ACS Catalysis

Research Article

Cite This: ACS Catal. 2017, 7, 8331-8337

pubs.acs.org/acscatalysis

A Micellar Catalysis Strategy for Suzuki–Miyaura Cross-Couplings of 2-Pyridyl MIDA Boronates: *No Copper*, in Water, Very Mild Conditions

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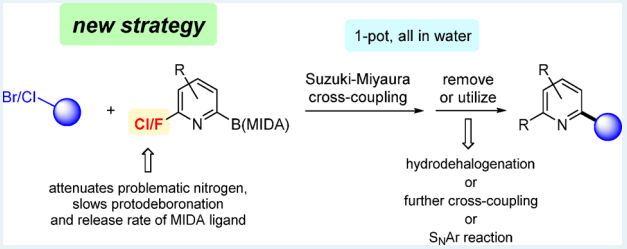
Supporting Information

ABSTRACT: Suzuki–Miyaura (SM) cross-couplings of 2-pyridyl MIDA boronates can be successfully carried out in the complete absence of copper by attenuation of the Lewis basicity associated with the pyridyl nitrogen using selected substituents (e.g., fluorine or chlorine) on the ring. This strategy imparts additional synthetic options compared with existing approaches based on the use of Lewis acids or *N*-oxides. Thus, access to highly valued 2-substituted pyridyl rings via an initial Suzuki–Miyaura coupling can be followed by dehalogenation, S_NAr reactions, or a second SM coupling to arrive at 2,6-disubstituted pyridyl arrays, all run in a single pot, enabled by micellar catalysis in water. Accessing targets within drug-like space is demonstrated in a four-step, one-pot sequence. Computational data suggest that the major role being played by electron-withdrawing substituents in promoting these cross-couplings without the need for copper is to slow the rates of protodeboronation of intermediate 2-pyridylboronic acids.

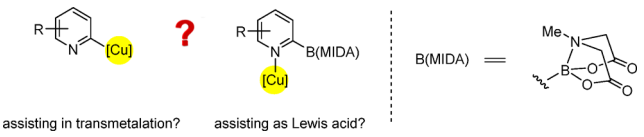


KEYWORDS: *micellar catalysis, green chemistry, E factor, MIDA boronates, Suzuki–Miyaura*

Within the privileged family of pyridines,[1] the presence of the 2-pyridyl-substituted moiety exists in many arenas, including materials,[2] biologically active natural products,[3] pharmaceuticals,[4] ligands,[5] and fluorescent probes,[6] emphasizing its broad-based occurrence. Nonetheless, 2-pyridyl organometallic reagents remain notably underdeveloped with respect to both their preparation and their use in cross-coupling chemistry.[7] Because of the Lewis basic and electronegative nitrogen of the pyridyl unit, participation by the 2-position in a transmetalation event onto a transition metal remains quite challenging, as competing protioquenching is commonplace.[7] Only a handful of reports have attempted to solve this difficult issue using 2-pyridyl zincate salts,[8] trialkylstannanes,[9] silanes,[10] or boron with various ligands or protecting groups.[11] The 2-substituent that allows pyridyl building blocks to be free-flowing crystalline solids that can be stored on the benchtop in air for extended periods and purifiable via flash chromatography is the *N*-methyliminodiacetic acid (MIDA) boronate ligand. Rehybridization of boron to sp^3 by this ligand results in these desired attributes and is remarkably effective in Suzuki–Miyaura (SM) cross-couplings via a slow-release mechanism.[12]

One challenging aspect associated with 2-pyridyl MIDA boronate-mediated cross-couplings is the elevated levels of copper required in the reaction mixture.[11] Although reports on copper-only-catalyzed SM cross-couplings are known,[13] copper's role in palladium-catalyzed cross-couplings of 2-pyridyl systems is still poorly understood (Scheme 1). While recent work provided evidence that copper additives affect the rate of protodeboronation of 2-pyridyl systems under atypical

