

Suzuki–Miyaura coupling of arylthianthrenium tetrafluoroborate salts under acidic conditions

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The palladium-catalysed Suzuki–Miyaura cross-coupling (SMC) is currently the most commonly used reaction to construct carbon–carbon bonds in the pharmaceutical industry. Typical methods require the use of a base, which limits the substrate scope. To mitigate this shortcoming, substantial effort has been made to develop base-tolerant organoboron reagents, efficient catalysts and reaction conditions that do not require external bases. Still, many boronic acids cannot be used or must be independently protected, and many Lewis-basic functional groups poison the catalyst. Here we report a conceptually different SMC reaction that can proceed even under acidic conditions, with a broad substrate scope. Key to this advance is the formation of an acid-stable, palladium-based ion pair between the reaction partners that does not require base for subsequent productive transmetalation. Boronic acids that cannot be used directly in other SMC reactions, such as 2-pyridylboronic acid and boronic acids with strong Lewis bases, can now be used successfully.

Aryl(pseudo)halides and arylboronic acids serve as the common coupling partners for the Suzuki–Miyaura cross-coupling (SMC)^{1,2}. Many arylboronic acids³ are less toxic, more stable and easier to store and handle than other aryl nucleophiles, which contributes to the popularity of the SMC reaction. However, many heteroarylboronic acids are insufficiently stable^{4,5}, especially under the basic reaction conditions required for productive transmetalation^{6–9} of the aryl substituent from the arylboronic acid to the intermediate arylpalladium(II) (pseudo)halide complex (Fig. 1a)^{6,8,9}. The low stability of heteroarylboronic acids is especially problematic because heteroarenes such as pyridine, imidazole and thiophene are some of the most prevalent substructures in pharmaceuticals and agrochemicals^{10–12}. For example, the 2-pyridyl problem is a well-recognized challenge^{13,14}; it results in the unproductive protodeboronation of 2-pyridylboronic acid under the reaction conditions⁴. This problem has been tackled by independent protection of the boronic acid as its cyclic triolborate¹⁵ or *N*-methyliminodiacetic acid (MIDA) boronate derivatives¹⁶. These derivatives slowly hydrolyse to the boronic acids under basic reaction conditions for subsequent

transmetalation to palladium with the aid of a copper co-catalyst^{15–17}. No successful SMC protocol that uses 2-pyridylboronic acid directly is currently available. A successful approach to circumvent fast decomposition of other heteroaryl⁴ or otherwise also problematic polyfluoroaryl⁵ boronic acids include catalyst development^{18–20} to accelerate the rate of transmetalation, development of SMC under neutral reaction conditions^{21–23} and the use of aryl electrophiles other than common (pseudo)halides^{21,23}. For example, the Buchwald group developed a specific Pd-XPhos precatalyst that allowed for effective cross-coupling of 2-thiophenyl boronic acid in more than 90% yield¹⁸. The Sanford group succeeded in developing a nickel-catalysed SMC under neutral reaction conditions for benzoyl fluorides, in which an intermediate nickel fluoride is basic enough to engage in transmetalation, without the need for exogenous base (Fig. 1b)²¹. The Niwa group approached the problem from a similar angle, in which the zinc hydroxide complex [(TMEDA)Zn(OH)(OTf)]₃ exhibits sufficient halophilicity to allow for transmetalation from aryltrifluoroborates, and also under otherwise neutral reaction conditions (Fig. 1c)²². The Carrow

