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Research Article

Borane-Catalyzed C(sp^3)–F Bond Arylation and Esterification Enabled by Transborylation

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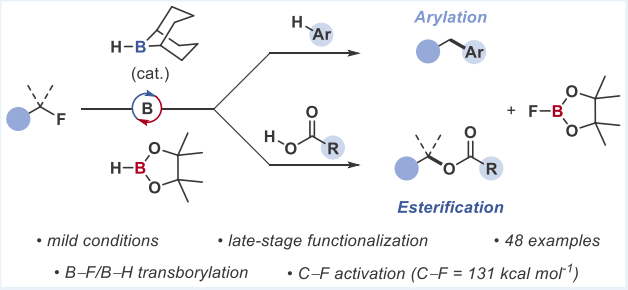
ABSTRACT: The activation and functionalization of carbon–fluorine bonds represent a significant synthetic challenge, given the high thermodynamic barrier to C–F bond cleavage. Stoichiometric hydridoborane-mediated C–F functionalization has recently emerged, but is yet to be rendered catalytic. Herein, the borane-catalyzed coupling of alkyl fluorides with arenes (carbon–carbon bond formation) and carboxylic acids (carbon–oxygen bond formation) has been developed using transborylation reactions to achieve catalytic turnover. Successful C–C and C–O coupling across a variety of structurally and electronically differentiated arenes and carboxylic acids was achieved using 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN) as the catalyst and pinacolborane (HBpin), with broad functional group tolerance. Experimental and computational studies suggest a mechanistic dichotomy for the carbon–carbon and carbon–oxygen coupling reactions. B–F transborylation (B–F/B–H metathesis) between F-*B*-9-BBN and HBpin enabled catalytic turnover for carbon–carbon bond formation, whereas direct exchange between the alkyl fluoride and acyloxyboronic ester (C–F/B–O metathesis) was proposed for carbon–oxygen coupling, where H-*B*-9-BBN catalyzed the dehydrocoupling of the carboxylic acid with HBpin.



KEYWORDS: *boron, arylation, esterification, bond-metathesis, C–F activation, ligand exchange, main group, transborylation*

The carbon–fluorine bond is the strongest single bond in organic chemistry (99 to 131 kcal mol^{-1}),[1] and thus, the catalytic functionalization of C–F bonds remains a significant challenge. Unlike the activation of other carbon–halogen bonds, C–F functionalization is less developed,[2,3] with only a limited number of examples reported to be mediated by main-group species.[4,5] Strong Lewis acids, including BF_3,[6] aluminum species,[7−11] low oxidation-state main-group compounds, such as Al(I) or Mg(I) species,[5,12−16] cationic silicon[17,18] and phosphonium complexes,[19,20] and HF[21−24] have been used for the functionalization of C–F bonds. These methods either required forcing reaction conditions or the use of highly reactive species. Overcoming the large thermodynamic barrier to C–F functionalization under mild conditions using main-group species presents a significant challenge. Stephan and, independently, Crimmin have shown that hydridoboranes undergo activation of C–F bonds, where the formation of a B–F product is proposed to provide a thermodynamic driving force for the reaction (Figure 1a).[25−27] The high bond strength of main-group-element–fluoride bonds presents a significant barrier to catalysis. For example, the B–F bond is up to 150 kcal mol^{-1}; so not only must the C–F bond strength be overcome, but also the B–F bond for catalyst turnover.[1]

Transborylation, boron–boron exchange, has emerged as a potential mechanism to enable the stoichiometric reactivity of organoboranes to be translated to catalysis. Boron–carbon (B–C/B–H metathesis)[28−33] and boron–oxygen (B–O/B–H metathesis)[34−37] transborylation have been used as turnover steps in boron-catalyzed hydroboration reactions and the C–H borylation of heterocycles.[38,39] Although stoichiometric exchange of B–F bonds has been achieved,[40−42] to the best of our knowledge, no catalytic examples have been reported. If B–F transborylation (B–F/B–H metathesis) could be developed, this would allow borane-mediated C–F bond functionalization to be rendered catalytic. However, the large thermodynamic barrier to turnover would need to be overcome and at a rate that facilitates synthetically useful turnover frequency. Herein, the C–F functionalization of alkyl fluorides has been developed for the formation of carbon–carbon and carbon–oxygen bonds using, commercially available, 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN) as the catalyst and pinacolborane (HBpin) as the turnover reagent (Figure 1b).

