LETTER

Base-free nickel-catalysed decarbonylative Suzuki-Miyaura coupling of acid fluorides

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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, the role of which is to enable transmetallation between the organoboron nucleophile and the metal catalyst³. This requirement limits the substrate scope of the reaction because the added base promotes competitive decomposition of many organoboron substrates³⁻⁵. As such, considerable research has focused on strategies for mitigating base-mediated side reactions⁶⁻¹². Previous efforts have primarily focused either on designing strategically masked organoboron reagents (to slow base-mediated decomposition)⁶⁻⁸ or on developing highly active palladium precatalysts (to accelerate cross-coupling relative to base-mediated decomposition pathways)¹⁰⁻¹². An attractive alternative approach involves identifying combinations of catalyst and electrophile that enable Suzuki-Miyaura-type reactions to proceed without an exogenous base¹²⁻ⁱ⁴. Here we use this approach to develop a nickel-catalysed coupling of aryl boronic acids with acid fluorides¹⁵⁻¹⁷, which are formed in situ from readily available carboxylic acids¹⁸⁻²². This combination of catalyst and electrophile enables a mechanistic manifold in which a 'transmetallation-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 palladiumcatalysed 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 'transmetallation-inactive' [Ar-Pd-X] intermediate (where X = chloride, bromide or iodide) to a 'transmetallationactive' intermediate $[Ar-Pd-X^*]$ (where $X^* =$ hydroxide or fluoride). [Ar-Pd-X*] then participates in fast transmetallation 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 homocoupling^{4,5}. Inspired by several literature reports^{13,16}, we proposed that the combination of a nickel catalyst and an acid fluoride electrophile would directly form a 'transmetallation-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 decarbonylation²⁶⁻³⁰. This approach offers several advantages, which include eliminating the requirement for exogenous base; using 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 using readily available and inexpensive carboxylic acid derivatives as coupling partners. Notably, a similar strategy was recently applied to the palladium-catalysed decarbonylative coupling of acid fluorides with triethyltrifluoromethylsilane¹⁶.

Stoichiometric studies were first conducted to assess the viability of each step of the proposed catalytic cycle. To investigate oxidative addition and decarbonylation, benzoyl fluoride **1** was reacted with $Ni(cod)_2$ and PCy_3 (Fig. 2a) (cod, 1,5-cyclooctadiene; PCy_3 , tricyclohexylphosphine). The benzoyl nickel fluoride intermediate **2** was formed rapidly





design for directly accessing transmetallation-active intermediates for the base-free decarbonylative coupling of acid fluorides with organoboron reagents. R, alkyl or aryl group; Ar, aryl group.

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Fig. 2 | Discovery of transmetallation-active nickel fluoride intermediates generated from decarbonylation enables Suzuki-Miyaura reaction of carboxylic acids and aryl boronic acids. a, Oxidative addition and decarbonylation of acid fluoride 1 at room temperature generates an Ar–Ni–F intermediate 3. b, Transmetallation and reductive elimination of 3 and aryl boronic acids. c, Base-free nickel-

catalysed decarbonylative Suzuki–Miyaura-type reaction. **d**, Direct conversion of aryl carboxylic acid to Suzuki–Miyaura biaryl product via in situ generation of acid fluoride. Yields are based on ¹⁹F NMR spectroscopy (**a**, **b**) and gas chromatography (**c**). Cy, cyclohexyl; RT, room temperature; THF, tetrahydrofuran. For details on reaction conditions, see Supplementary Information.

(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 'transmetallation-active', this complex was treated with 4-fluorophenyl boronic acid. As predicted, biaryl **5** (the product of transmetallation and subsequent C–C bond-forming reductive elimination) was formed in 90% yield 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 transmetallation with **3** is faster than protodeboronation. Notably, the analogous phenyl nickel chloride **7** and phenyl nickel bromide **8** do not react with aryl boronic acids to form **5** and **6**, respectively, even when heated at 100 °C.

These stoichiometric studies were next translated to a nickelcatalysed 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 by-product **12** (**11**:**12** = 85:15). Triethylphosphine afforded poorer selectivity (**11**:**12** = 30:70), whereas methyl(diphenyl)phosphine (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 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 1,8-bis(dimethylamino)naphthalene converts carboxylic acid 13 to acid fluoride 9 within 15 min at room temperature. The subsequent addition of nickel 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. Various aromatic and heteroaromatic carboxylic acids participate in this one-pot nickel-catalysed coupling with arylboronic acids (Fig. 3). Esters, nitriles, trifluoromethyl groups, methyl- and phenyl ethers, sulfonamides, amides, alkenes, imidazoles, oxazoles and pinacolboronate esters are tolerated. Aryl chlorides and phenyl esters^{26,28}—common electrophiles in other nickel-catalysed crosscoupling 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, analysis of the crude reaction mixtures by gas chromatography coupled with mass spectrometry 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, various carboxylic acid-containing bioactive molecules, including probenecid, bexarotene, tamibarotene,

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Fig. 3 | Scope of the nickel-catalysed decarbonylative Suzuki–Miyaura reaction with various carboxylic acids. A (in green), *p*-anisyl. ^aContains inseparable protodecarbonylated carboxylic acid fluoride (7%) as impurity. ^bTributyl(4-methoxyphenyl)stannane was used as the coupling

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 were 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 airsensitive 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 catalyst system of Ni(cod)₂ and PPh₂Me in the formation of product **61** (Fig. 4c), as well as in related transformations (Supplementary Fig. 9). All of the catalysts and reagents for the reactions with Ni(o-tolyl)(PPh₂Me)₂Cl and CsF 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.

partner. For details of reaction conditions and for examples of acid fluorides that did not undergo high-yielding decarbonylative coupling, see Supplementary Information.

Data availability

The main data supporting the findings of this study are available within the article and its Supplementary Information. 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 (https://www.ccdc. cam.ac.uk/) under reference numbers CCDC 1837039 and CCDC 1837038, respectively.

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Fig. 4 | **Scope of the nickel-catalysed decarbonylative Suzuki-Miyaura coupling with various organoboron reagents. a**, (Hetero)aryl, alkenyl, and alkyl boronic acids. **b**, Organoboron reagents that undergo facile protodeboronation. b.r.s.m., based on recovered starting material. **c**, Use of a commercial, air-stable precatalyst **63**. Method A involves standard conditions and is operated in a dry box. Method B: 10 mol% **63**, 10 mol%

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CsF, all catalysts and reagents are handled on the benchtop. P (in blue), probenecid aryl fragment; Boc, *tert*-butoxycarbonyl. ^aIsolated product contains inseparable ketone by-product (5%). For details on reaction conditions and for examples of organoboron reagents that did not undergo high yielding decarbonylative coupling, see Supplementary Information.

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Additional information

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