Scheme 1. Two Potential Roles of Cu for Suzuki–Miyaura Cross-Couplings of 2-Pyridyl Units



cross-coupling conditions (i.e., in the absence of Pd and aryl halide),[14] it has also been thought to assist in the transmetalation step to palladium via an initially formed 2-pyridylcopper species.[11] Although some 2-pyridylcopper species have been isolated and upon exposure to the reaction conditions do lead to the desired product, such a species has never been directly implicated in the reaction.[11,15] Given that copper is used at sub- to stoichiometric levels (i.e., noncatalytic amounts), not only for palladium-catalyzed SM cross-couplings of 2-pyridyl boryl,[11] 2-pyridyl thiomethyl,[16] and other systems[17] but also in Stille[9] and Hiyama[10] 2-pyridyl cross-couplings as well, we hypothesized early on[18] that copper may act as a Lewis acid toward the pyridyl nitrogen. This might be favored over the corresponding N-to-Pd bonding that would otherwise remove Pd from the catalytic cycle and slow the overall coupling, as is oftentimes observed with Lewis basic

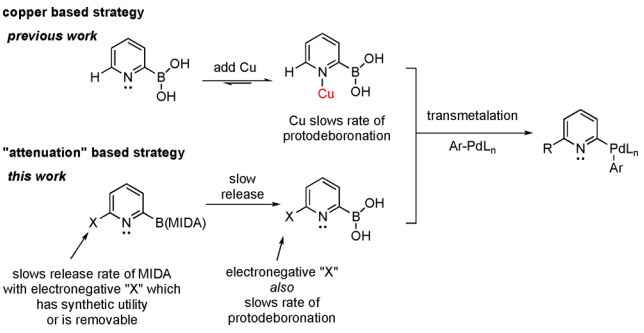
Received: September 21, 2017
Revised: October 23, 2017

DOI: 10.1021/acscatal.7b03241
ACS Catal. 2017, 7, 8331–8337

heterocyclic coupling partners. This is analogous to recent reports of iridium-catalyzed pyridyl C−H borylation, where the catalytic activity of iridium is impacted when Ir is bound to a pyridyl center.[19] Thus, on the basis of the rich history of pyridyl-based directing group chemistry involving both Cu and Pd,[20] we moved forward with our hypothesis that copper might act as a Lewis acid, freeing up Pd to allow cross-coupling to take place.

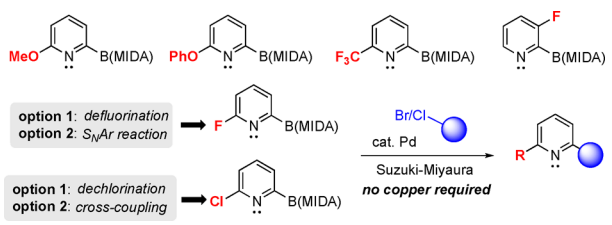
To discourage palladium from interacting at the pyridyl nitrogen in the absence of copper, we initially envisioned a substituent on the pyridine ring that could be easily removed or utilized for subsequent reactions and that would inductively attenuate the basicity at nitrogen. Placing the substituent at the 6-position might also provide steric hindrance at the nitrogen center, with both effects hypothetically weakening N−Pd bonding and aiding in the desired cross-coupling without reliance on copper. Moreover, each newly substituted pyridine would also, after a cross-coupling, provide a new series of pyridyl analogues of potential interest. Such an approach would be complementary to the use of the corresponding *N*-oxide, as recently reported in related couplings.[21] This new strategy, however, would uniquely offer further options for synthetic planning if the group could not only be easily removed but also serve as a handle for downstream functionalization(s). As this study progressed, it was found that substituents at the 6-position attenuated the rate of release of the MIDA ligand and, more importantly, attenuated the rates of protodeboronation, which can otherwise lead to reduced yields of coupled products (Scheme 2).

