Borane-Catalyzed C(sp3)–F Bond Arylation and Esterification Enabled by Transborylation

Borane-Catalyzed C(sp³)–F Bond Arylation and Esterification Enabled by Transborylation

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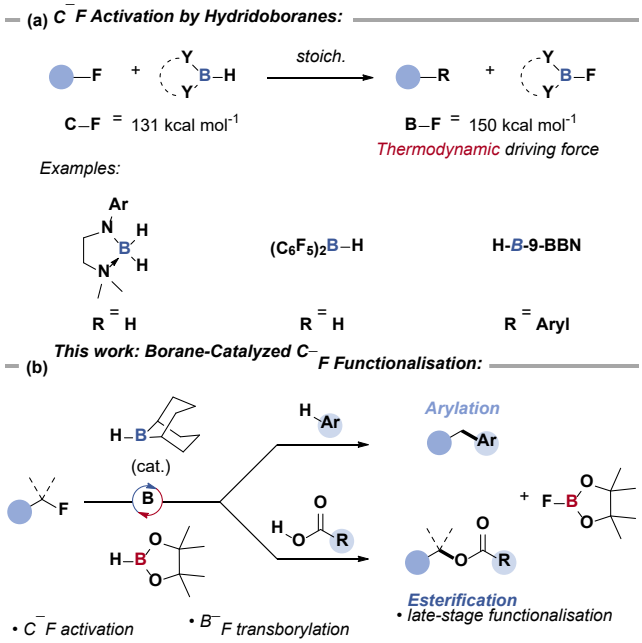
ABSTRACT: The activation and functionalization of carbon–fluorine bonds represents a significant synthetic challenge given the high thermodynamic barrier to C–F bond cleavage. Stoichiometric hydridoborane-mediated C–F functionalization has recently emerged, but has yet to be rendered catalytic. Herein, 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.

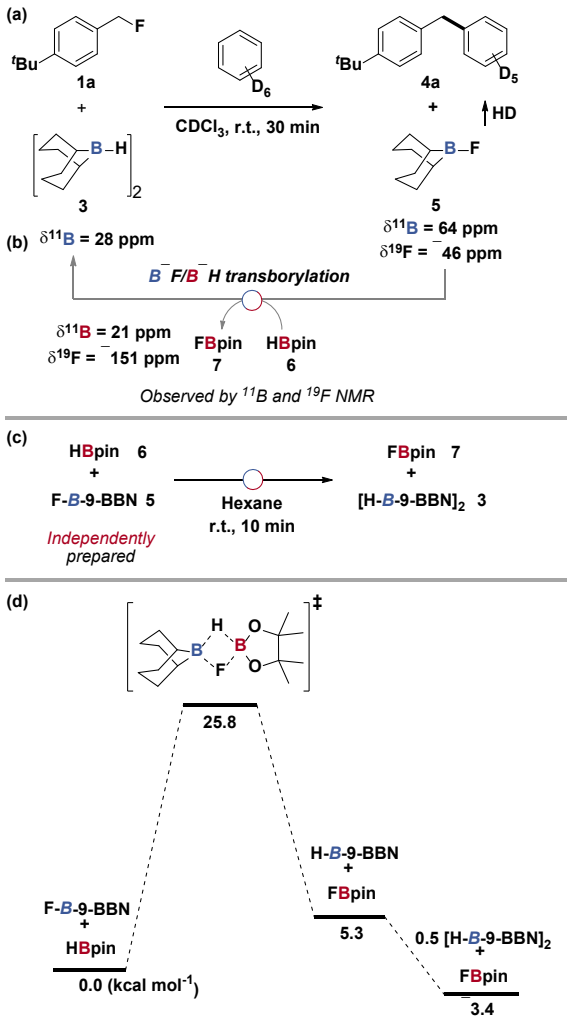
The carbon–fluorine bond is the strongest single bond in organic chemistry (99 to 131 kcal mol^{-1})[1] and thus the catalytic functionalization of C–F bonds remains a significant challenge. Unlike the activation of other carbon–halogen bonds, C–F functionalization is less developed[2,3] with only a 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 harsh 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 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 (Scheme 1, a).[25–27] The potential barrier to catalysis using main-group elements lies in the strength of the bonds made to fluorine. 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 the catalyst to be regenerated.[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 1, b).