To validate the possibility of using B–F transborylation as a mechanism of catalytic turnover, single-turnover experiments were conducted for the Friedel–Crafts-type arylation of 4-(*tert*-butyl)benzyl fluoride **1a** with d_6-benzene **2a** (Scheme 1).[25,26]

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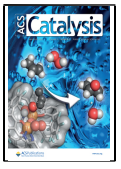


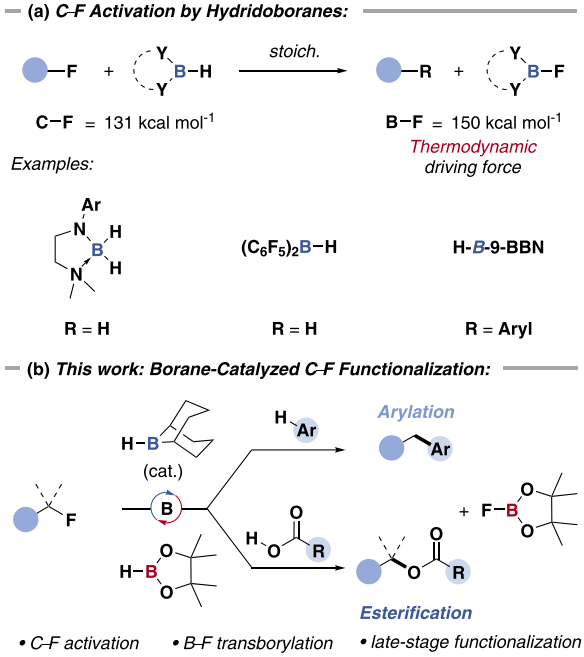


Figure 1. Examples of C−F functionalization with main-group compounds.

Reaction of benzyl fluoride **1a** with 0.5 equiv of $[H\text{-}9\text{-}B\text{-}BBN]_2$ **3** in d_6-benzene/$CDCl_3$ (1:2) was monitored by ^{11}B and ^{19}F NMR spectroscopies (Scheme 1a). $[H\text{-}B\text{-}9\text{-}BBN]_2$ **3** (δ ^{11}B = 28 ppm) was consumed within 30 min, and the formation of F-*B*-9-BBN **5** (δ ^{11}B = 64 ppm, δ ^{19}F = −46 ppm) was observed. Importantly, the rate of F-*B*-9-BBN **5** formation was observed to be consistent with the rate of formation of the C−C coupled product, 4-(*tert*-butyl)benzyl benzene **4a**. Upon the addition of HBpin **6** (δ ^{11}B = 29 ppm), the amount of F-*B*-9-BBN **5** decreased with concurrent formation of FBpin **7** (δ ^{11}B = 21 ppm, δ ^{19}F = −151 ppm) and, significantly, the regeneration of $[H\text{-}B\text{-}9\text{-}BBN]_2$ **3** (δ ^{11}B = 28 ppm) was observed (Scheme 1b).[43] Thus, the potential of B−F transborylation as a method for catalytic turnover had been established. To further support B−F transborylation, independently prepared F-*B*-9-BBN **5**[44] was reacted with two equivalents of HBpin **6** and again the formation of FBpin **7** was observed at the same rate as the loss of F-*B*-9-BBN **5**, as monitored by ^{11}B NMR spectroscopy over 10 min (Scheme 1c). An energy profile for B−F/B−H transborylation between F-*B*-9-BBN **5** and HBpin **6** was calculated using DFT [ωB97XD/6-311++G(d,p)], and the barrier was found to be relatively large (25.8 kcal mol^{-1})[45] when compared to B−C(sp^2)/B−H (20.3 kcal mol^{-1})[30] and B−O/B−H (22.7 kcal mol^{-1})[37] transborylation (Scheme 1d), although the barrier was lower than B−C(sp^3)/B−H (28 kcal mol^{-1}) transborylation.[32] The overall reaction was found to be exergonic, following H-*B*-9-BBN dimersation.[30,46]

To translate the stoichiometric B−F transborylation to catalysis, the arylation of benzylic C−F bonds[26] was investigated (Table 1). 4-(*tert*-Butyl)benzyl fluoride **1a** was reacted with sub-stoichiometric $[H\text{-}B\text{-}9\text{-}BBN]_2$ **3** (5 mol %) in the presence of excess d_6-benzene **2a** and HBpin **6** (1 equivalent) at 30 °C to give the corresponding diaryl methane in 95% yield, showing the viability of B−F transborylation for catalytic turnover (for full optimization see Supporting Information). Control reactions without H-*B*-9-BBN **3** or HBpin **6** gave no reactivity. Benzyl chlorides and bromides were unreactive, presumably as H-*B*-9-

Scheme 1. (a) Stoichiometric H-*B*-9-BBN-Mediated C−F Arylation; (b) B−F/B−H Transborylation; (c) B−F/B−H Transborylation from Independently Prepared F-*B*-9-BBN; and (d) Density Functional Theory (DFT)-Computed Free Energies for B−F/B−H Transborylation [ωB97XD/6-311++G(d,p), kcal mol^{-1}]

