Deoxygenative Suzuki-Miyaura Arylation of Tertiary Alcohols

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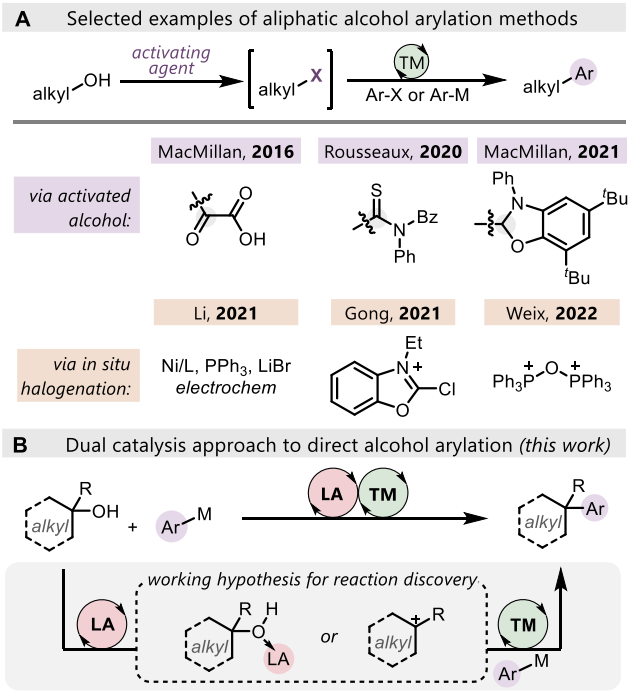
Abstract

The coupling of tertiary alcohols with boronic esters is described, providing a direct access to quaternary carbon scaffolds without needing to proceed by a highly activated intermediate such as an alkyl halide. A dual catalyst system is employed with both Ni(0) and Bi(III) components playing a critical role along with a mild chlorosilane reactant that enhances the yield by alcohol silylation. This method was found to tolerate diverse functional groups including chloro, nitro, olefin, ketone, ester and phenol moieties, while also being applicable to the derivatization of heterocyclic scaffolds. Mechanistic studies suggest the combination of Lewis acid catalyst and organosilane promote heterolytic cleavage of the substrate C–O bond by an S_N1-like reaction pathway, providing a powerful strategy for derivatizing readily available alcohols.

Cross-coupling reactions are among the most utilized reactions in the contemporary pharmaceutical industry, with Suzuki-Miyaura coupling standing out primarily due to the ease of handling, commercial availability, and mildness of organoboron reactants.[1, 2] With aryl halides and pseudohalides as the most common and reliable electrophilic coupling partners,[3, 4] there is demand for better methods to engage C(sp^3)-hybridized electrophiles[5, 6] and for the use of surrogates for halides, such as C–O bonds.[7, 8]

In recent years, several strategies have emerged to enable alcohols to participate in cross-coupling chemistry. For example, unprotected alcohols bearing a nearby π-electron system such as phenols,[9, 10] benzyl alcohols[11, 12] and allylic alcohols[13] have been shown to be sufficiently activated to undergo catalytic arylation. Towards reacting aliphatic alcohols, stoichiometric activation of the C(sp^3)–O bond to provide a reactive intermediate that may either be isolated or formed in situ has emerged as a powerful strategy. For instance, oxalates[14], thiocarbamates[15], and NHC-alcohol adducts[16] have all been demonstrated to participate in deoxygenative arylation chemistry, [17-19] while electrochemical activation,[20] oxazolium salts,[21] or triphenylphosphonium anhydride[22] have been demonstrated to enable alcohol coupling by in situ halogenation and subsequent arylation.

Scheme 1. Strategies for cross-coupling of unprotected alcohols



Lewis acid catalysis is another powerful strategy to facilitate activation and derivatization of alcohols via an S_N1-type pathways.[23] While this approach is primarily documented with traditional nucleophiles, we speculated that a similar approach may enable direct alcohol arylation by trapping with a transition metal catalyst and organoboron reagent, providing a more direct pathway to alcohol arylation than recently reported stoichiometric activation methods.[24-26] Disclosed herein are our efforts towards this goal, culminating in a direct and general method for arylating cyclic tertiary alcohols to form quaternary carbon centers.

