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Base-Free Nickel-Catalysed Decarbonylative Suzuki-Miyaura Coupling of Acid Fluorides

Christian A. Malapit, James R. Bour, Conor E. Brigham, and Melanie S. Sanford

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, USA

The Suzuki-Miyaura cross-coupling of organoboron nucleophiles with aryl halide electrophiles is one of the most widely used carbon-carbon bond-forming reactions in organic and medicinal chemistry^{1,2}. A key challenge associated with these transformations is that they generally require the addition of an exogenous base, whose role is to enable transmetalation between the organoboron nucleophile and the metal catalyst³. This requirement limits the reaction's substrate scope because the added base promotes competitive decomposition of many organoboron substrates^{3–5}. As such, significant research has focused on strategies for mitigating base-mediated side reactions^{6–12}. Prior efforts have primarily focused on (i) designing strategically masked organoboron reagents (to slow base-mediated decomposition)^{6–8} or (ii) developing highly active palladium pre-catalysts (to accelerate cross-coupling relative to base-mediated decomposition pathways)^{10–12}. An attractive alternative approach involves identifying catalyst/electrophile combinations that enable Suzuki-Miyaura-type reactions to proceed without an exogenous base^{12–14}. The current report leverages this approach to develop a nickel-catalysed coupling of aryl boronic acids with acid fluorides^{15–17} (formed *in situ* from readily available carboxylic acids)^{18–22}. This catalyst/electrophile combination enables a mechanistic manifold in which a 'transmetalation active' aryl-nickel-fluoride intermediate is generated directly in the catalytic cycle^{13,16}. As such, this transformation does not require an exogenous base and is applicable to a wide range of base sensitive boronic acids and biologically active carboxylic acids.

The traditional Suzuki-Miyaura reaction involves the Pd-catalyzed coupling of an aryl halide (Ar-X) with a boronic acid in the presence of exogenous base (MX*). The role of the base (Fig 1b, cycle I) is to convert the 'transmetalation-inactive' [Ar-Pd-X] intermediate (where

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Author Contributions:

C.A.M., J.R.B. and C.E.B. developed the stoichiometric reactions. C.A.M. discovered and developed the catalytic reactions. C.A.M., J.R.B. and M.S.S. conceived and designed the investigations. M.S.S. directed and supported the research. C.A.M., J.R.B. and M.S.S. wrote and revised the manuscript.

Data Availability The authors declare that the main data supporting the findings of this study are available within the article and its Supplementary Information files. Additional data are available from the corresponding author upon request. Metrical parameters for the structures of complexes **2b** and **3** (see Supplementary Information) are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC-1837039 and CCDC-1837038, respectively.

Author Information The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to M.S.S. (mssanfor@umich.edu).

X = chloride, bromide, or iodide) to a ‘transmetalation-active’ intermediate [Ar–Pd–X*] (where X* = hydroxide or fluoride). [Ar–Pd–X*] then participates in fast transmetalation with a boronic acid^{23–25}. However, the base also mediates the off-cycle formation of organoboronate intermediates that competitively decompose via protodeboronation, oxidation, and/or homo-coupling^{4,5}. Inspired by several literature reports^{13,16}, we hypothesized that the combination of a nickel catalyst and an acid fluoride electrophile would directly form a ‘transmetalation-active’ intermediate [Ar–Ni–F] via oxidative addition and subsequent decarbonylation (Fig 1b, cycle **II**). Importantly, Ni⁰ is well-known to participate in oxidative addition reactions with carboxylic acid derivatives^{15,26–30}. Furthermore, with appropriate selection of supporting ligands, the resulting Ni^{II}-acyl intermediates are known to undergo decarbonylation^{26–30}. This approach offers the advantages that it: (1) eliminates the requirement for exogenous base; (2) uses highly electrophilic ArC(O)F substrates, which should undergo rapid oxidative addition under mild conditions (compared to, for example, the corresponding aryl fluorides^{13,31–33}, esters^{26,28}, or amides²⁷); and (3) leverages readily available and inexpensive carboxylic acid derivatives as coupling partners. Notably, a similar strategy was recently applied to the palladium-catalyzed decarbonylative coupling of acid fluorides with triethyltrifluoromethylsilane¹⁶.