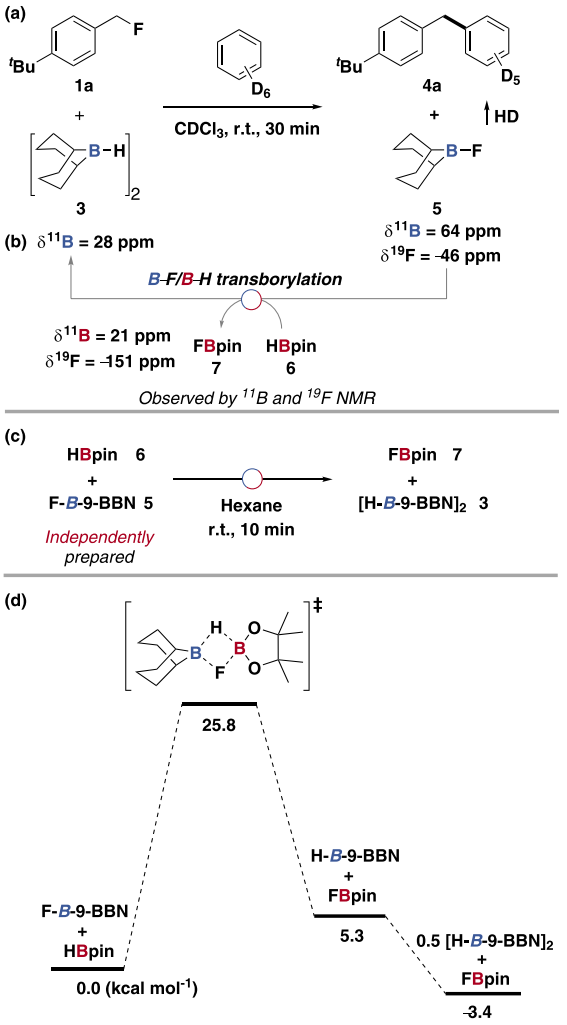
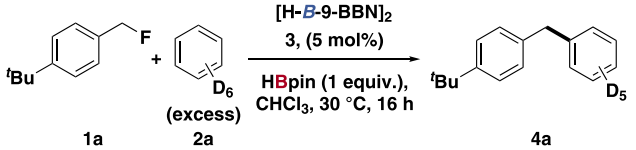


Table 1. H-*B*-9-BBN-Catalyzed C−F Arylation Control Reactions



deviation from conditions	yield (%)
none	95
No $[H\text{-}B\text{-}9\text{-}BBN]_2$	0
neat	0
1 equiv C_6D_6	trace
benzyl chloride (no BnF)	0
benzyl bromide (no BnF)	0

[a]Yields obtained by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. 4-(*tert*-Butyl)benzyl fluoride (1 equiv), C_6D_6 (23 equiv), HBpin (1 equiv), $CHCl_3$ (1 M), and $[H\text{-}B\text{-}9\text{-}BBN]_2$ (5 mol %).

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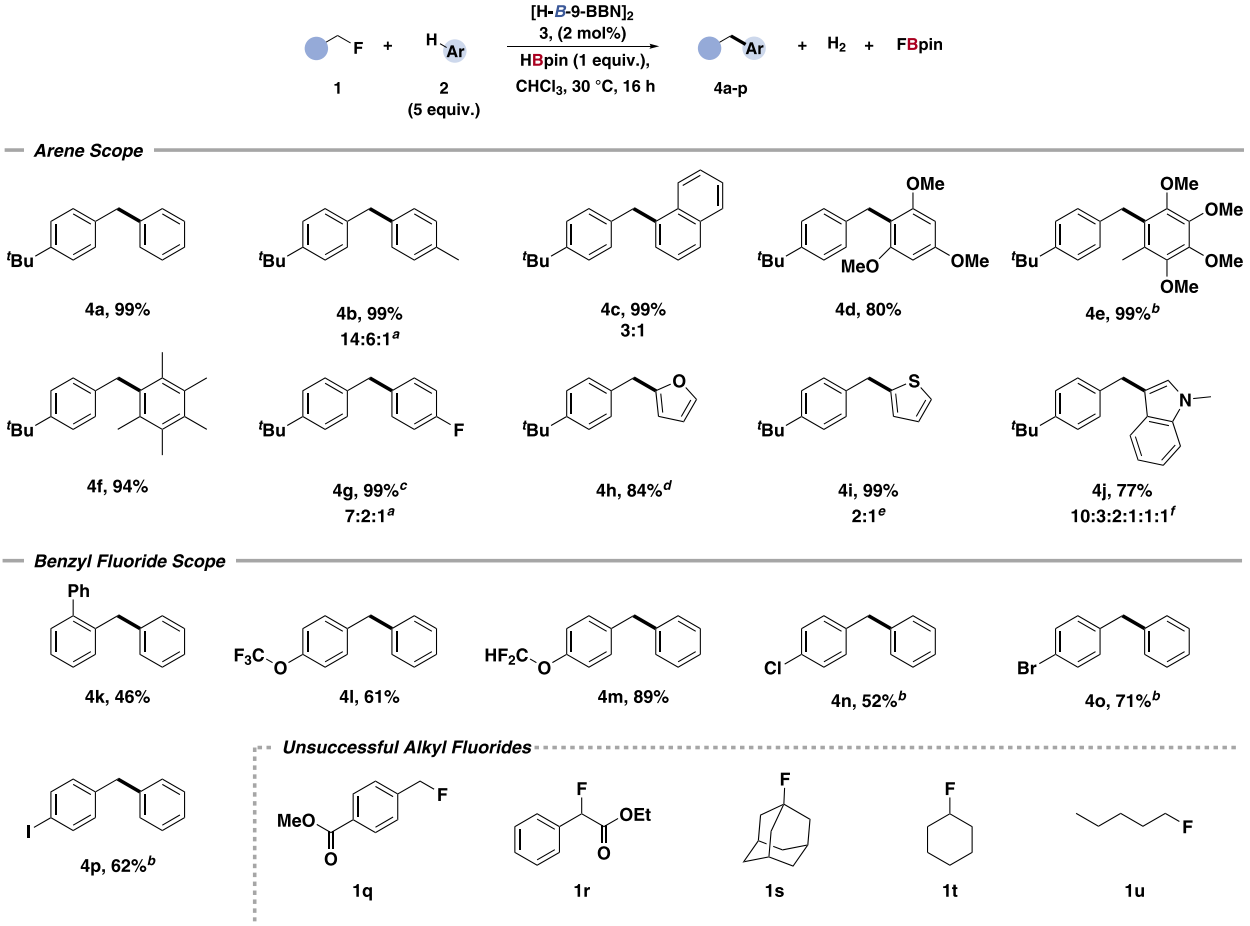
Table 2. Scope of Borane-Catalyzed C−F Arylation[a]