Scheme 2. "Attenuation" Strategy To Avoid the Use of Copper in 2-Pyridyl MIDA Boronate SM Cross-Couplings



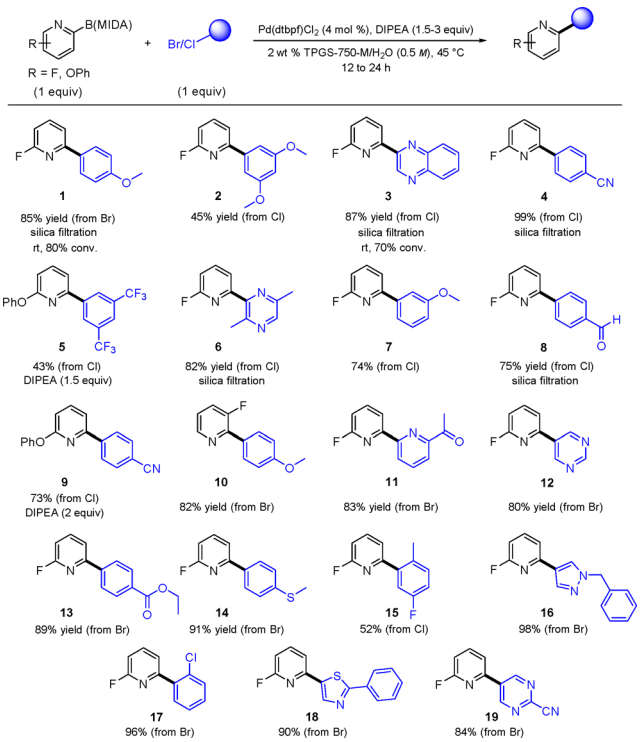
Herein we report the development of this strategy using a fluorine or chlorine residue at the 6-position of 2-B(MIDA)-pyridyl systems, which allows these long-sought cross-couplings to take place in the complete absence of copper (Scheme 3). Examples of SM couplings using such 6-halo-2-pyridyl MIDA boronates, to our knowledge, are not to be found in the literature.[22] After the cross-coupling event, the halogenated product can be used as a coupling partner en route to 2,6-disubstituted pyridines, can participate in S_NAr reactions, or may simply be removed, a process amenable to a one-pot sequence. The resulting technology fulfills several of "The 12 Principles of Green Chemistry,"[23] including (1) the use of a 1:1 ratio of the two coupling partners, (2) a benign reaction medium, (3) mild conditions, and (4) catalytic use of Pd, along with micellar catalysis.[24] The substrate scope is notably broad, using either aryl/heteroaryl chlorides or bromides. In certain cases, *no organic solvent* (including purification) is necessary, as the desired product can simply be filtered and collected. In other cases, the crude material can be filtered through a pad of silica gel to obtain the product in high purity. Lastly, preliminary computational data also provide support for the hypothesis that placement of a halogen at selected sites on the pyridyl ring does indeed lower the rate of protodeboronation after in situ generation of the boronic acid.

Scheme 3. Summary of Substituents That Eliminate the Need for Cu in 2-Pyridyl SM Cross-Couplings



On the basis of an early observation[25] that a methoxy group at the 6-position of a 2-pyridyl MIDA boronate permitted cross-coupling to occur without copper, alternative substituents were investigated in efforts to mimic its role. A variety of 2-B(MIDA)-pyridyl derivatives were synthesized (Scheme 4 and the Supporting Information), including 6-fluoro and 6-chloro derivatives, anticipating that the halogens might be removed or utilized after the initial cross-coupling. We were delighted to find that each halo derivative led to clean couplings without copper. The established conditions were found to be 4 mol % $Pd(dtbpf)Cl_2$ with DIPEA as the base in 2 wt % TPGS-750-M/H_2O at 45 °C *using a 1:1 ratio of the two coupling partners* (Scheme 4). Although the reaction does proceed at room temperature, protodeboronation occurs occasionally (**1**, **3**) in

Scheme 4. Reactions of 6-Fluoro-, 3-Fluoro-, and 6-Phenoxy-2-pyridyl MIDA Boronates with Aryl/Heteroaryl Chlorides and Bromides