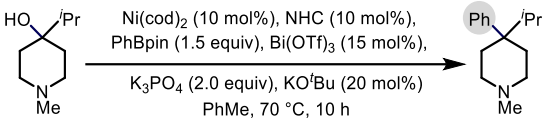
With the working hypothesis that a dual transition metal/Lewis acid co-catalyst system to enable direct alcohol arylation (Scheme 1B), a high throughput screening campaign .was carried out to investigate different metals, ligands, Lewis acids, and organometallic nucleophiles.[27] A hit was identified when using a combination of Ni(0), an atypical ligand bearing two NHC units,[28] $Bi(OTf)_3$ as a mild Lewis acid,[29] and PhBpin, which enabled the functionalization of piperidinol **1** to provide arylated product **2** in 16% yield (Table 1, entry 1). Lewis acid-catalyzed activation of alcohols has often been facilitated by the addition of organosilane reagents.[30-32] In our reaction, introducing dimethyldichlorosilane (Me_2SiCl_2) led to an increased yield of 34% (entry 2).[33] Pre-mixing the alcohol with the organosilane to first form the intermediate silyl ether led to a further increase in the yield to 73% (entry 3). The nature of the NHC ligand proved important, with more common ligands like IPr and ICy being ineffective (entries 4, 5). Running the reaction in the absence of either the Ni or $Bi(OTf)_3$ provided no evidence of arylation, confirming the importance of the dual catalytic conditions.

To explore the scope of this deoxygenative arylation, a range of *N*-methyl-piperidinyl scaffolds were first examined. Variously sized substitutions adjacent to the alcohol were tolerated with larger groups generally providing higher yields (**2**-**5**). A vinyl group (**6**) and an allyl group (**7**) were also tolerated with no evidence of isomerization or rearrangement. Heterocyclic substituents including pyridine (**8**) and furan (**9**) were tolerated, albeit in low yields. No product was obtained upon placing an electron-withdrawing group adjacent to the reactive center (**10**) or upon subjecting a secondary alcohol (**11**) to this methodology.

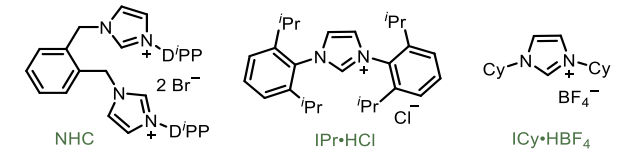
An assortment of cyclic hydrocarbon rings ranging in size from 4-10 carbons were next arylated (**12-17**), as was 1-adamantanol (**18**), a tetrahydropyran (**19**) and a cyclohexenol (**20**). The arylation of various bioactive scaffolds was also evaluated, enabling the preparation of derivatives

of desmethylvenlafaxine (**21**), loperamide (**22**) and cedrol (**23**). While we found that tertiary cyclic alcohols were privileged substrates in this reaction,[34] primary (**24, 25**) and secondary (**26**) alcohols could also be arylated provided they were located adjacent to a π-system.

Table 1. Reaction Optimization



Entry	Deviation from initial conditions	yield[a]
1	none	16%
2	with 1 equiv Me_2SiCl_2	34%
3	with 1 equiv Me_2SiCl_2 *pre-mixed*[b]	77%
4	as in entry 3, IPr•HCl instead of NHC	6%
5	as in entry 3, ICy•HBF_4 instead of NHC	9%
6	*as in entry 3,* no $Bi(OTf)_3$ *or* no $Ni(cod)_2$	0%