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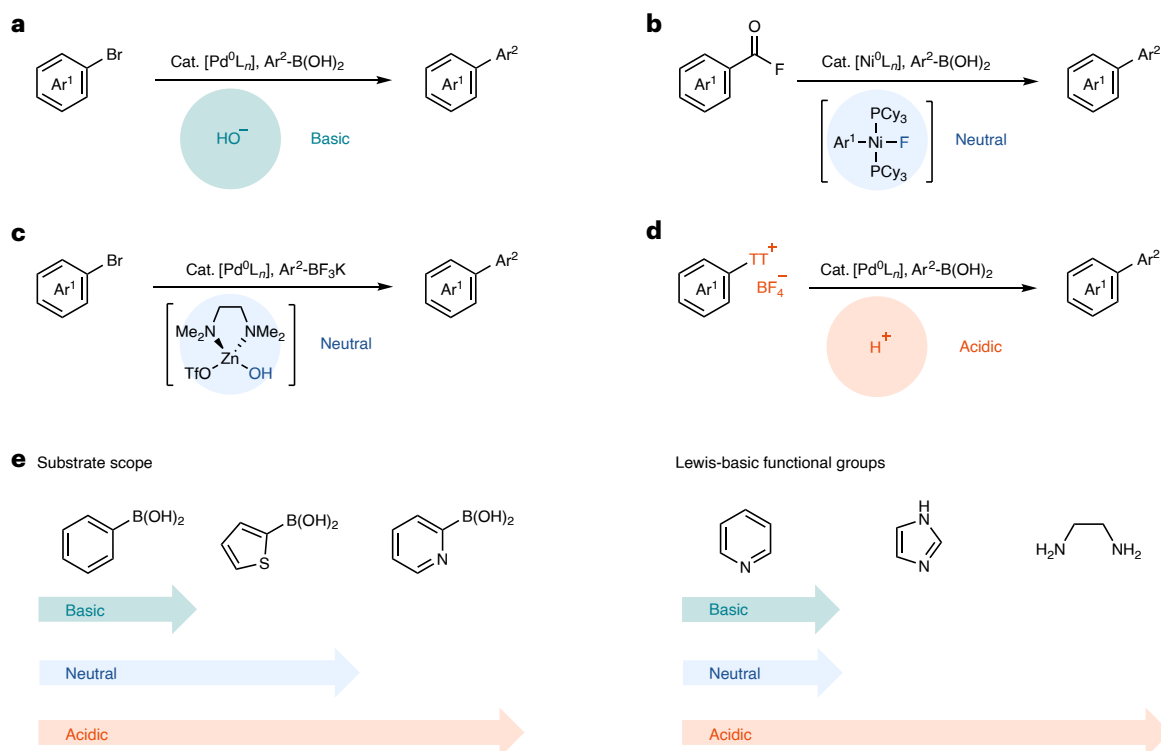


Fig. 1 | Suzuki–Miyaura coupling. **a**, Traditional SMC of aryl halides. **b**, Nickel-catalysed SMC of benzoyl fluoride²¹. **c**, Zinc-hydroxide-mediated SMC of aryl halides²². **d**, This work: SMC of arylthianthrenium salts with acid. **e**, Comparison of substrate scope and Lewis-basicity tolerance under basic, neutral and acidic conditions. L, ligand; TT, thianthrene; Tf, trifluoromethanesulfonyl.

group developed a SMC from aryldiazonium salts that can also proceed without exogenous base²³. Finally, the Liotta group reported a SMC of aryl halides at pH 3–7 via a hydroxo palladium intermediate, which shows Lewis basic group tolerance for several substrates^{24,25}. All of these modern advances have substantially increased the substrate scope in arylboronic acid derivatives compared with the otherwise robust, conventional SMC reaction. However, despite all of the advances so far, the 2-pyridyl problem, for example, remains unsolved because 2-pyridylboronic acid is unstable towards protodeboronation even under neutral conditions^{4,21–23}; the rate constant for protodeboronation from pH 4–10 under SMC reaction conditions is 10^{-2} s^{-1} , as determined by the Lloyd-Jones group⁴. Moreover, reactions under both conventional basic and modern neutral conditions fail in the presence of a variety of functional groups with high Lewis basicity, probably due to catalyst poisoning upon coordination to the transition metal catalyst^{26,27}. Despite the advances made on catalyst improvement^{18–20} and conditions in acidic buffer^{24,25}, challenges in heteroaryl SMC persist.

Herein we report a conceptually different SMC that can also tolerate acidic conditions (Fig. 1d); it solves both the difficulty in engaging otherwise fragile coupling partners, including heteroarylboronic acids such as 2-pyridylboronic acid, and also provides a general solution to avoid catalyst poisoning caused by Lewis-basic functional groups (Fig. 1e). Acid prevents transmetalation in other SMC reactions, basic and neutral, because the Lewis-basic groups that are required for productive transmetalation—such as the uncharged palladium hydroxide in conventional SMC (Fig. 1a)⁶, palladium fluorides^{7,28}, Pd⁰-O-B pre-transmetalation intermediates⁹ from anionic aryltrihydroxyborates (Supplementary Figs. 25–27), and possibly also the nickel fluoride and zinc hydroxide shown in Fig. 1—are protonated. Our goal was to develop a reaction in which an ion pair, stable to acid, can function as a pre-transmetalation intermediate and thereby enable transmetalation even in the presence of acid (Fig. 2). Our group previously disclosed arylthianthrenium