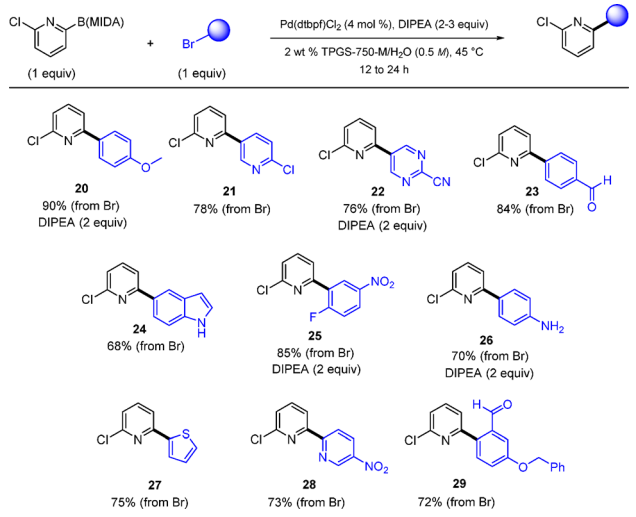


DOI: 10.1021/acscatal.7b03241
ACS Catal. 2017, 7, 8331−8337

competition with cross-coupling. A wide range of functional groups are compatible, including cyano (**4**, **9**), aldehyde (**8**), ketone (**11**), thioether (**14**), and ester (**13**). A variety of heterocycles, including quinoxaline (**3**), pyrazine (**6**), pyridine (**11**), pyrimidine (**12**, **19**), thioazole (**18**), and pyrazole (**16**), also smoothly participate under these conditions. Noteworthy is the high yield achieved for 1-bromo-2-chlorobenzene, where the selectivity for coupling of the bromide is nearly quantitative to give product **17**. Use of the 6-phenoxy group also enables a copperless coupling, but in situ protodeboronation was observed to be far more rapid compared with reactions of 6-methoxy- and 6-fluoro derivatives.

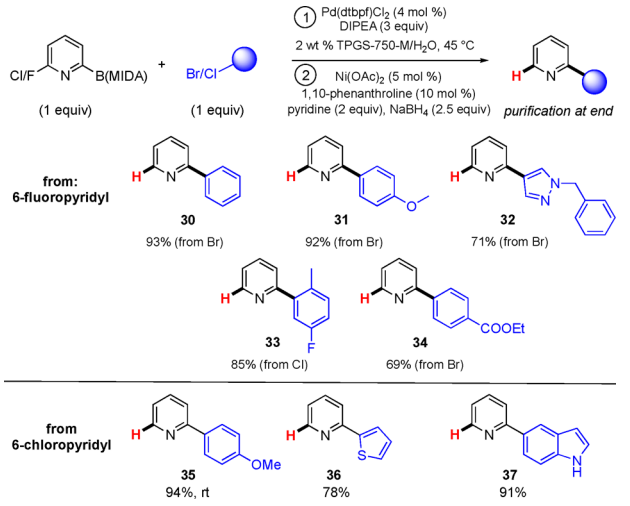
These same conditions apply as well to 6-chloro-2-pyridyl MIDA boronates. Thus, as with the 6-fluoro analogues, a variety of functional groups are tolerated, including a free aniline (**26**), nitro groups (**25**, **28**), a heteroaryl chloride (**21**), aldehydes (**23**, **29**), a cyano group (**22**), and a benzyl-protected phenol (**29**) (Scheme 5). Heterocycles such as pyridine (**21**, **28**), pyrimidine (**22**), and thiophene (**27**) could all be successfully cross-coupled. One particularly interesting aspect of these conditions is that no homocoupling of the B(MIDA)-pyridyl system was observed in either the presence or the absence of the aryl halide coupling partner. Moreover, the chloride at the 6-position remained intact, as oxidative addition was observed only with the aryl/heteroaryl bromide coupling partner.