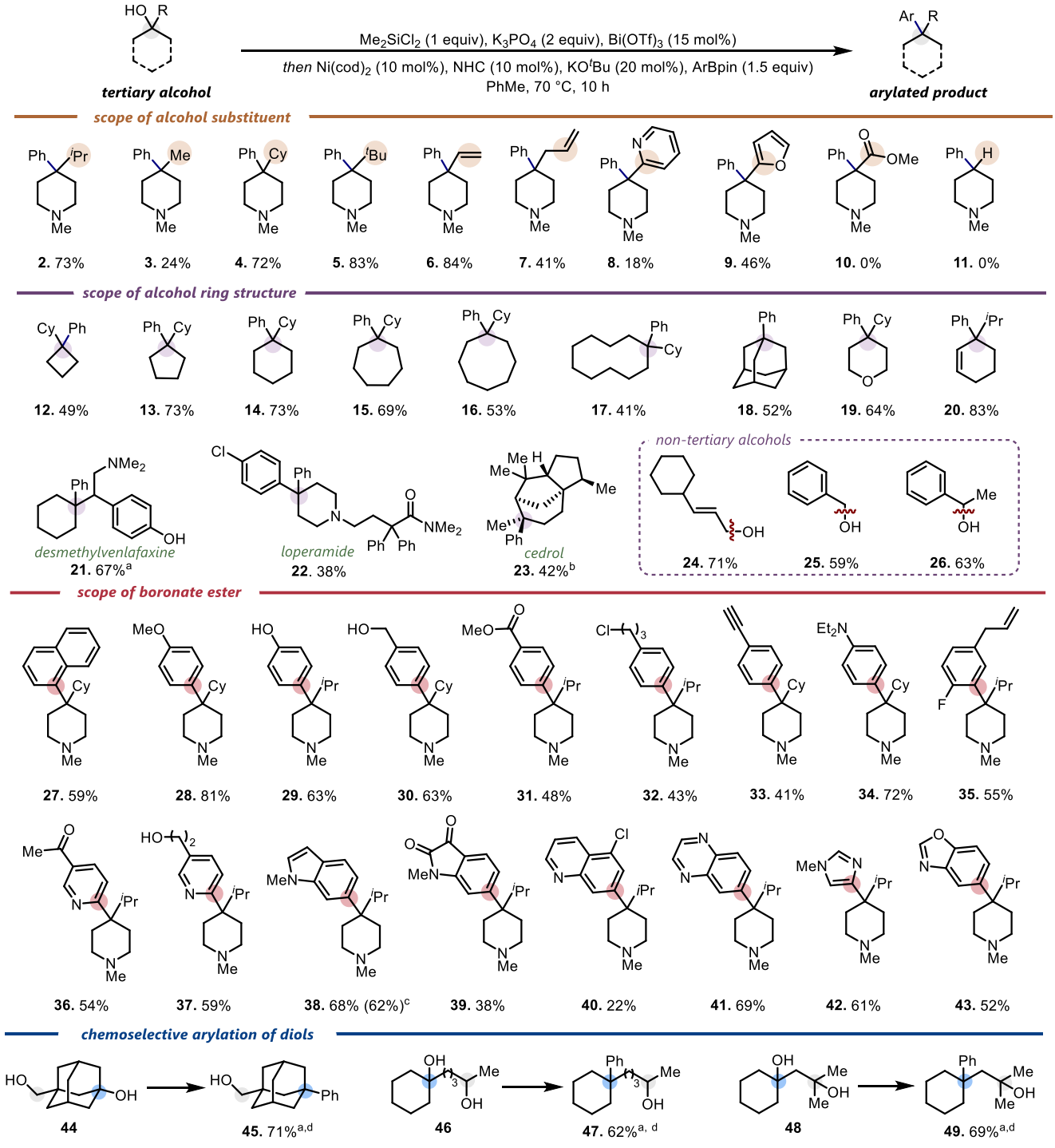


General reaction conditions: 0.20 mmol starting material, 0.02 mmol $Ni(cod)_2$, 0.02 mmol NHC ligand, 0.30 mmol PhBpin, 0.03 mmol $Bi(OTf)_3$, 0.20 mmol Me_2SiCl_2, 0.40 mmol K_3PO_4, 0.04 mmol KO^{t}Bu in 0.8 mL PhMe. [a]yields acquired by GC-FID using 1,3,5-trimethoxybenzene as internal standard. [b]starting material (0.20 mmol) stirred with Me_2SiCl_2 (0.20 mmol) and K_3PO_4 (0.40 mmol) in 0.4 mL PhMe at rt for 30 minutes before adding other reagents.

Functional group compatibility was further investigated by varying the structure of the boronate ester coupling partner (**27-43**). Notable examples demonstrate tolerance of unprotected O-H groups (**29**, **30**, **37**), halogens (**32**, **35**, **40**), and heterocycles (**36-43**). A gram-scale reaction was performed at reduced catalyst loading to reveal indole **38** in yields reflective of the optimized conditions. Lastly, we investigated if the coupling of diols could occur chemoselectively. Using 3 equiv of chlorosilane, cyclic tertiary alcohols bearing a primary (**44**), secondary (**46**), or tertiary acyclic (**48**) alcohol provided good yields of the monoarylated product after work-up with TBAF.

Armed with an adequate knowledge of the reaction scope and functional group tolerance, we sought to gain mechanistic insight. The silane additive was confirmed to silylate the alcohol under the reaction conditions and various silyl ethers were shown to undergo arylation without the need for additional chlorosilane, confirming that the silyl ether is a viable reactive intermediate

Scheme 2. Reaction scope of the arylation reaction



General reaction conditions: 0.20 mmol starting material, 0.02 mmol $Ni(cod)_2$, 0.02 mmol NHC ligand, 0.30 mmol PhBpin, 0.03 mmol $Bi(OTf)_3$, 0.20 mmol Me_2SiCl_2, 0.40 mmol K_3PO_4, 0.04 mmol KO^tBu in 0.8 mL PhMe. [a]0.60 mmol K_3PO_4. [b]*d.r.* 2.6:1. [c]Yield obtained upon reacting 1.0 g (6.37 mmol) of substrate; 0.64 mmol $Ni(cod)_2$, 0.64 mmol NHC ligand, 1.28 mmol KO^tBu. [d]0.60 mmol Me_2SiCl_2; 0.40 mmol TBAF added upon reaction completion.