salts^{29–31}—which are more readily accessible selectively in late-stage functionalization than halides or diazonium salts—as versatile coupling partners for cross-coupling chemistry. Upon oxidative addition to Pd(0), arylthianthrenium reagents deliver cationic Ar-[Pd^{II}]⁺ complexes without strongly coordinating anions³¹. We anticipated that aryltrifluoroborates might form a suitable ion pair with the cationic palladium intermediates obtained from arylthianthrenium salts. Aryltrifluoroborates exhibit high stability to acid^{32,33} and can be formed by B-X bond metathesis³⁴ from arylboronic acids and HBF₄, as well as external BF₄[−] ions directly, which seemed ideal, given that arylthianthrenium salts are most commonly obtained as tetrafluoroborates salts²⁹.

Results and discussion

Reaction development

A commercially available Pd(0) complex catalyses the SMC between phenylboronic acid and arylthianthrenium tetrafluoroborate **1-BF₄**, both in the absence and presence of HBF₄ (Fig. 2a). Acid is not required for productive cross-coupling, but it is tolerated. Such tolerance enables reactions in the presence of Lewis-basic functional groups because they are in situ protected by protonation where they otherwise would not be under basic or neutral conditions (Fig. 2a)³⁵. Previous work has demonstrated tolerance of several basic functional groups under pH 3–7 when aryl halides are used as substrates^{24,25}. Yet, various heterocycles that failed under previous conditions²⁵ are tolerated in our acidic SMC of arylthianthrenium salts (Supplementary Table 2). Basic intermediates that are required for other SMC reactions (for example, the pre-transmetalation intermediate shown in Fig. 2b) are not required in the SMC with arylthianthrenium salts: although oxidative addition generates a cationic arylpalladium complex **A**, the corresponding aryltrifluoroborate counter-ion is generated from the arylboronic acid, and either the tetrafluoroborate counter-ion of the thianthrenium salt under neutral conditions, or HBF₄ under acidic conditions (Fig. 2c and