Scheme 5. Substrate Scope in Couplings of 6-Chloro-2-pyridyl MIDA Boronates with Aryl/Heteroaryl Bromides



To complement our nanomicelle-enabled couplings, micellar conditions were also newly developed for removal of both the fluoride and chloride groups via nickel-catalyzed hydrodehalogenation. Following the SM cross-coupling, the nickel catalyst, ligand, base, and hydride source can be added directly to the reaction vessel to smoothly afford the desired dehalogenated pyridyl ring. A number of reactions were demonstrated in which an initial coupling of either a 6-chloro- or 6-fluoro-2-B(MIDA)-pyridine with an aryl/heteroaryl bromide could be followed by removal of the 6-halogen, both at 45 °C (Scheme 6). Catalytic conditions for hydrodefluorination of 2-fluoropyridines are unknown; nonetheless, this reduction could not only be effected under these conditions but done so with 100% selectively in the presence of Ar−F bonds, as in **33**. Defluorination occurs readily in the presence of an activated

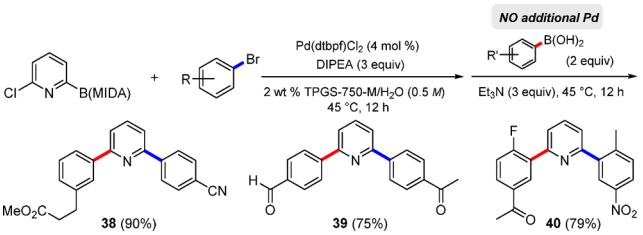
Scheme 6. Coupling/Dehalogenation Reactions under Micellar Catalysis Conditions



ester (**34**). 6-Chloropyridines react under the same conditions, with some reactions taking place at room temperature (e.g., to afford **35**) and in the presence of thiophene (**36**) and free-indole (**37**) functionalities.

The 6-chloro group within the initial product can also be subjected to a second SM cross-coupling *without any additional palladium* being added to the reaction vessel (Scheme 7). More base, in addition to an arylboronic acid, is all that is needed to promote the second coupling. Representative diarylated products derived from insertion of functionalized aryl bromide partners at both the 2- and 6-positions on the pyridyl ring include products **38**, **39**, and **40**, which were formed in good overall yields.

Scheme 7. One-Pot Access to 2,6-Disubstituted Pyridines Using Micellar Catalysis

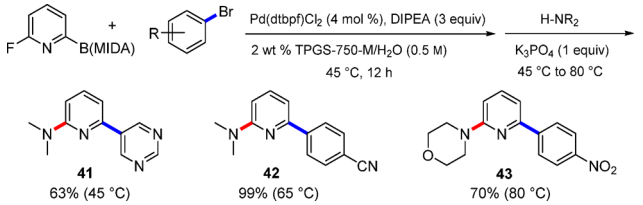


While traditional S_NAr reactions involving 2-fluoropyridyl systems typically take place in organic solvents (e.g., DMF),[26] the 6-fluoro residue is susceptible to subsequent nucleophilic attack in the same aqueous reaction mixture (Scheme 8). Upon completion of the initial cross-coupling, addition of K_3PO_4 along with, e.g., an amine nucleophile leads to displacement reaction products **41**, **42**, and **43**.

Given the prominent role played by 2,6-disubstituted pyridines in pharmaceuticals and agrochemicals (see the examples in Figure 1), we endeavored to demonstrate access to such structures using our micellar technology at each step in a synthesis, in this case of a known antagonist.[27] Beginning with 6-chloro-2-B(MIDA)-pyridine, two successive SM cross-couplings gave product **44** (Scheme 9). Without isolation, a zinc-mediated nitro group reduction[28] yielded the free amine, to which was added benzoyl chloride at room temperature to afford the desired product **45** in a four-step, one-pot sequence