[a]Reaction conditions: benzyl fluoride, arene (5 equiv), HBpin (1 equiv), [H-*B*-9-BBN]$_2$ (2 mol %), $CHCl_3$ (1 M), 30 °C, and 16 h. Isolated yields reported. [b]Ratio of the para/ortho/meta isomers. [c]Temperature = 60 °C. [d]Time = 48 h [e]10 equiv of arene used. [f]Ratio of the 2-:3-isomers. [g]Ratio of the 3-:2-:*x*-isomers (see Supporting Information).

BBN **3** is not a strong enough Lewis acid to initiate the Friedel−Crafts-type reaction.

The scope and limitations of the boron-catalyzed C−C coupling were investigated using 4-(*tert*-butyl)benzyl fluoride **1a** at 30 °C with five equivalents of arene **2** (Table 2, and see Supporting Information). Arenes bearing electron-donating groups such as toluene, naphthalene, and 1,3,5-trimethoxybenzene gave high yields and regioselectivity of the diarylmethane products **4b**, **4c,** and **4d**, respectively, with the regioselectivity equaling that achieved using stoichiometric borane.[26] Highly substituted arenes were also tolerated, giving hexa-substituted arenes, **4e** and **4f**, as dictated by the reagent substitution pattern. Reaction of fluorobenzene gave 1-benzyl-4-fluorobenzene **4g** in 99% yield and good regioselectivity, showing chemoselective functionalization of the alkyl fluoride over the aryl fluoride bond. Heterocycles were successfully coupled to give the furan **4h**, thiophene **4i**, and *N*-methylindole **4j** C−F arylation products. However, strongly coordinating arenes such as pyridine were found to be unreactive.

The use of substituted benzyl fluorides was next explored. An *ortho*-phenyl group **4k** was tolerated without intramolecular coupling. Trifluoromethoxy and difluoromethoxy substituents were tolerated to give 4-benzyl-α,α,α-trifluoromethoxybenzene **4l** (61%) and 4-benzyl-α,α-difluoromethoxybenzene **4m** (89%), respectively, again showing chemoselectivity for arylation at the benzylic C−F bond. The chloro- **4n**, bromo- **4o**, and iodo-arenes **4p** were all chemoselectively coupled at the C−F bond without any loss of the aryl halide or decrease in regioselectivity, although a higher reaction temperature of 60 °C was required. The chemoselectivity of the reaction for the benzyl fluoride offers a simple means for further functionalization of the aryl halide products by classical cross-coupling reactions. Electron-withdrawing substituents, such as a potentially reducible ester (**1q**, **1r**), were not tolerated. Fluorocyclohexane **1s**, 1-fluoropentane **1t**, and 1-adamantylfluoride **1u** gave no conversion, even upon heating to 80 °C, presumably because of the increased C−F bond strengths of these substrates (e.g., benzyl fluoride C−F = 99 kcal mol^{-1}; **1t** C−F = 114 kcal mol^{-1}).[1]