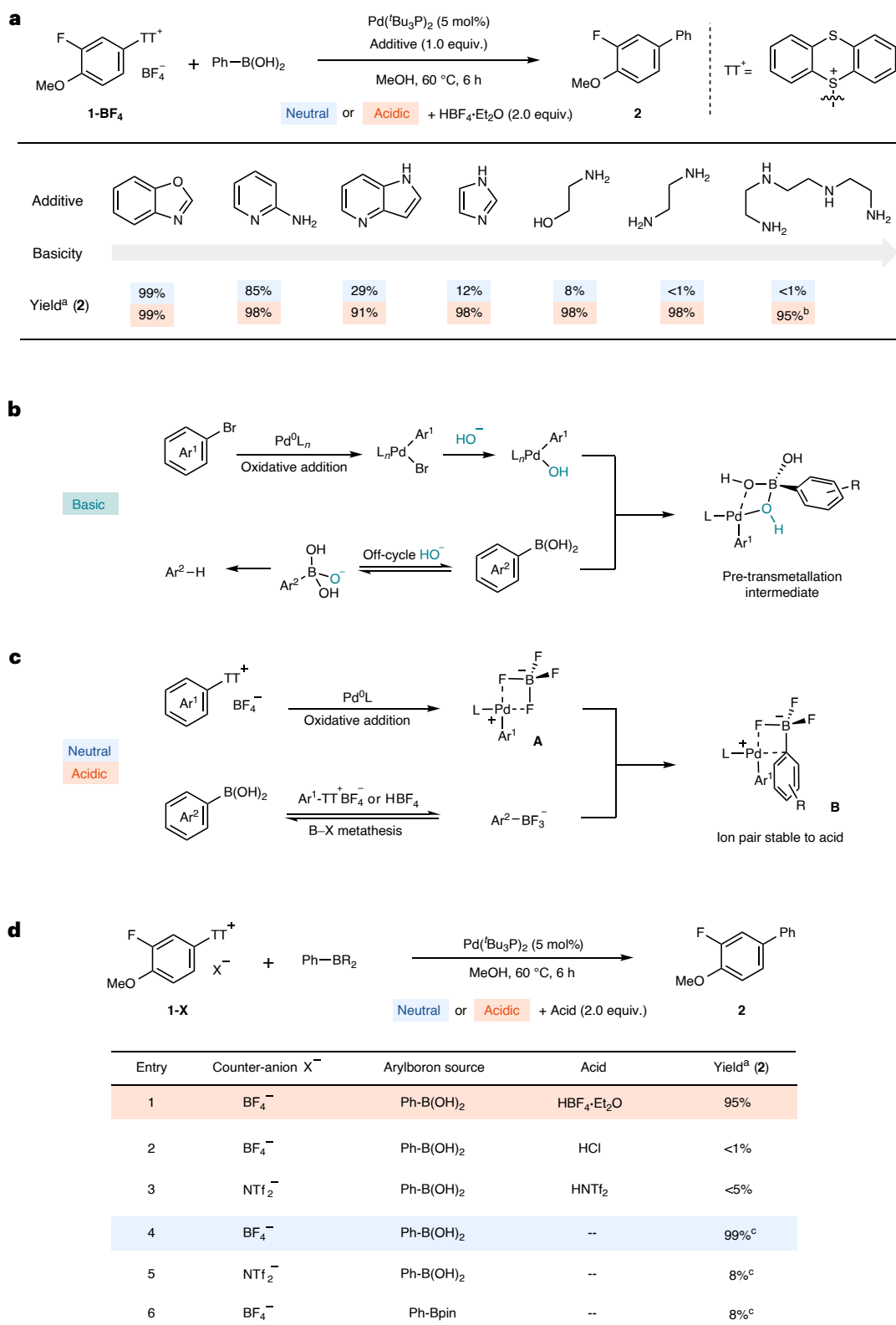


Fig. 2 | Suzuki–Miyaura coupling reaction of arylthianthrenium salts.

a, Robustness screening. **b**, Pre-transmetalation mechanism in traditional SMC. **c**, The formation of an acid-tolerant ion pair **B** in the SMC of arylthianthrenium salts. **d**, The effects of counter-anion and arylboron source. ^aYield determined

from ¹⁹F NMR spectroscopic analysis with fluorobenzene as an internal standard. ^bHBF₄·Et₂O (4.0 equiv.), 60 °C, 10 min. Non-covalent interactions are depicted with dashed bonds.

Supplementary Fig. 3–9). Both ions result in the formation of ion pair **B**. The anion's aryl π system and the cationic palladium may engage in a cation– π interaction^{36,37} that could both facilitate formation of **B**

while being geometrically appropriate for ensuing transmetalation under both neutral and acidic conditions. [Pd(^tBu₃P)₂], with sterically hindered monodentate ligands³⁸, is the optimal palladium catalyst,