DOI: 10.1021/acscatal.7b03241
ACS Catal. 2017, 7, 8331−8337

Scheme 8. One-Pot Sequence Involving a Second-Stage S_NAr Coupling



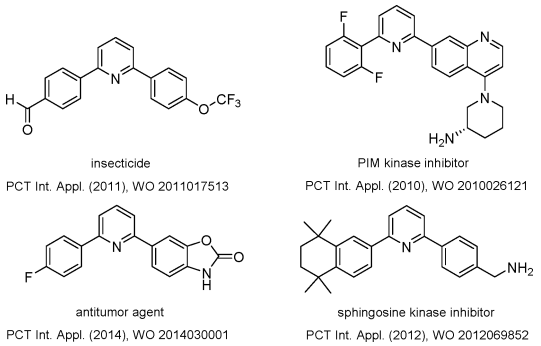
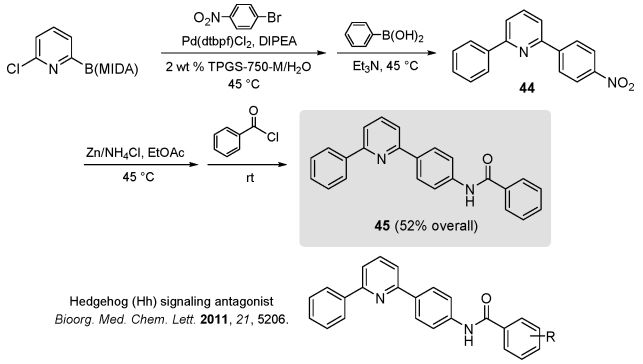


Figure 1. Examples of biologically active 2,6-disubstituted pyridines.

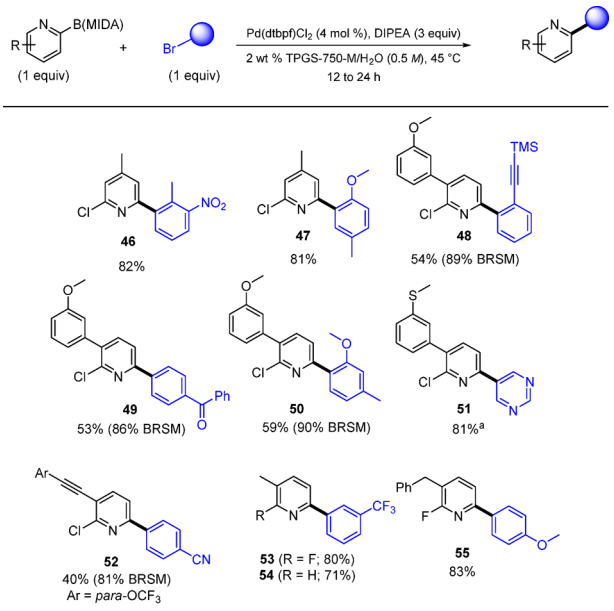
Scheme 9. One-Pot, Four-Step Sequence Leading to a Drug Analogue



in 52% overall yield. To ensure that the reaction mixture remained semihomogeneous, EtOAc as a cosolvent was added to the reaction vessel after both SM cross-couplings, leading to full conversion for the two subsequent reactions. After completion of this four-step, one-pot reaction, more EtOAc was added to effect *in flask* extraction of the product.

To demonstrate that these conditions are also amenable to more highly substituted 2-B(MIDA)-pyridyl arrays, additional complexes were prepared and subjected to the same Pd-catalyzed cross-couplings to arrive at products **46**–**53** and **55** (Scheme 10). It is worth mentioning that when aryl or alkynyl substituents were placed para to the B(MIDA) residue, a significant amount of the starting 2-B(MIDA)-pyridyl complex remained unreacted, suggesting that release of the MIDA ligand is quite slow under these conditions. Thus, for examples leading to moderate yields (e.g., **48**, **49**, **50**, **52**), some of the 2-B(MIDA)-pyridyl starting material could be recovered intact. In general, the yields of the desired biaryl products were good, albeit in some cases they are based on recovered starting material (BRSM). If desired, the reaction yield can be increased (e.g., **51**) by adding additional Ar–Br and base after 24 h to fully consume the remaining 2-B(MIDA)-pyridyl starting

Scheme 10. Expanded Substrate Scope of Substituted 2-Pyridyl MIDA Boronates Coupled with Aryl/Heteroaryl Bromides