(see Supporting Information Table S12). The corresponding alkyl chloride and alkyl triflate were also prepared and found to be ineffective starting materials, suggesting that the in situ halogenation mechanism is not operative.[20-22]

During the reaction discovery and screening efforts, a mechanism in which a reactive carbocation intermediate was generated and intercepted was envisioned. An alternative pathway involves dehydration to the olefin and subsequent metal-catalyzed hydroarylation.[35, 36] Indeed, olefins such as compound **50** were commonly observed in the crude reaction mixture. However, subjecting **50** directly to the standard reaction conditions did not afford arylated product, indicating it is a side-product rather than a reactive intermediate. Another alternative pathway may involve formation of a carbon-centered radical, as commonly proposed in the coupling of alkyl halides.[37, 38] However, this reaction was found to be unaffected by the presence of TEMPO or other radical scavenging reagents (Scheme 3A). Further, cyclopropane (**51**) [39] and 5-hexenyl (**54**)[40] bearing substrates were arylated to form products **52** and **55** without evidence of rearrangement products **53** and **56**, which would be expected if a carbon-centered radical was formed.

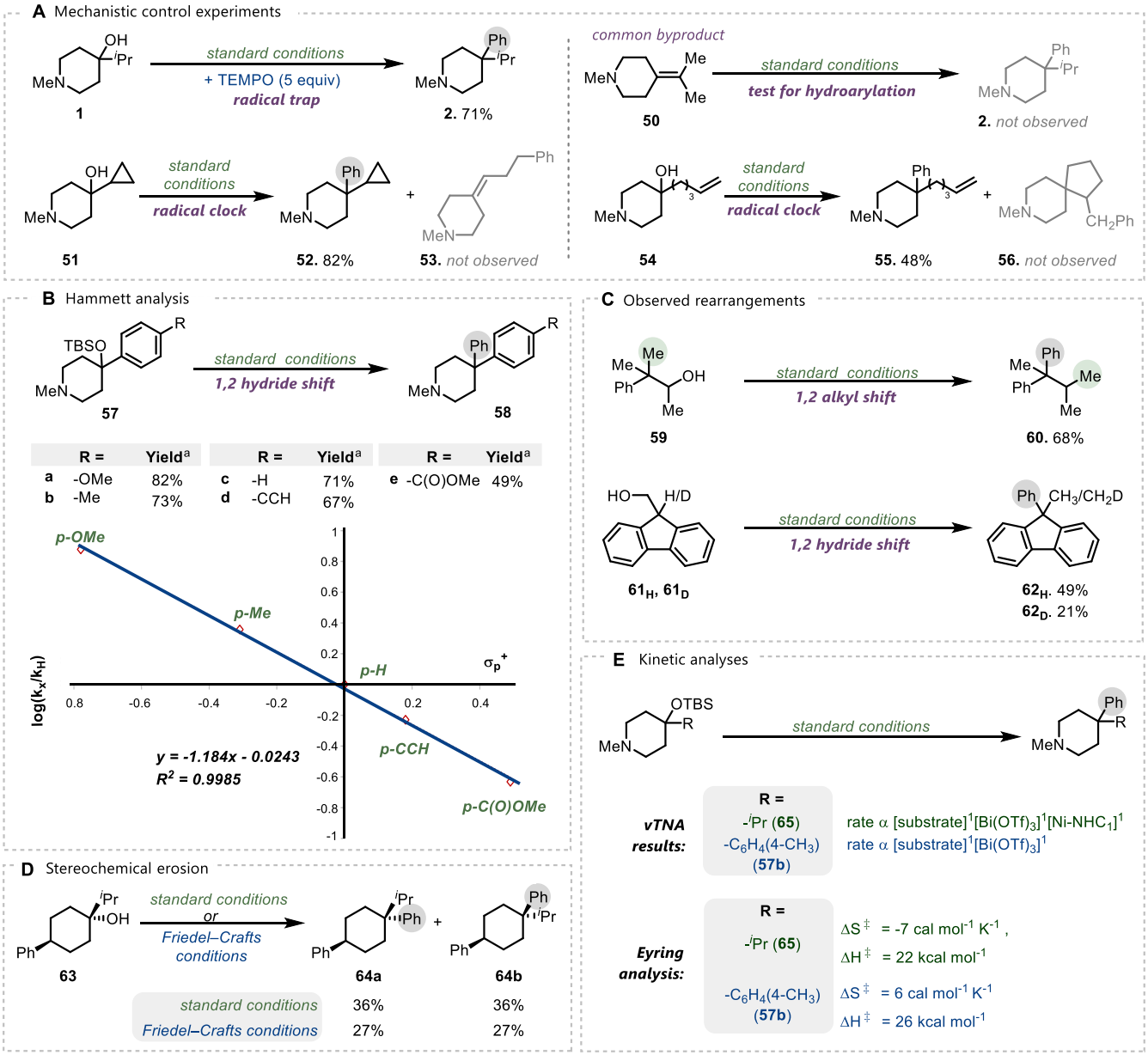
Towards exploring the plausibility of a carbocation intermediate, a Hammett study was carried out on a series of silylated alcohols with varying electronic properties (Figure 3B).[41] Silyl ethers **57a-e** were found to be smoothly arylated under the reaction conditions to afford piperidines **58a-e** with the lowest yields resulting from the more electron-deficient alcohols. The same trend was observed when studying the reaction kinetics – more electron-deficient alcohols led to slower rates of reaction. A linear relationship was observed upon plotting the normalized rate constants against the σ_p^+ parameter, with a ρ value of -1.19 suggesting a substantial buildup of positive charge in the transition state in this particular benzylic example.[42]

