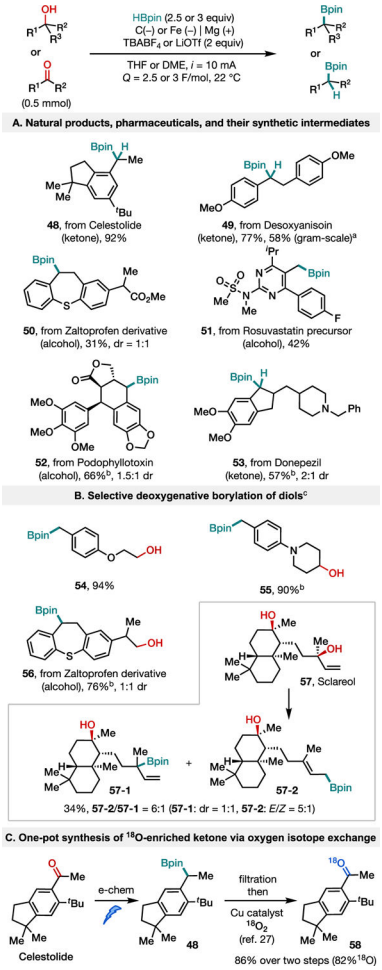
Isolated yields are reported unless otherwise noted. [a]Determined by ^{1}H NMR spectroscopy. [b]Using a mixture of HBpin (1.1 equiv) and MeOBpin (2.0 equiv) and LiOTf as the electrolyte in DME. [c]Et_3N (1 equiv) was added and the reaction was pre-stirred for 5 h before electrolysis.



Scheme 4.

Scope for allylic substrates

[a]Determined using gas chromatography.



Scheme 5.

Synthetic applications

[a]Isolated yield for reaction on a 5 mmol scale. [b]Yields were determined using ^{1}H NMR spectroscopy. [c]4 equiv of HBpin was used and 0.5 equiv of K_2CO_3 was added.