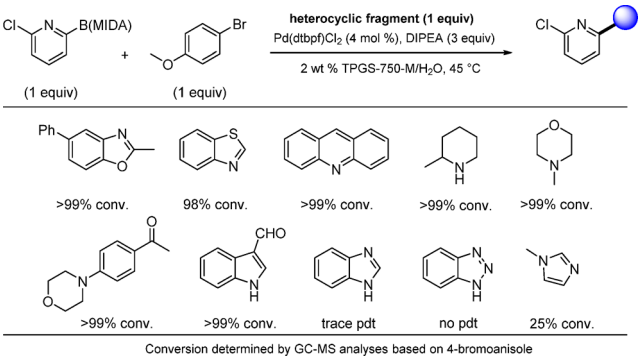


a) More Br-Ar (1 equiv) and DIPEA (3 equiv) was added after 24 hours

material. As shown previously (vide supra), product **53** could be dehalogenated to afford the final product **54**.

To further demonstrate additional functional group compatibility with couplings of 6-chloro-2-pyridyl MIDA boronates under micellar conditions, various heterocycles were added to the reaction mixture, as this has been established as an effective and quick tool for such an assessment.[21a,29] For the system shown (Scheme 11), no additional products beyond the desired

Scheme 11. Doping of the Reaction Mixture with Heterocyclic Fragments To Demonstrate Additional Functional Group Compatibility



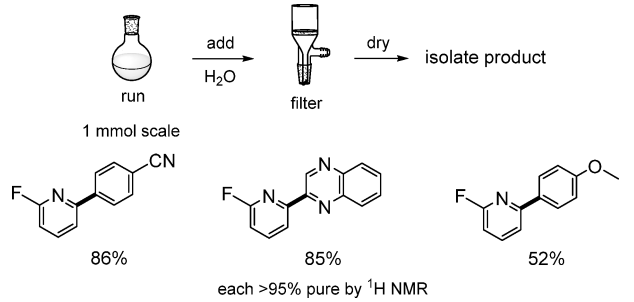
coupling product were observed via GC–MS in addition to the added material. Heterocycles containing oxazole, thiazole, piperidine, morpholine, acridine, and free indole did not affect conversion to the biaryl product. On the other hand, in the presence of *N*-methylimidazole, only 25% conversion took place, while with benzimidazole or benzotriazole present, only a trace of product, at most, was observed.

Another attractive aspect of using 6-halo-2-B(MIDA)-pyridines under micellar catalysis conditions is that simple filtration of the aqueous reaction mixture leads directly to biaryl products, as demonstrated previously using aryl-B(MIDA)

DOI: 10.1021/acscatal.7b03241
ACS Catal. 2017, 7, 8331–8337

complexes (Scheme 12).[25] Thus, on the basis of organic solvents involved in the overall process, the E factor[30] using this

Scheme 12. Examples Using 6-Fluoro-2-B(MIDA)-pyridine in Organic-Solvent-Free Suzuki–Miyaura Reactions

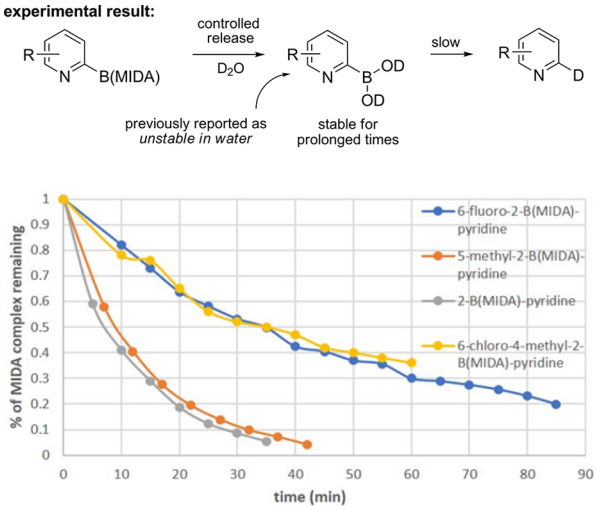


procedure is zero, as no organic solvent is used at any time. After the reaction, only minimal amounts of recyclable water are used to isolate solid product(s) in high yield and purity (>95%, as determined by ^{1}H NMR spectroscopy).