The intermediacy of a formal carbocation presented the possibility of diverse functionalization through trapping by other nucleophiles[19,22,26] and expansion of this transformation beyond Friedel−Crafts-type C−C bond formation. Carboxylic acids **8** were found to give the C−O coupled ester products **9a−ae** (Table 3), a formal nucleophilic substitution at an alkyl C−F bond. Control reactions showed no background C−F substitution by the carboxylic acid (see Supporting Information for details).[6] For C−O coupling, ethyl acetate was found to be the optimal reaction solvent, giving a high yield of the ester in 1 h at room temperature with only one equivalent of the carboxylic

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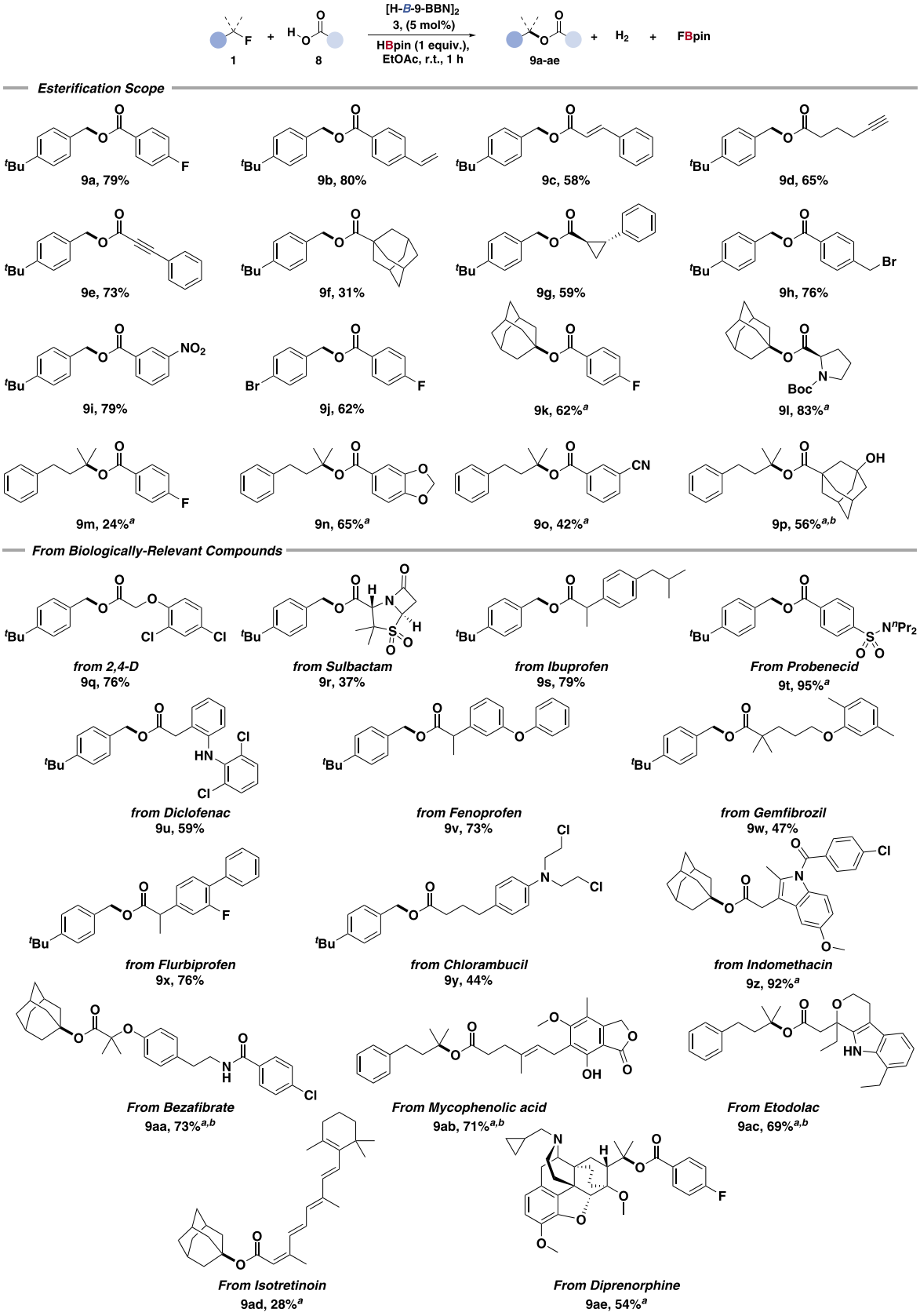
Table 3. Scope of Borane-Catalyzed C−F Esterification[a]



[a]Reaction conditions: Alkyl fluoride, carboxylic acid (1 equiv), HBpin (1 equiv), $[H\text{-}B\text{-}9\text{-}BBN]_2$ (5 mol %), EtOAc (0.33 M), room temperature, and 1 h. Isolated yields reported. a = 16 h and b = HBpin (2 equiv), followed by the $MeOH/SiO_2$ workup.