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



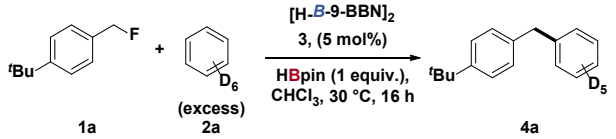
Scheme 1. (a) Stoichiometric H-*B*-9-BBN-mediated C–F arylation. (b) B–F/B–H Transborylation. (c) B–F/B–H transborylation from independently prepared F-*B*-9-BBN. (d) DFT-Computed free energies for B–F/B–H transborylation (ωB97XD/6-311++G(d,p), kcal mol^{-1})



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] Reaction of benzyl fluoride **1a** with 0.5 equivalents of [H-9-*B*-BBN]$_2$ **3** in d_6-benzene/$CDCl_3$ (1:2) was monitored by ^{11}B and ^{19}F NMR spectroscopy (Scheme 1, **a**). [H-*B*-9-BBN]$_2$ **3** (δ ^{11}B = 28 ppm) was consumed within 30 minutes and the formation of F-*B*-9-BBN **5** (δ ^{11}B = 64 ppm, δ ^{19}F = −46 ppm) 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 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-*B*-9-BBN]$_2$ **3** (δ ^{11}B = 28 ppm) was observed (Scheme 1, **b**).[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 minutes (Scheme 1, **c**). An energy profile for B–F/B–H transborylation between F-*B*-9-BBN **5** and HBpin **6** was calculated using density functional theory (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 1, **d**). Although, the barrier was lower than B–C(sp^3)/B–H (28 kcal mol^{-1}) transborylation.[32] The overall reaction was calculated to 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 was investigated (Table 1). 4-(*tert*-Butyl)benzyl fluoride **1a** was reacted with sub-stoichiometric [H-*B*-9-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 the for catalytic turnover (for full optimization see SI). 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-BBN **3** is not a strong enough Lewis acid to initiate the Friedel-Crafts-type reaction.

Table 1. H-*B*-9-BBN-catalyzed C–F arylation control reactions.



Deviation from conditions	Yield (%)
None	95
No [H-*B*-9-BBN]$_2$	0
Neat	0
1 equiv. C_6D_6	Trace
Benzyl chloride (no BnF)	0
Benzyl bromide (no BnF)	0

Yields obtained by ^{1}H NMR spectroscopy with 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), [H-*B*-9-BBN]$_2$ (5 mol%).