Stoichiometric studies were first conducted to interrogate the viability of each step of the proposed catalytic cycle. To probe oxidative addition and decarbonylation, benzoyl fluoride **1** was reacted with Ni(cod)₂/PCy₃ (Fig. 2a). The benzoyl-nickel-fluoride intermediate **2** was formed rapidly (within 10 min at room temperature), and this complex underwent decarbonylation to afford phenyl-nickel-fluoride complex **3** in 90% yield after 15 h. To confirm that **3** is ‘transmetalation-active’, this complex was treated with 4-fluorophenyl boronic acid. As predicted, biaryl **5** (the product of transmetalation and subsequent C–C bond-forming reductive elimination) was formed in 90% after 1 h at room temperature. An analogous reaction with 2,4,6-trifluorophenylboronic acid (which is known to undergo rapid protodeboronation under basic conditions)^{4,10} provided **6** in >95% yield, indicating that transmetalation with **3** is faster than protodeboronation. Notably, the analogous phenyl-nickel-chloride **7** and -bromide **8** do not react with aryl boronic acids to form **5/6** even when heated at 100 °C.

These stoichiometric studies were next translated to a Ni-catalysed decarbonylative coupling between acid fluoride **9** and 4-methoxyphenyl boronic acid (**10**). The use of 10 mol % Ni(cod)₂ and 20 mol % PCy₃ as catalyst afforded biaryl **11** along with a ketone byproduct **12** (**11:12** = 85:15). PEt₃ afforded poorer selectivity (**11:12** = 30:70), while PPh₂Me provided **11** as a single detectable product in 95% yield. These changes in selectivity as a function of phosphine arise from ligand effects on the decarbonylation step (see Supplementary Information section VIII for details).

A key advantage of acid fluoride electrophiles is that they are directly accessible from carboxylic acids via deoxyfluorination. Evaluation of various deoxyfluorinating reagents and bases revealed that the combination of tetramethylfluoroformamidinium hexafluorophosphate (TFFH) and proton sponge converts carboxylic acid **13** to acid fluoride **9** within 15 min at room temperature. The subsequent addition of Ni-catalyst and boronic acid **10** to the same pot and heating for 16 h at 100 °C then affords biaryl product **11** in 86%

yield. A variety of aromatic and heteroaromatic carboxylic acids participate in this one-pot Ni-catalysed coupling with arylboronic acids (Fig. 3). Esters, nitriles, trifluoromethyl groups, methyl/phenyl ethers, sulfonamides, amides, alkenes, imidazoles, oxazoles, and pinacolboronate esters are tolerated. Aryl chlorides and phenyl esters^{26,28}, common electrophiles in other Ni-catalysed cross-coupling reactions, are also compatible, demonstrating the orthogonality of the current method. Moderate yields were obtained with acid fluorides bearing electron-donating substituents (products **17-23**) as well as those with *ortho*-substituents (products **20-23**). For the former, GCMS analysis of the crude reaction mixtures showed ketone side-products, indicating that decarbonylation is relatively slow with electron-rich substrates. With the latter, unreacted starting material remained, suggesting that oxidative addition is sluggish when the acid fluoride is sterically hindered. Heteroaromatic carboxylic acids, including thiophene, benzofuran, indole, pyridine, and quinoline derivatives, are also effective coupling partners. Finally, a variety of carboxylic acid-containing bioactive molecules, including probenecid, bexarotene, tamibarotene, telmisartan, flavone, and febuxostat, participate in this one-pot decarbonylative cross-coupling.

The generality of this method with respect to the boronic acid coupling partner was explored using probenecid as the substrate (Fig. 4a). Aryl boronic acids containing fluorine, ester, and methyl ketone substituents proved compatible. Alkenyl boronic acids underwent coupling to generate **45** and **46**. Cyclopropyl, allyl, and benzyl boronic acids reacted under the optimized conditions to afford moderate yields of **47-49**. Additionally, without any modification on the conditions, arylstannane nucleophiles afforded the flavone and febuxostat analogues **36** and **37** (Fig. 3). Base-sensitive α -heteroaryl boronic acids, including furans, thiophenes, and pyrroles, also underwent coupling (Fig. 4b). Finally, highly base sensitive *ortho*-difluorophenyl boronic acids^{4,10}, underwent high yielding coupling with probenecid acid fluoride.