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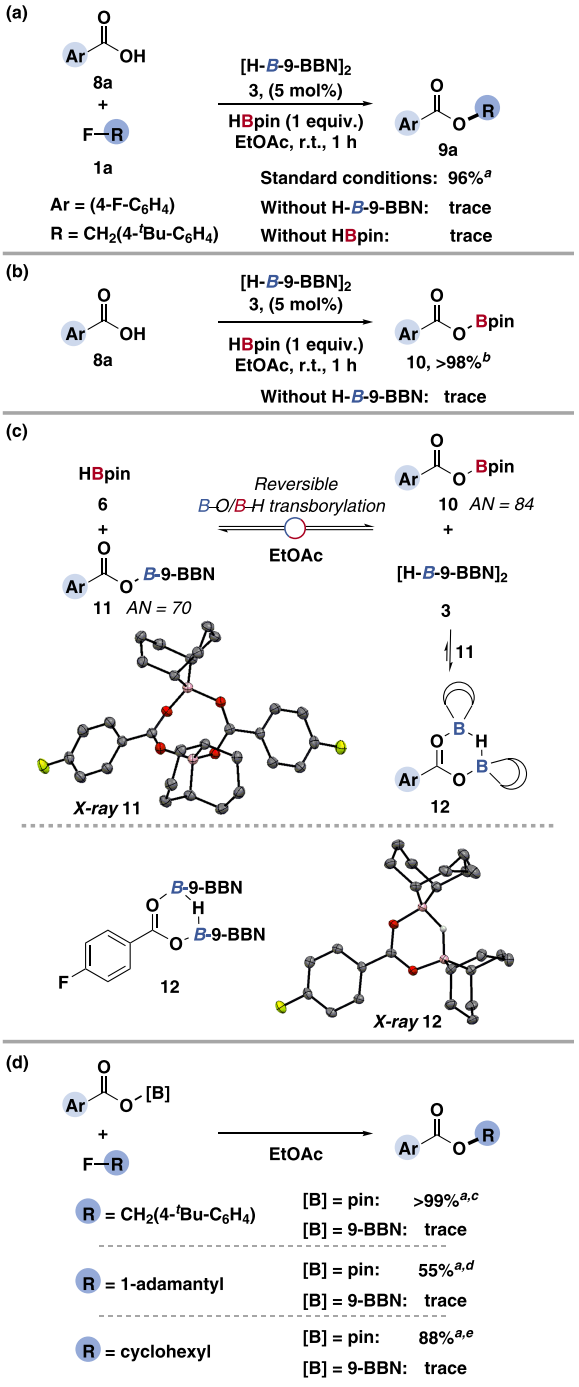
acid required. Broad functional group tolerance was observed, which was significantly greater than the C−C coupling reaction. An aryl fluoride **8a** underwent chemoselective alkyl fluoride bond functionalization. Reducible functional groups, such as alkenes and alkynes **8b**−**8e**, were tolerated under reaction conditions without any borane-catalyzed hydroboration[28] or other deleterious reactivity observed. The sterically demanding carboxylic acid, 1-adamantanecarboxylic acid **8f**, gave a good yield of the ester product **9f**. A cyclopropyl-containing carboxylic acid **8g** was tolerated, without formation of products resulting from ring-opening, suggesting an ionic rather than a radical mechanism.

Coupling of 4-bromomethylbenzoic acid **8h** was chemoselective for C−F esterification **9h**, with no reaction at the benzyl bromide bond observed. Electron-withdrawing groups, such as a nitro group **9i**, were preserved under reaction conditions. 1-Adamantyl fluoride was successfully coupled to the adamantyl ester **9k** in good yield after 16 h. *N*-Boc-proline **8l** was reacted to give the corresponding adamantyl ester **9l** without loss of the carbamate. A further tertiary alkyl fluoride was also coupled, showing unique reactivity when compared to traditional esterification methods. 2-Fluoro-2-methyl-4-phenylbutane gave the corresponding tertiary ester **9m** when coupled to 4-fluorobenzoic acid. Furthermore, acetal-bearing carboxylic acid **8n** was coupled in good yield to the corresponding ester **9n** without hydrolysis of the acetal. A nitrile-substituted carboxylic acid **8o** was tolerated without any reduction of the nitrile observed. Using an extra equivalent of HBpin, a tertiary alcohol **8p** was tolerated to give ester **9p** in high yield.