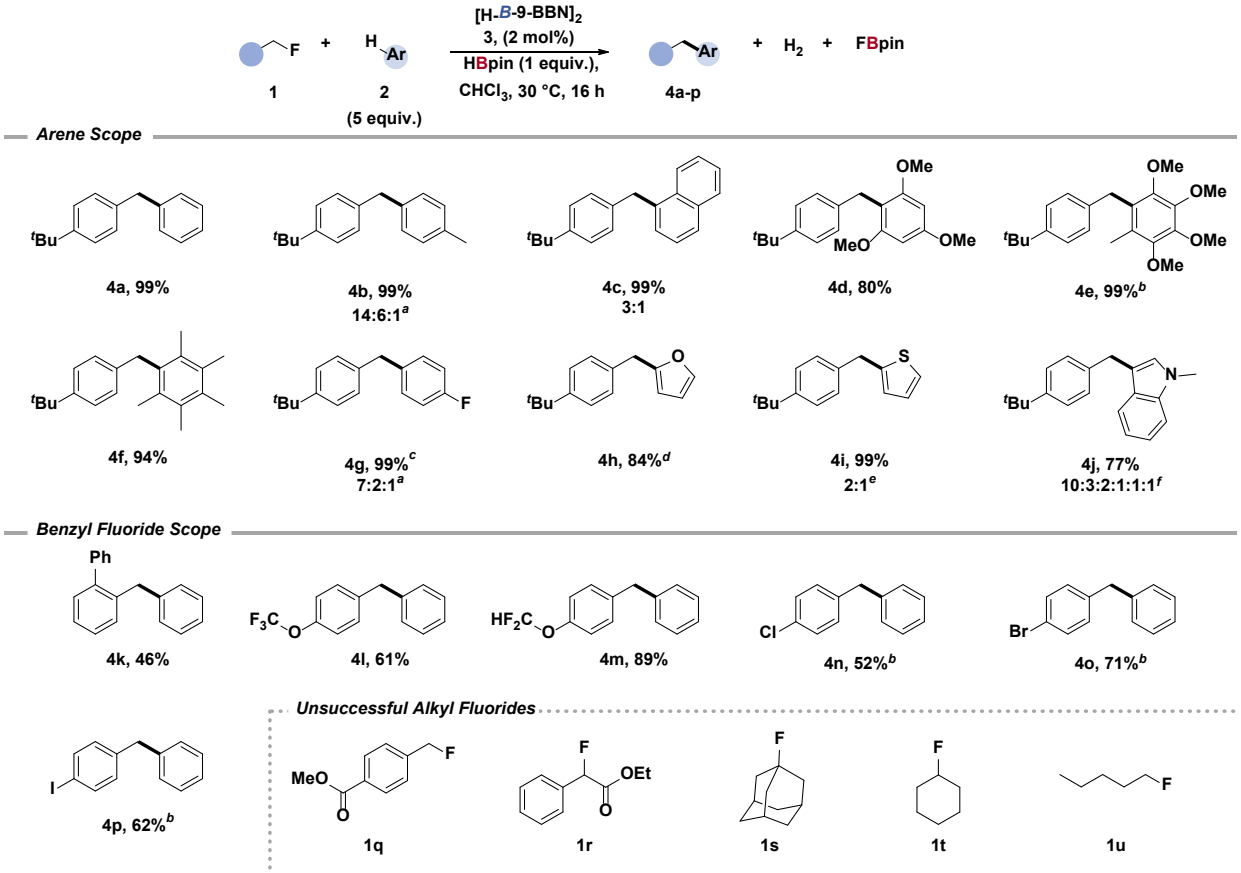
The scope and limitations of the boron-catalyzed C–C coupling were investigated using 4-(*tert*-butyl)benzyl fluoride **1a** at 30 °C with five equivalents of arene **2** (Table 2, and see SI). Arenes bearing electron-donating groups such as toluene, naphthalene, and 1,3,5-trimethoxybenzene gave high 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 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 alkyl fluoride 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 at a higher reaction temperature of 60 °C. The chemoselectivity for reaction at 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 due to 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]