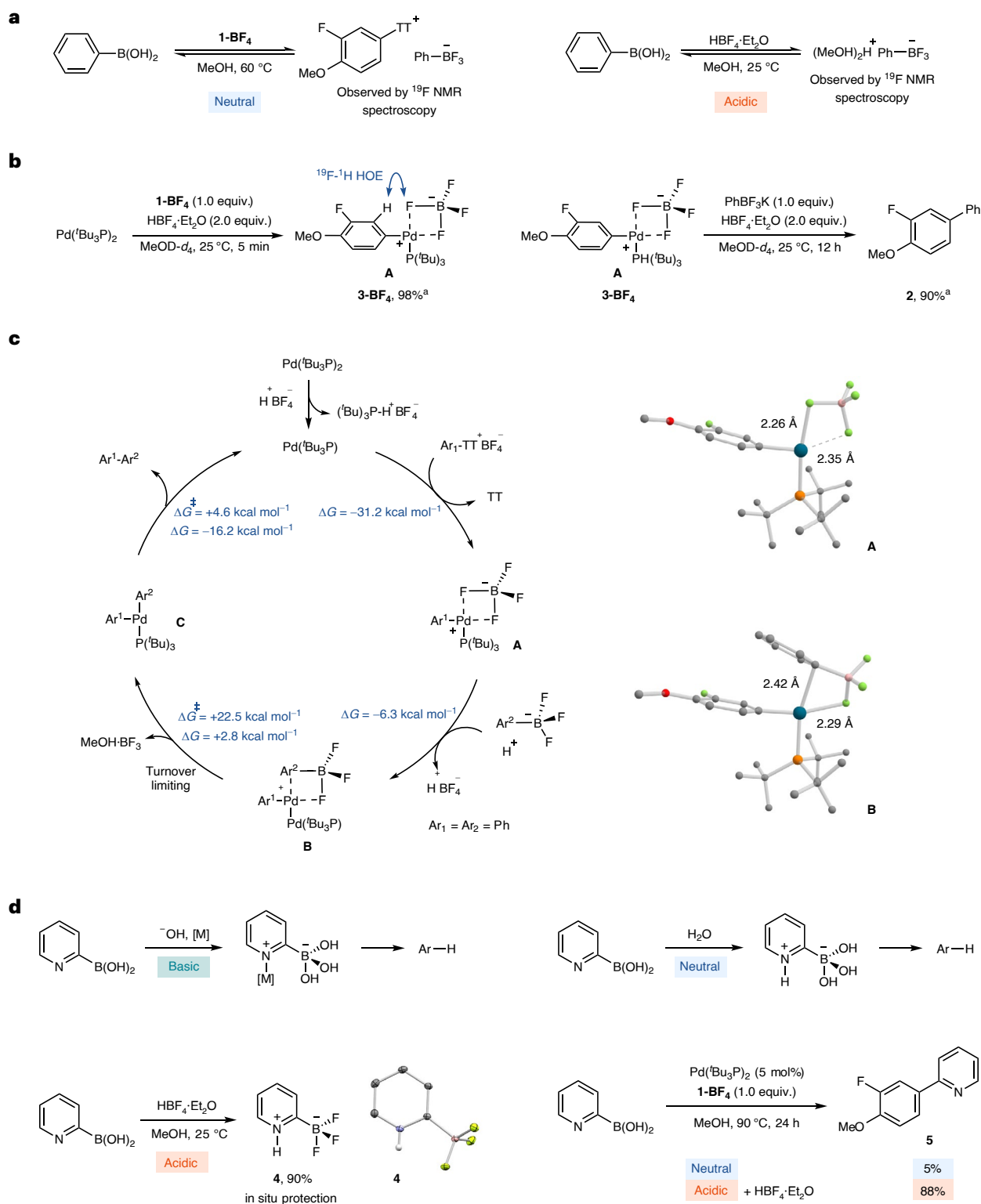


Fig. 3 | Mechanistic analysis. **a**, Observed B-X bond metathesis equilibrium in methanol. **b**, Preparation of the cationic palladium intermediate **3-BF₄** and its reaction with phenyltrifluoroborate. **c**, Proposed catalytic cycle and DFT calculation results. The Gibbs free energy (ΔG) is calculated at the PBE0-D3(BJ)/def2-TZVPP//PBE0-D3(BJ)/def2-SVP level in methanol. The carbon-bound hydrogen atoms have been omitted from the DFT-calculated structures of **A** and **B** for clarity. ΔG^\ddagger , difference in G between the transition state and reactant.

d, Reactions of 2-pyridylboronic acid under basic, neutral and acidic conditions. We also show the X-ray crystal structure of $[\text{H}]^+[\text{Py-BF}_3]^-$ (**4**) with 50% probability ellipsoids; the hydrogen atoms were refined isotropically and carbon-bound hydrogen atoms are omitted for clarity. Pink, boron; yellow, fluorine; blue, nitrogen; grey, carbon; white, hydrogen. The SMC was between arylthianthrenium salt and 2-pyridylboronic acid. ^aYield determined by ¹⁹F NMR spectroscopy with fluorobenzene as an internal standard. HOE, heteronuclear Overhauser effect.