Late-stage esterification was carried out on a number of biologically relevant carboxylic acids **9q**−**9ae** with a large degree of functional group diversity tolerated. The β-lactamase inhibitor, sulbactam, which contains lactam and sulfone groups, gave a modest yield of the corresponding ester **9r**. The nonsteroidal anti-inflammatory drug (NSAID), diclofenac, which contains a secondary amine, gave a good yield of the ester **9u** without dehydrocoupling of the amine observed.[47] Indomethacin, another NSAID, gave the corresponding adamantyl ester **9z** in 92% isolated yield, improving on traditional esterification methods for the same substrate (55%).[48] Using an extra equivalent of HBpin, an amide **8aa**, alcohol **8ab**, and unprotected indole **8ac** were coupled in high yield to the corresponding esters **9aa-ac**, respectively, where *N*/*O*-Bpin is presumably acting as a traceless protecting group.[32,49,50] The highly conjugated carboxylic acid isotretinoin **8ad**, gave a modest yield of the corresponding adamantyl ester **9ad**. A deoxy-fluorinated derivative of the opioid antagonist, diprenorphine, reacted with 4-fluorobenzoic acid to give the corresponding ester **9ae** in good yield. Compounds containing ketones and aldehydes were not tolerated in the reaction, as well as highly coordinating groups, such as pyridine.

As previously unreactive alkyl fluorides, such as 1-adamantyl fluoride, were found to be suitable coupling partners in the C−F esterification reaction, the mechanism of esterification was investigated through a series of single-turnover reactions to establish any divergence from the C−C coupling reaction (Scheme 2). The direct esterification of alkyl fluorides has, to the best of our knowledge, not been reported.[51,52] In the absence of [H-*B*-9-BBN]$_2$ or HBpin, only trace ester formation was observed (Scheme 2a). When stoichiometric [H-*B*-9-BBN]$_2$ was used in the place of HBpin, very slow formation of the ester product was observed, suggesting that HBpin played a role other than facilitating turnover. In the absence of alkyl fluoride, the

Scheme 2. Probing Stoichiometric Reactivity



For clarity, all hydrogen atoms except for the bridged borohydride are omitted from the X-ray crystal structures; displacement ellipsoids are drawn at 50% probability. a = yield calculated using fluorobenzene as an internal standard. b = conversion calculated from ^{19}F NMR. c = r.t., 1 h, d = r.t., 16 h, and e = 80 °C, 16 h.

rapid formation of acyloxyboronic ester **10** was observed, indicating that dehydrocoupling was an initial step of catalysis (Scheme 2b). In the absence of H-*B*-9-BBN, HBpin was found to be unreactive with carboxylic acids under reaction conditions, indicating that H-*B*-9-BBN catalyzed the dehydrocoupling reaction (Scheme 2b).

To support this, stoichiometric H-*B*-9-BBN was found to react rapidly with a carboxylic acid **8a** to give the acyloxy-*B*-9-

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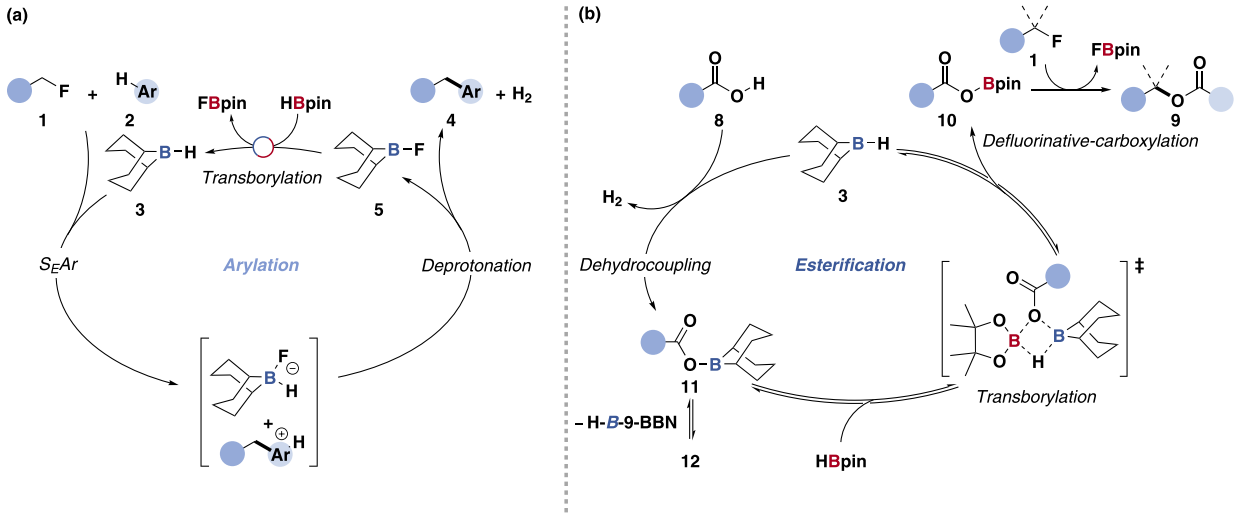
Scheme 3. (a) Proposed Mechanism for H-*B*-9-BBN-Catalyzed C−F Arylation and (b) Proposed Mechanism for H-*B*-9-BBN-Catalyzed C−F Esterification