A final set of studies focused on eliminating the need for air-sensitive Ni(cod)₂ as the nickel source in these transformations. These investigations revealed that the combination of air-stable, commercially available Ni(*o*-tolyl)(PPh₂Me)₂Cl (**63**, 10 mol %) and CsF (10 mol %) affords a relatively comparable yield to the original Ni(cod)₂/PPh₂Me catalyst system in the formation of product **61** (Fig. 4c) as well as in related transformations (Figure S9). All of the catalysts and reagents for the Ni(*o*-tolyl)(PPh₂Me)₂Cl/CsF reactions were weighed on the benchtop, without the requirement for an inert atmosphere glove-box. As such, this advance should render these coupling reactions even more practical and accessible to a wide variety of synthetic and medicinal chemistry researchers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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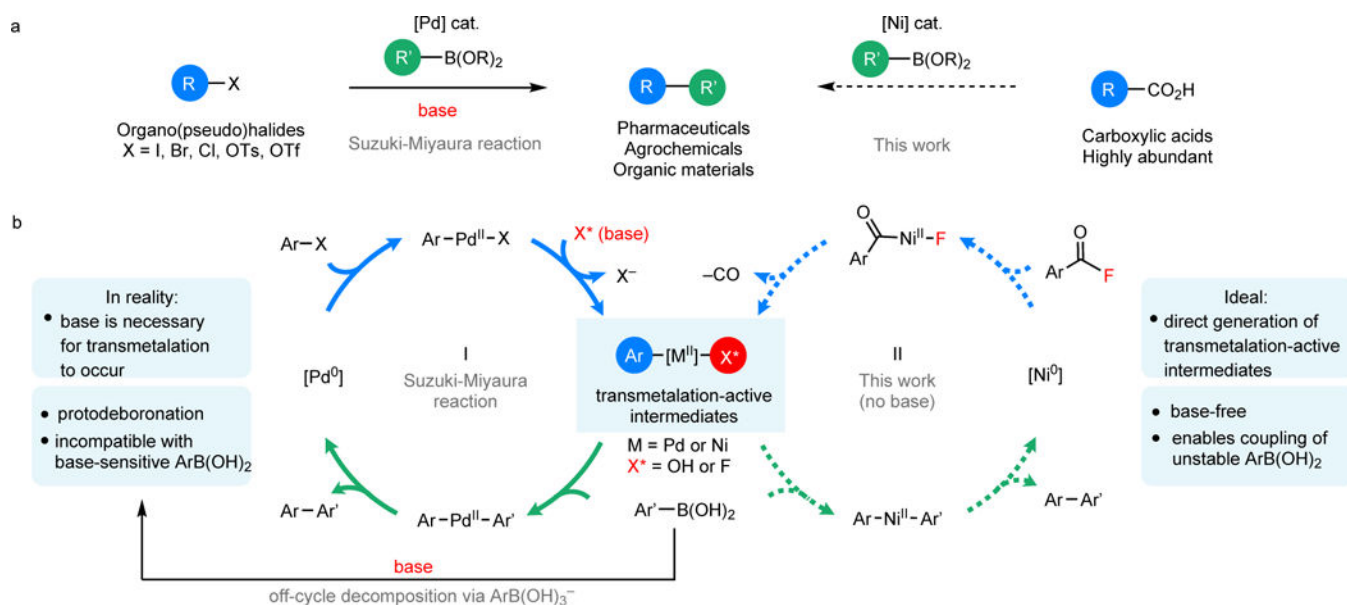


Figure 1 | Suzuki-Miyaura reaction and mechanistic design for direct generation of transmetalation-active $[\text{Ar}-\text{M}-\text{X}^*]$ intermediates.

a, Cross-coupling reactions with organoboron reagents. **b**, Mechanistic design for directly accessing transmetalation-active intermediates for the base-free decarbonylative coupling of acid fluorides with organoboron reagents. R or Ar, an alkyl or aryl group.