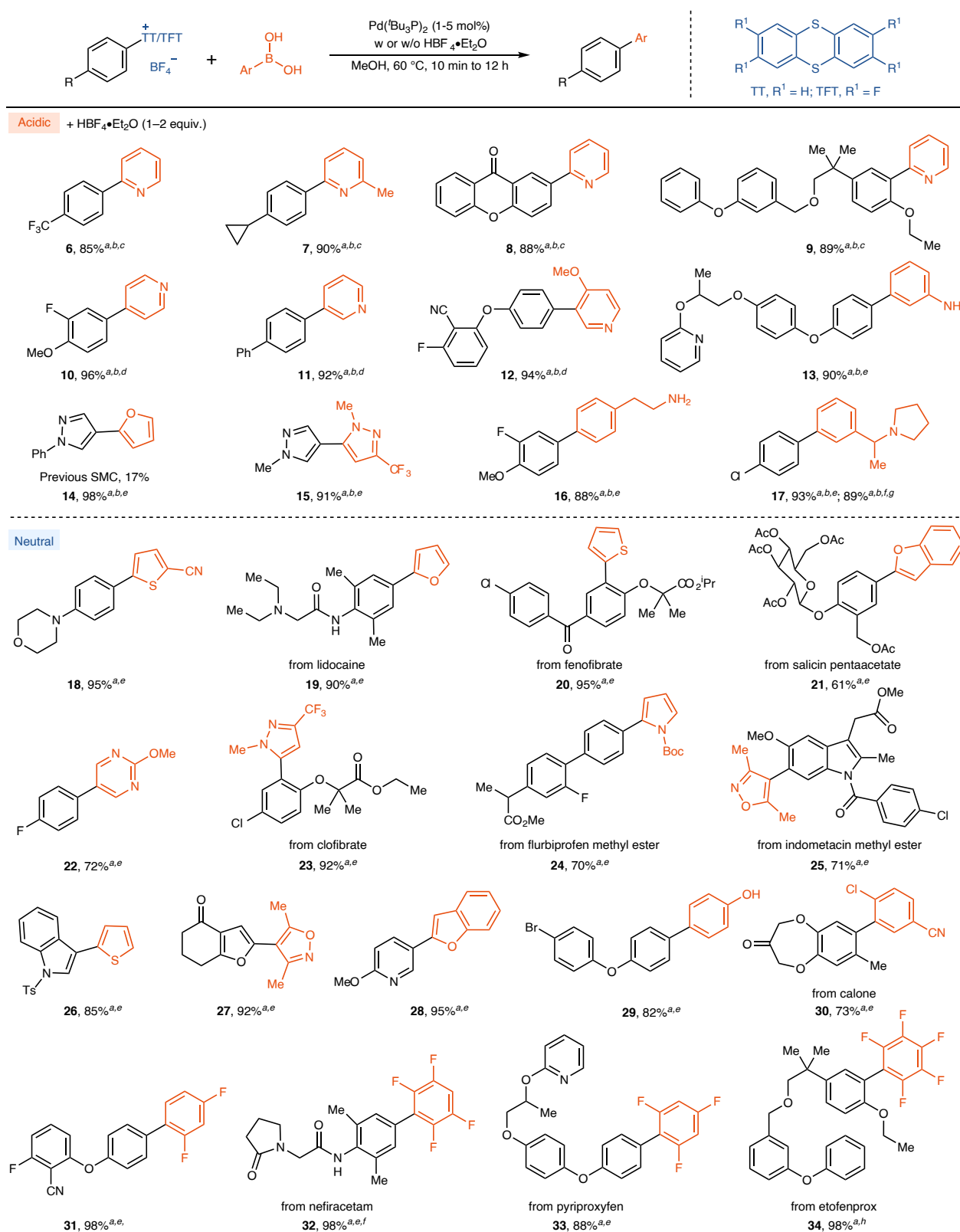


Fig. 4 | Substrate scope for Suzuki–Miyaura coupling reaction of arylthianthrenium salts. ^aArylthianthrenium salt or aryl(tetrafluoro)thianthrenium salt (0.1 or 0.2 mmol), arylboronic acid (1.1–2.0 equiv.),

Pd(^tBu₃P)₂ (5 mol%), MeOH (0.1 M). ^bHBF₄·Et₂O (1.0–2.0 equiv.). ^c110 °C, 12 h. ^d90 °C, 10 min to 12 h. ^e60 °C, 10 min to 12 h. ^fPd(^tBu₃P)₂ (1 mol%). ^gPerformed on 4 mmol scale; 1.02 g product. ^h25 °C, 30 s. Ac, acetyl; Boc, *tert*-butyloxycarbonyl.

consistent with ion pair formation (Supplementary Table 3); a second ^tBu₃P is reluctant to coordinate to **A** due to steric repulsion³⁸, leaving a coordinating site for the cation– π interaction of substrates. Past

research has demonstrated boron-to-palladium transmetalation via cationic arylpalladium intermediate in the presence of zinc hydroxide²², but the process fails in the presence of acid (Supplementary page 15).

The reaction reported here provides a transmetallation pathway for SMC that can tolerate stoichiometric strong acids.

To better probe the potential relevance of ion pair **B**, we evaluated different acids and thianthrenium counter-ions that would not allow formation of similar ion pairs (Fig. 2d). For example, when HCl was used instead of HBF₄, less than 5% conversion was observed, consistent with chloride binding to **A**, which should preclude ion pair formation (Fig. 2d, entry 2). Likewise, no arylboronate anion should form when the BF₄⁻ counter-ion is swapped for the triflamide counter-ion (Fig. 2d, entry 3). Under neutral conditions, the aryltrifluoroborate anion in **B** can be generated from the BF₄⁻ counter-anion originating from the thianthrenium salt (Supplementary Figs. 3–7), yet triflamide (NTF₂⁻) cannot form a similar structure (Fig. 2d, entry 5). Furthermore, arylpinacolboronate is less effective than arylboronic acid (Fig. 2d, entry 6). When aryltriflate is used as the coupling partner with organoboron reagents, the yield is less than 1% (Supplementary Table 3). Methanol is the best solvent for the reaction (Supplementary Table 1), consistent with the observed fast B–X metathesis in alcohol solvents³². All observed results are consistent with the relevance of ion pair **B** under both neutral and acidic conditions for productive coupling.