BBN **11**. Independently prepared 4-fluorobenzoate-*B*-9-BBN **11** was reacted with HBpin in EtOAc, and again 4-fluorobenzoate-Bpin **10** was observed, along with H-*B*-9-BBN-coordinated 4-fluorobenzoate-*B*-9-BBN **12**, the structure of which was determined by X-ray crystallography (Scheme 2c). This B−O/B−H transborylation was found to be reversible; reaction of 4-fluorobenzoate-Bpin **10** with $[H\text{-}B\text{-}9\text{-}BBN]_2$ **3** gave no observable 4-fluorobenzoate-*B*-9-BBN **11**, but the H-*B*-9-BBN adduct **12** was observed (Scheme 2c). 4-Fluorobenzoate-*B*-9-BBN **11** was found to be unreactive with benzyl fluoride **1a** under standard reaction conditions (Scheme 2d). However, 4-fluorobenzoate-Bpin **10** reacted with 4-(*tert*-butyl)benzyl fluoride **1a** to give the corresponding ester **8a** and FBpin **7** at room temperature in EtOAc, as monitored by ^{19}F and ^{11}B NMR spectroscopy (Scheme 2d). Similar reactivity was found for 4-fluorobenzoate-Bpin **10**, 1-adamantyl fluoride **1s**, and cyclohexyl fluoride **1t** to give the esters **9k** and **9af**, respectively (Scheme 2d), though in the latter case, this reactivity was not translated to catalysis and required heating to 80 °C.

To the best of our knowledge, the reactivity of the acyloxyboronic ester **10** toward an alkyl fluoride is unreported and represents unexplored reactivity for organoboron compounds. Modified Gutmann−Beckett analysis[53,54] showed 4-fluorobenoate-Bpin **10** to be more Lewis acidic than 4-fluorobenzoate-*B*-9-BBN **11** (4-fluorobenoate-Bpin **10** AN = 84, 4-fluorobenzoate-*B*-9-BBN **11** AN = 70), suggesting that Lewis acidity controls chemoselectivity and the exclusive ability of the acyloxyboronic ester species to react with alkyl fluorides.

Based on the single-turnover studies, DFT calculations, and catalytic observations, a catalytic cycle with a turnover facilitated by B−F transborylation was proposed for the C−F arylation of alkyl fluorides (Scheme 3a). Dissociation of the borane dimer $[H\text{-}B\text{-}9\text{-}BBN]_2$ **3** and coordination to the benzyl fluoride **1** initiates carbon−carbon bond formation by generation of putative (formal) carbocation and a fluoroborohyride by fluoride extraction. Nucleophilic attack of the arene to give a Wheland intermediate, followed by deprotonation by the fluoroborohydride, generated H_2 and the C−C coupled product **4**.[25] Catalytic turnover was achieved by F-*B*-9-BBN **5** undergoing B−F transborylation with HBpin **6** to give FBpin **7** and regenerate the H-*B*-9-BBN catalyst **3**.

For C−F esterification, a catalytic cycle where instead of B−F/B−H transborylation driving turnover, the boron-mediated direct esterification of the C−F bond was proposed to facilitate catalytic turnover (Scheme 3b). Upon formation of monomeric H-*B*-9-BBN **3**, rapid dehydrocoupling with the carboxylic acid **8** gave the acyloxy-*B*-9-BBN **11** and released dihydrogen. Acyloxy-*B*-9-BBN **11** reversibly formed the corresponding H-*B*-9-BBN adduct **12**. Reversible B−O transborylation with HBpin **6** gave acyloxy-Bpin **10** and regenerated the H-*B*-9-BBN catalyst **3**. The acyloxy-Bpin **10** underwent C−F esterification with the alkyl fluoride **1** and gave the C−O coupled product **9** and FBpin **7**.

In conclusion, the use of transborylation as a turnover mechanism for catalytic C−F arylation and esterification reactions has been demonstrated with broad functional group tolerance. Mechanistic analysis showed that B−F transborylation was performed between F-*B*-9-BBN and HBpin and that this reaction was rapid at room temperature. This B−F transborylation further demonstrates the potential of transborylation for the discovery and development of main group catalysis. Further , a unique mode of C−F functionalization was also demonstrated with acyloxy-Bpin compounds for the formation of esters, which will continue to be explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00282.

General experimental details; system optimization; substrate synthesis; general reaction setup and procedure; product data; synthesis of reactive intermediates; single-turnover experiments; crystal data and experimental details; computational details; and NMR spectra (PDF)

Coordinates for DFT calculations (ZIP)

Crystallographic data for compound 11 (CIF)

Crystallographic data for compound 12 (CIF)

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Author Contributions

D.R.W. performed the practical and computational work. G.S.N. carried out X-ray crystallography. D.R.W and S.P.T. conceived the reactions and wrote the manuscript. S.P.T. advised investigations.

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Notes

The authors declare no competing financial interest.

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