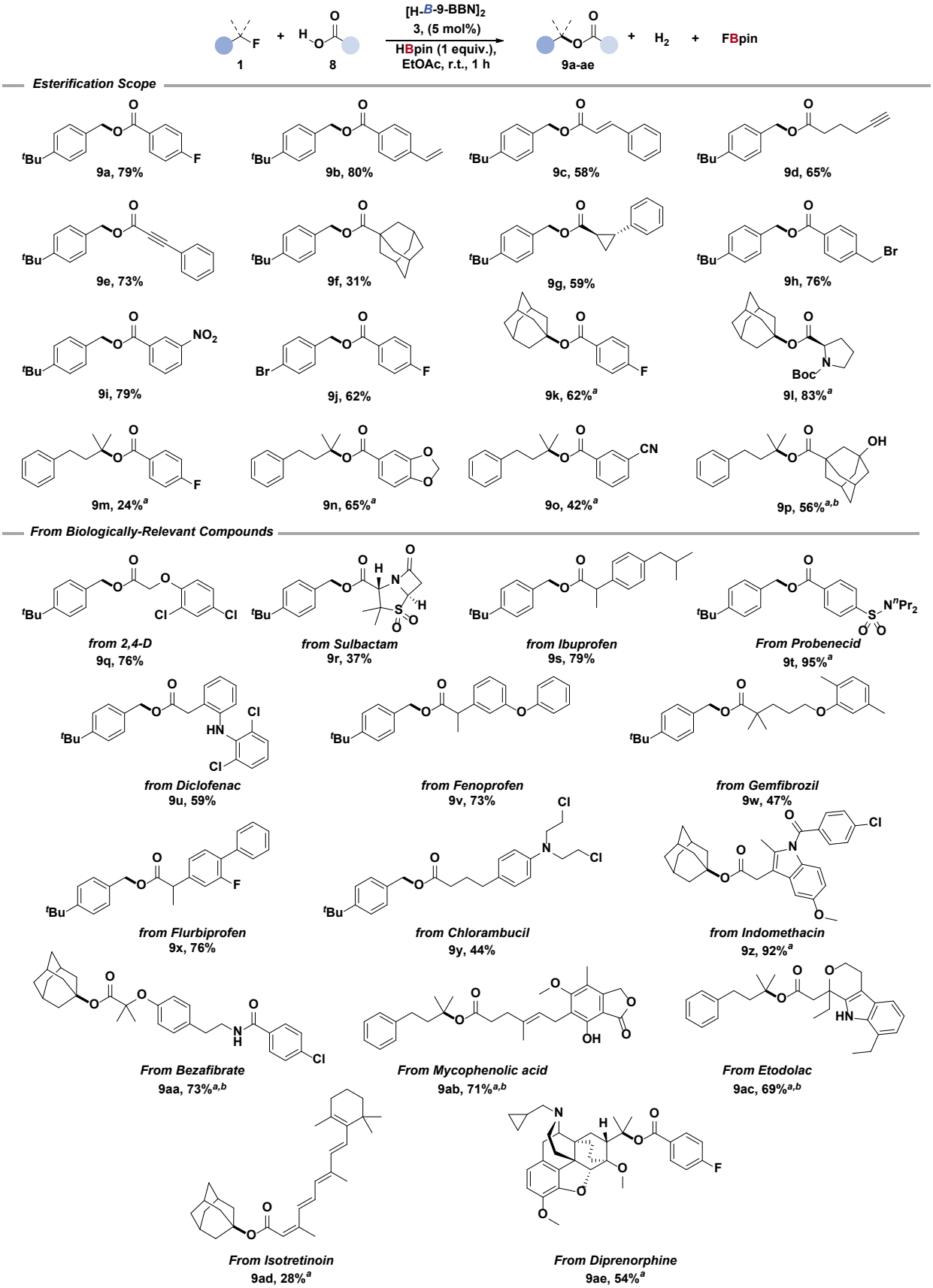
The intermediacy of a formal carbocation presented the possibility of diverse functionalization through trapping by other nucleophiles[19,22,26] and expansion of this transformation beyond Friedel-Crafts-type C–C bond formation. Carboxylic acids **8** were found to give the C–O coupled ester products **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 SI 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 hour at room temperature with only one equivalent of the carboxylic acid required. Broad functional group tolerance was observed, 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 good yield of the ester product **9f**. A cyclopropyl-containing carboxylic acid was tolerated **8g**, without formation of products resulting from ring-opening, suggesting an ionic rather than radical mechanism.

Table 2. Scope of borane-catalyzed C–F arylation.



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

Table 3. Scope of borane-catalyzed C–F esterification.



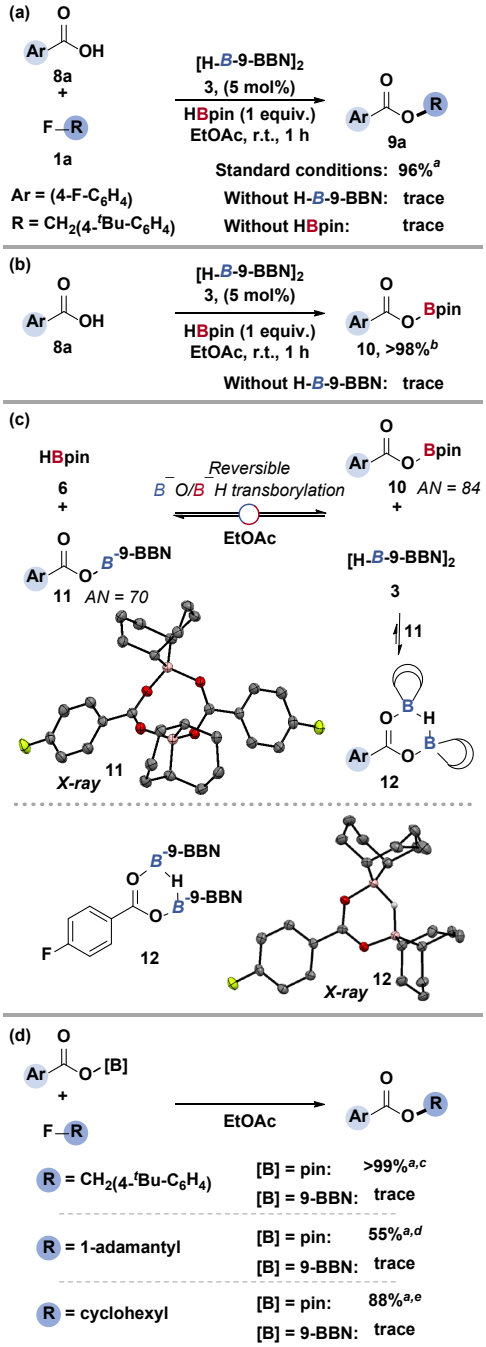
Reaction conditions: alkyl fluoride, carboxylic acid (1 equiv.), HBpin (1 equiv.), [H-B-9-BBN]2 (5 mol%), EtOAc (0.33 M), room temperature, 1 hour. Reported yields are isolated. a = 16 hours. b = HBpin (2 equiv.), followed by MeOH/SiO2 workup.