Mechanistic study

The reactions between phenylboronic acid, and **1-BF₄** and HBF₄·Et₂O, respectively, were investigated by nuclear magnetic resonance (NMR) spectroscopy to establish a fast metathesis equilibrium to phenyltrifluoroborate under both acidic and neutral conditions (Fig. 3a and Supplementary Figs. 3–9). Oxidative addition of the arylthianthrenium salt **1-BF₄** to the palladium catalyst proceeds quickly in the presence of HBF₄ to afford palladium(II) intermediate **A** (specifically **3-BF₄**), which we could observe spectroscopically, but was unstable in the attempts to isolate its pure form (Fig. 3b and Supplementary Fig. 10). Our data suggest a weak interaction between the BF₄⁻ counter-ion and the palladium cation in **3-BF₄** because we can observe a heteronuclear Overhauser effect between the two ions (Supplementary Fig. 6) yet no *J*-coupling between the ³¹P of the ligand and the ¹⁹F nuclei of the anion. Following addition of phenyltrifluoroborate, the spectroscopic data are consistent with the formation of an ion pair **B** that also evaded more detailed characterization; however, it did afford cross-coupling product **2** in 90% yield, as determined by NMR spectroscopy with an internal standard in the presence of HBF₄ (Fig. 3b and Supplementary Fig. 16). Density-functional theory (DFT) calculations predict that the anion exchange between [H]⁺[Ph-BF₃]⁻ and [Ph-Pd^{II}]⁺BF₄⁻ (**A**)²⁶ to form the ion pair **B** and HBF₄ is exergonic by 6.3 kcal mol⁻¹ (Fig. 3c), and has a Pd–C(*ipso*) distance in **B** of 2.42 Å, consistent with η¹ coordination³⁷. The key transmetallation from **B** has an activation energy of 22.5 kcal mol⁻¹ and is turnover limiting for subsequent facile reductive elimination. Given the mechanism, we also probed the SMC reaction for aryl diazonium salts because a similar ion pairing should be accessible; however, the need for elevated temperatures to overcome the activation barrier to transmetallation leads to much lower yields due to the thermal instability of aryl diazonium salts (Supplementary Table 4). In contrast to aryl diazonium salts^{23,39}, arylthianthrenium salts are thermally stable and, given their accessibility at a late-stage, seem to occupy a sweet spot for accessing ion pairs; that is, they are (1) sufficiently stable to form and resist acid, and (2) are reactive enough to proceed in the catalytic cycle of the SMC.

Substrate scope

Acid is not required for the catalytic mechanism shown in Fig. 3c and is not expected to influence the formation of the ion pairs. Yet, acidic conditions allow substrates that would otherwise not be tolerated to participate. For example, protodeboronation of 2-pyridylboronic acid proceeds too quickly under both basic and neutral reaction conditions (Fig. 3d). Previous protocols to address the 2-pyridyl problem under basic conditions require an additional step to prepare base-tolerant

organoboron reagents^{15,16} or stoichiometric copper additives¹⁷. Under traditional basic SMC conditions, Lewis acids can coordinate to the pyridine ring and form a zwitterionic intermediate [M]⁺[Py-B(OH)₃]⁻, whereas under neutral reaction conditions, the related zwitterion [H]⁺[Py-B(OH)₃]⁻ is formed. Both readily hydrolyse, and the transition state of protodeboronation proceeds via heterolytic C–B bond fragmentation with protonation of the carbanionic carbon as boric acid (B(OH)₃) is expelled⁴. We rationalize that a similar heterolytic fragmentation in **4** would proceed at a much slower rate because BF₃ is more Lewis-acidic than B(OH)₃, and is therefore more stable towards hydrolysis because C–B bond heterolysis does not proceed at an appreciable rate (Supplementary Fig. 23). Zwitterion [H]⁺[Py-BF₃]⁻ (**4**) is formed via a reaction between 2-pyridylboronic acid and HBF₄·Et₂O in methanol. The related structure potassium 2-pyridyltrifluoroborate was reported but decomposes quickly in non-acidic SMC reaction conditions³³. By contrast, **4** is stable towards hydrolysis in acid (Supplementary Fig. 24)⁴⁰. The reaction between 2-pyridylboronic acid and arylthianthrenium salt only produces coupling product **5** in 5% yield under neutral conditions, yet, in the presence of external HBF₄·Et₂O furnished **5** in 88% yield, consistent with the claims made in this manuscript about the relevance of stoichiometric strong acid.