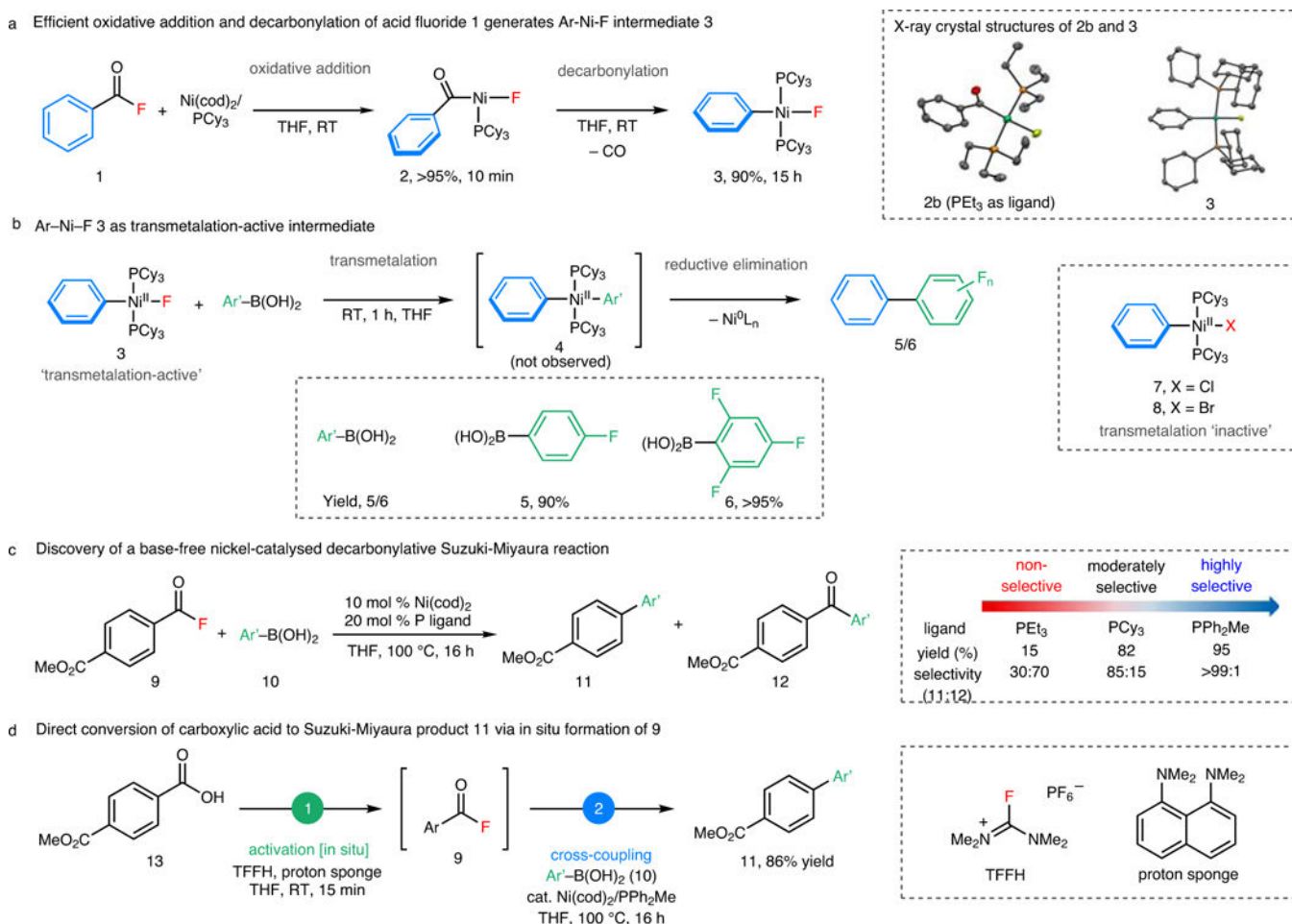


Figure 2 | Discovery of transmetalation-active nickel fluoride intermediates generated from decarbonylation enables Suzuki-Miyaura reaction of carboxylic acids and aryl boronic acids. **a**, Oxidative addition/decarbonylation of **1** at room temperature. **b**, Transmetalation/reductive elimination of **3** and aryl boronic acids. **c**, Base-free Ni-catalysed decarbonylative Suzuki-Miyaura-type reaction. **d**, Direct conversion of aryl carboxylic acid to biaryl product via *in situ* generation of acid fluoride. Yields are based on ¹⁹F NMR spectroscopy (**a** and **b**) and gas chromatography (**c**). Cod, 1,5-cyclooctadiene; Cy, cyclohexyl; THF, tetrahydrofuran; RT, room temperature; Ar, aryl; Ph, phenyl; Me, methyl; Et, ethyl; TFFH, tetramethylfluoroformamidinium hexafluorophosphate. See Supplementary Information (sections III, VI and VII) for details on reaction conditions.