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 hours. *N*-Boc-proline **8l** was successfully reacted to give the corresponding adamantyl ester **9l**, without loss of the carbamate. A further tertiary alkyl fluoride was also successfully 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. Further, acetal-bearing carboxylic acid **8n** was coupled in good yield to the corresponding ester **9n**, and without hydrolysis of the acetal. A nitrile substituted carboxylic acid **8o** was tolerated, without any reduction observed at the nitrile. Using an extra equivalent of HBpin, a tertiary alcohol **8p** was well tolerated and gave 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 a lactam and sulfone group, 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 able to be coupled in high yield to the corresponding esters **9aa-ac**, 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 deoxyfluorinated 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.

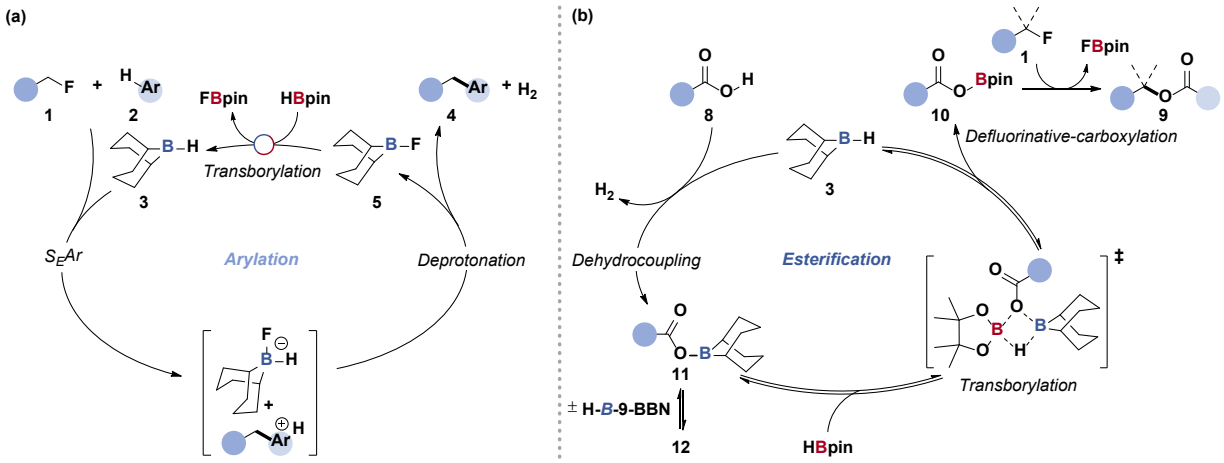
As previously unreactive alkyl fluorides, such as 1-adamantyl fluoride, were found to be suitable coupling partners in the C–F esterification reaction, the mechanism of esterification was investigated through a series of single-turnover reactions to establish any divergence from the C–C coupling reaction (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 2, **a**). When stoichiometric [H-*B*-9-BBN]$_2$ was used, in place of HBpin, very slow formation of the ester product was observed, suggesting HBpin played a role other than facilitating turnover. In the absence of alkyl fluoride, the rapid formation of acyloxyboronic ester **10** was observed, indicating that dehydrocoupling was an initial step of catalysis (Scheme 2, **b**). In the absence of H-*B*-9-BBN, HBpin was found to be unreactive with carboxylic acids under reaction conditions, indicating H-*B*-9-BBN was catalyzing the dehydrocoupling reaction (Scheme 2, **b**).

Scheme 2. Probing stoichiometric reactivity.



Ar = 4-F-C$_6$H$_4$. For clarity, all hydrogen atoms except for 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 hour. d = r.t., 16 hours. e = 80 °C, 16 hours.