Due to favourable ion pair formation, a large variety of substrates that are incompatible with conventional SMC reaction conditions can now participate directly when using boronic acids as starting materials (Fig. 4 and Supplementary Table 2). Tolerance towards acid extends the substrate scope to compounds that cannot be covered through other reported SMC reactions directly from boronic acids without additional independent protection steps. For example, cross-couplings featuring basic heterocycles or amines (**6–17**) participate well in acid—a previous SMC to synthesize the nematicidal active compound⁴¹ **14** resulted in a yield of 17% due to the presence of coordinative nitrogen atoms, but now can be obtained in 98% yield under acidic conditions through ion pair formation. Electron-donating or -withdrawing groups are well-tolerated on boronic acids (Supplementary Table 5). The scope of the ion-pair-based cross-coupling reaction also includes all those compound classes that are accessible with other modern SMC reactions, for example for heteroarylboronic acids that are sensitive to base, such as 2-thiophenyl (**18, 20**), 2-furanyl (**19**), 2-benzofuranyl (**21**), 5-pyrimidyl (**22**), 3-pyrazolyl (**23**), 2-pyrrolyl (**24**) and 4-isoxazolyl (**25**). Likewise, base-sensitive pentafluorophenylboronic acid^{5,42} can be coupled with the etofenprox-derived thianthrenium salt to produce **34** in 30 s at ambient temperature, which positions the SMC as a general solution to all compound classes for SMC. The reaction is robust and can be executed in ambient atmosphere and wet solvent; for example, SMC to produce **2** in 95% yield tolerates up to 50 vol% water (Supplementary Table 1).

Conclusion

Our study reveals an unusual mechanism that can facilitate a general transmetallation pathway for C–C bond formation reactions under acidic conditions that has not been illustrated for other cross-coupling reactions. We anticipate that the ion-pair-interaction-promoted transmetallation can serve as a fundamentally different mechanism that is also suitable for other cross-coupling reactions such as carbon–heteroatom bond formations, which is under investigation in our laboratory.

Methods

General procedure for the SMC under neutral conditions

Under an ambient atmosphere, arylthianthrenium salt (0.200 mmol, 1.00 equiv.), arylboronic acid (0.220 mmol, 1.10 equiv.) and Pd(^tBu₃P)₂ (5.0 mg, 10 μmol, 5.0 mol%) were added to a 4 ml vial containing a magnetic stir bar, followed by MeOH (2 ml, 0.1 M). The vial was sealed with a septum cap, and the reaction mixture was stirred vigorously at 60 °C on a heating block. After the indicated time, the reaction vessel was opened to air, and the resulting mixture was concentrated by rotary

evaporation. The residue was purified by chromatography on silica gel to obtain the pure product.

General procedure for the SMC under acidic conditions

Under an ambient atmosphere, arylthianthrenium salt (0.200 mmol, 1.00 equiv.), arylboronic acid (0.220 mmol, 1.10 equiv.), Pd(^tBu₃P)₂ (5.0 mg, 10 μmol, 5.0 mol%) and MeOH (2 ml, 0.1 M) were added to a 4 ml vial containing a magnetic stir bar, followed by HBF₄·OEt₂ (28 μl, 33 mg, 0.20 mmol, 1.0 equiv.). The vial was sealed with a septum cap, and the reaction mixture was stirred vigorously at 60 °C on a heating block. After the indicated time, the reaction vessel was opened to air, and the resulting mixture was concentrated by rotary evaporation. The residue was purified by chromatography on silica gel to obtain the pure product.

Data availability

Crystallographic data for the structure reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition no. CCDC 2280716. Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>. The data reported in this Article are available in the main text or Supplementary Information.

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Author contributions

L.Z. developed the SMC. L.Z. and Y.X. investigated the mechanism. L.Z., Y.X. and Z.B. explored the substrate scope. L.Z. and T.R. wrote the paper. T.R. directed the project.

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Competing interests

T.R. may benefit from royalty payments related to sales from thianthrene-based compounds. The other authors declare no competing interests.

Additional information

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