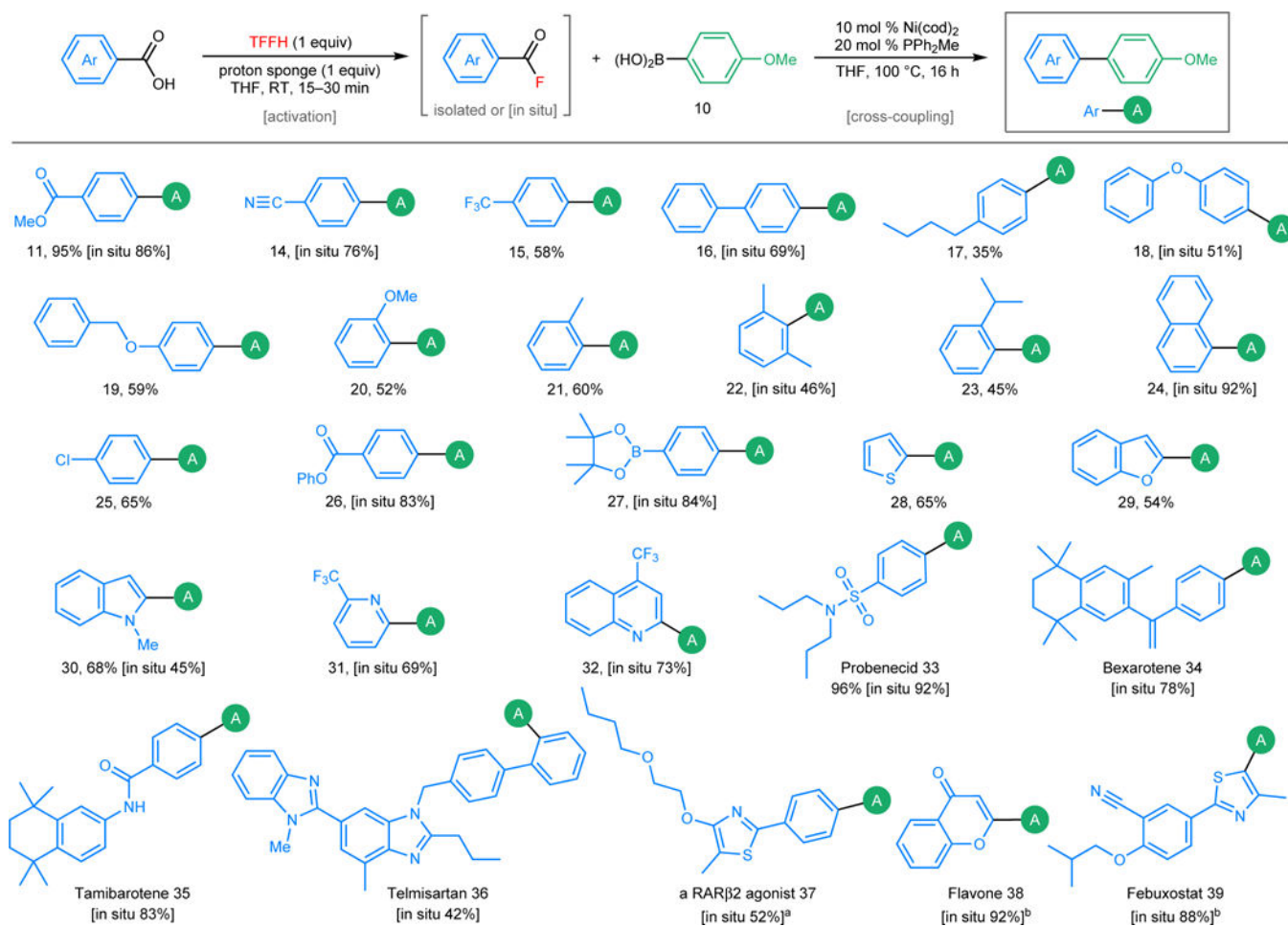


Figure 3 | Scope of Ni-catalyzed decarbonylative Suzuki-Miyaura reaction with various carboxylic acids.

A (in green), *p*-anisyl; Bu, butyl. ^aContains inseparable protodecarbonylated carboxylic acid fluoride (7%) as impurity. ^bTributyl(4-methoxyphenyl)stannane was used as the coupling partner. See the Supplementary Information (section X) for details on reaction conditions and for examples of acid fluorides (Fig. S7) that did not undergo high-yielding decarbonylative coupling.