Carbocations are known to be susceptible to rearrangements such as 1,2-alkyl and 1,2-hydride shifts. Accordingly, substrate **59**, and **61H** were prepared, which we speculated would rearrange if a carbocation is a reaction intermediate Scheme 3C). Rearranged scaffolds **60** and $\mathbf{62_H}$ were observed as the only identifiable arylation products. Furthermore, the deuterated analog $\mathbf{61_D}$ was also found to rearrange to $\mathbf{62_D}$, albeit in just 21% yield, suggesting a more sluggish migration of deuterium.

To probe if the reaction proceeds by retention, inversion, or loss of stereochemical information, diastereomerically pure alcohol **63** was subjected to the general reaction conditions

(Scheme 3D). Diastereomeric products **64A** and **64B** were obtained in a 1:1 ratio. The same substrate was subject to Friedel-Crafts conditions (refluxing sulfuric acid in benzene),[43] and was found to provide the same ratio of products, suggesting a similar reactive intermediate is likely.

Scheme 3. Examining reactive intermediates



Lastly, kinetic analysis was performed on alcohols **57b** and **65** according to the variable time–normalization analysis method.[44] For tertiary aliphatic alcohol **65**, results suggest positive, apparent first order involvement of the substrate, Ni-NHC catalyst and Lewis-acid catalyst at the transition state of this reaction (Scheme 3E). In contrast, tertiary benzylic silyl ether **57b** exhibited

first-order dependence on *only* the substrate and $Bi(OTf)_3$. While all data thus far was supportive of the presence of an S_N1-type pathway, we were surprised at the suggested rate dependence of Ni in the arylation of **65**. We thus conducted an Eyring analysis[45] on both substrates, revealing a positive entropy of activation for **57b** and a negative entropy of activation in **65**, further corroborating the different rate equations observed in the kinetic analysis. Collectively, this data suggests that the benzylic alcohol **57b** may be arylated via a carbocation in an S_N1-like process with Lewis acid catalysis alone, while the Ni-catalyst may be involved in the arylation of the aliphatic alcohol **65**. [46-48] Further efforts are underway to further understand the nature of the key C–O bond cleavage step, the origin for high selectivity towards tertiary cyclic alcohols, and how the reactive carbocation-like intermediate may react with the Ni catalyst and organoboronate ester to form new C–C bonds.

In summary, we have described a straightforward method to directly arylate unactivated tertiary alcohols with organoboron reagents. A Ni(0) catalyst is used in concert with a mild Lewis acid, enabling coupling a broad scope of arenes including those bearing heterocyclic rings, carbonyl groups, halides, and more. Chemoselectivity is demonstrated for polyols, with arylation occurring selectively on tertiary cyclic alcohols. The observation of rearranged products, stereochemical erosion, a strong Hammett relationship, and first order rate dependance on substrate and Lewis acid are consistent with an S_N1-like alcohol activation process, which to our knowledge is a largely undeveloped strategy for facilitating cross-coupling reactions with bulky aliphatic coupling partners.

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