Scheme 3. (a) Proposed mechanism for H-*B*-9-BBN-catalyzed C–F arylation. (b) Proposed mechanism for H-*B*-9-BBN-catalyzed C–F esterification.



To support this, stoichiometric H-*B*-9-BBN was found to react rapidly with a carboxylic acid **8a** to give the acyloxy-*B*-9-BBN **11**. Independently prepared 4-fluorobenzoate-*B*-9-BBN **11** was reacted with HBpin in EtOAc and again the 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 2, **c**). This indicated that B–O/B–H transborylation was operating, which was found to be reversible; reaction of 4-fluorobenzoate-Bpin **10** with [H-*B*-9-BBN]$_2$ **3** gave no observable 4-fluorobenzoate-*B*-9-BBN **11**, but the H-*B*-9-BBN adduct **12** was observed (Scheme 2, **c**). 4-Fluorobenzoate-*B*-9-BBN **11** was found to be unreactive with a benzyl fluoride **1a** under standard reaction conditions (Scheme 2, **d**). 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 2, **d**). Similar reactivity was found between 4-fluorobenzoate-Bpin **10,** and 1-adamantyl fluoride **1s** and cyclohexyl fluoride **1t** to give the esters **9k** and **9af**, respectively, (Scheme 2, **d**), 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** towards an alkyl fluoride is unreported and represents unexplored reactivity for organoboron compounds. Modified Gutmann-Beckett analysis[53,54] showed the 4-fluorobenoate-Bpin **10** to be more Lewis acidic than the 4-fluorobenzoate-*B*-9-BBN **11** (4-fluorobenoate-Bpin **10** AN = 84, 4-fluorobenzoate-*B*-9-BBN **11** AN = 70), suggesting that Lewis acidity is controlling 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 turnover facilitated by B–F transborylation was proposed for the C–F arylation of alkyl fluorides (Scheme 3, **a**). Dissociation of the borane dimer [H-*B*-9-BBN]$_2$ **3** and coordination to the benzyl fluoride **1** initiates carbon–carbon bond formation by generation of a putative carbocation and a fluoroborohyride, by fluoride extraction. This was proceeded by nucleophilic attack of the arene to give a Wheland intermediate, followed by deprotonation by the fluoroborohydride, which 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**.

Conversely, for C–F esterification, a catalytic cycle where instead of B–F/B–H transborylation being the driving force, the previously unreported boron-mediated defluorinative-carboxylation step is proposed to drive turnover (Scheme 3, **b**). Upon formation of monomeric H-*B*-9-BBN **3** a rapid dehydrocoupling with the carboxylic acid **8** gave the acyloxy-*B*-9-BBN **11**, and released dihydrogen. The acyloxy-*B*-9-BBN **11** reversibly formed the corresponding H-B-9-BBN adduct **12**. Reversible B–O transborylation with HBpin **6** gave the 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 operating 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. We have also demonstrated a unique mode of C–F activation with acyloxy-Bpin compounds for the formation of esters, which we will continue to explore.

ASSOCIATED CONTENT

This material is available free of charge via the Internet at http://pubs.acs.org.
Crystallographic data (CIF)

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

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Author Contributions

D.R.W. performed the practical 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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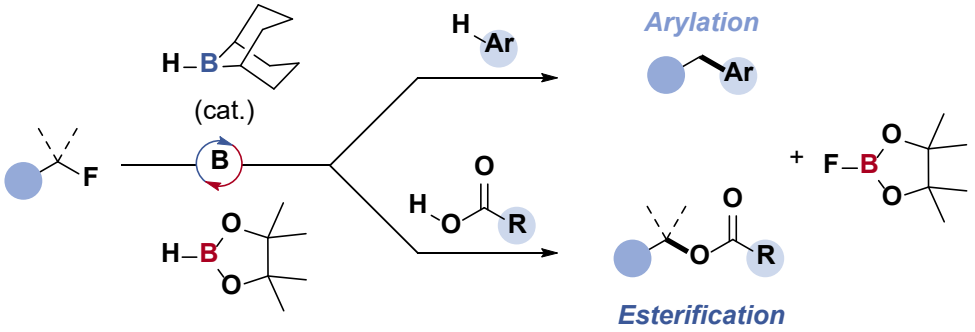

• *mild conditions* • *late-stage functionalisation* • *48 examples*

• *B¯F/B¯H transborylation* • *C¯F activation (C¯F = 131 kcal mol^{-1})*