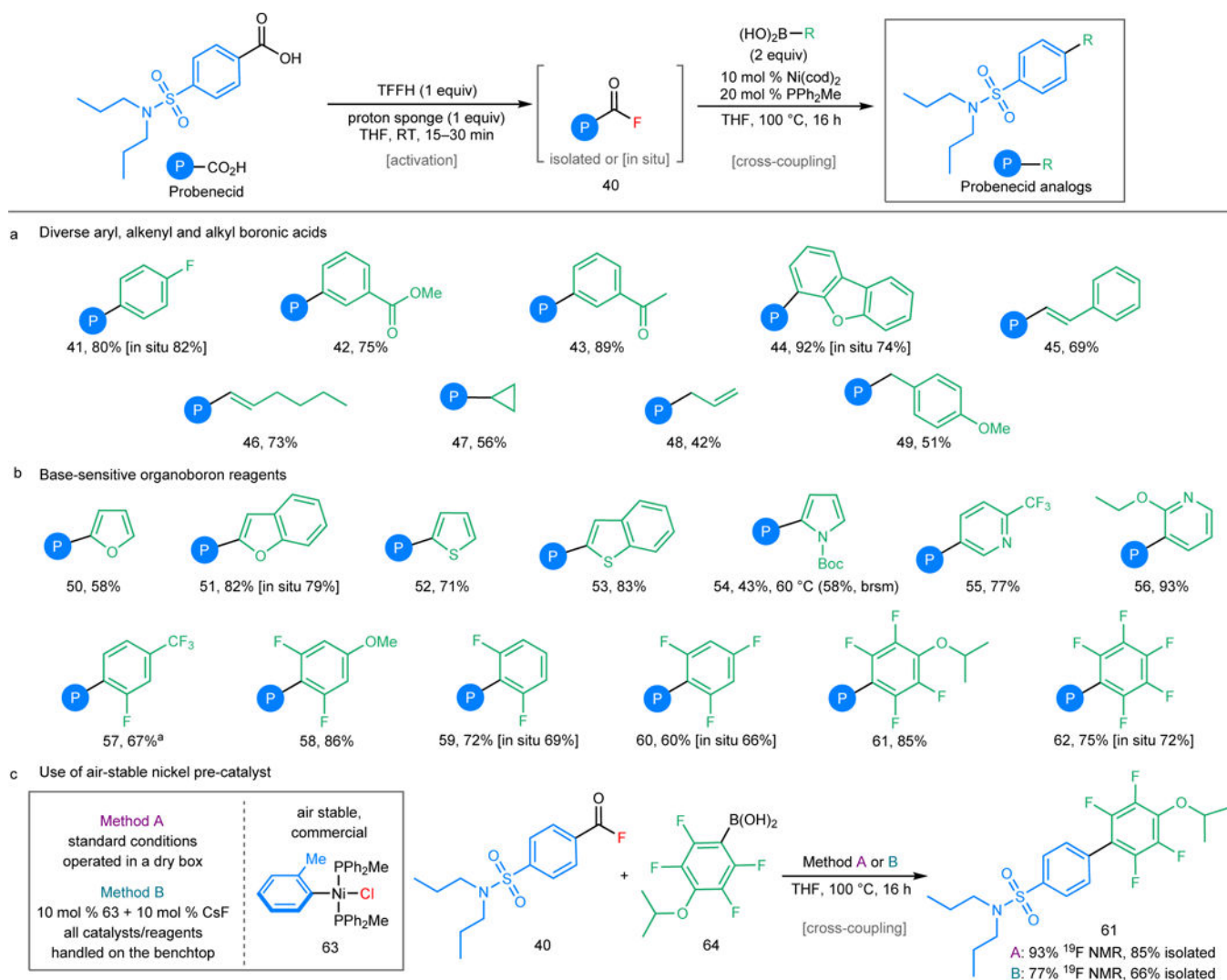


Figure 4 |. Scope of Ni-catalyzed decarbonylative Suzuki-Miyaura coupling with various organoboron reagents.

a, (Hetero)aryl, alkenyl, and alkyl boronic acids. **b**, Organoboron reagents that undergo facile protodeboronation. **c**, Use of a commercial, air-stable precatalyst **63**. Method B conditions: 10 mol % of **63**, 10 mol % of CsF, all catalysts/reagents handled on the benchtop. P (in blue), probenecid aryl fragment; Boc, *tert*-butoxycarbonyl. ^aIsolated product contains inseparable ketone byproduct (5%). See the Supplementary Information (section XII) for details on reaction conditions and for examples of organoboron reagents (Fig. S8) that did not undergo high yielding decarbonylative coupling.