To gain insight as to why fluorine and other inductively electron-withdrawing substituents at the 6-position allow the cross-coupling to occur without copper in the pot, we considered three possible explanations: (1) that an electron-withdrawing substituent, as in 6-fluoro-2-B(MIDA)-pyridine, might weaken binding to palladium and promote transmetalation by opening a coordination site on palladium, (2) that attenuation of the rate of release of the MIDA ligand would lead to slow release of the boronic acid to help prevent competitive protodeboronation, and (3) that direct attenuation of the rates of protodeboronation would promote cross-coupling. For explanation (1), however, it is not clear whether prior binding to the pyridyl nitrogen would cause any problem in attachment of pyridyl group of the boronic acid onto palladium.[12c,31] To investigate the role of pyridyl binding, we note that experimental gas-phase and solution basicities are substantially reduced by inductively electron-withdrawing substituents.[32] Furthermore, density functional theory calculations for 2-B(MIDA)-pyridine show that it can bind to palladium competitively with a water ligand and that 6-fluoro-2-B(MIDA)-pyridine binds with a 4.0 kcal/mol less favorable free energy in toluene (see the Supporting Information for details).

The second possibility for how a 6-fluoropyridyl substituent could function is by affecting the rate of MIDA hydrolysis. Several 2-pyridyl-B(MIDA) complexes were examined by ^{1}H NMR spectroscopy, each in a solution of D_2O, to determine their relative stabilities in an aqueous environment, as 2-pyridylboronic acid complexes (Scheme 13, top) were previously reported to be unstable in water.[7e] We were surprised to find that this conversion worked as well as it did in water, since previously reported studies were *strictly* anhydrous.[11] Recent work has elucidated mechanisms for MIDA hydrolysis under neutral and basic conditions to form boronic acids in aqueous THF.[33] The relative rates of release of the MIDA ligand in D_2O were examined for different pyridyl complexes. As illustrated in Scheme 13 (bottom), both the 6-fluoro-2-B(MIDA)-pyridine derivative and the 6-chloro-2-B(MIDA)-pyridine analogue had significantly slower conversions to their corresponding boronic acids compared with both the parent 2-B(MIDA)-pyridine and the 5-methyl-2-B(MIDA)-pyridine analogue. These data suggest an explanation for why the 6-halopyridyl analogues successfully undergo cross-

Scheme 13. (top) ^{1}H NMR Studies of 2-B(MIDA)-pyridyl Complexes in D_2O; (bottom) Relative Rates of Release of the MIDA Ligands of Various 2-B(MIDA)-pyridyl Complexes in D_2O



coupling, as their slower MIDA release rate reduces the amount of protodeboronation-prone boronic acid in the pot at any given time, though it is not clear that such an effect would be important enough by itself to be effective.

The best explanation, however, is the third one above, that added copper or a 6-fluoro or other electron-withdrawing substituent can promote transmetalation by directly reducing the rates of protodeboronation of 2-pyridylboronic acids. Recent experimental and computational results provide critical insights into the rates at which aryl/heteroaryl boronic acids undergo protodeboronation in acidic, neutral, and basic aqueous dioxane solution.[14] The proposed mechanisms suggest that protodeboronation of 2-pyridylboronic acid is fastest in the pH range 4–11. In these experiments, addition of cupric chloride (0.10 M) slowed protodeboronation of 2-pyridylboronic acid more than 20-fold. This provides the best explanation for how copper salts permit cross-coupling to occur in good yields prior to a protodeboronation side reaction. The 6-trifluoromethyl and 6-methoxy derivatives were also observed to protodeborylate at a reduced rate, suggesting an inductive effect that could be related to how the 6-fluoro and other substituents function. In detailed calculations on the mechanism for protodeborylation of the 6-fluoroboronic acid, we indeed predict that this reaction should occur at a substantially slower rate than with the parent boronic acid.[34]

In summary, new technology has been developed that allows use of stoichiometric amounts of 2-pyridyl MIDA boronates as coupling partners in Suzuki–Miyaura cross-coupling reactions with aryl halides to be run under environmentally responsible micellar catalysis conditions. In particular, excessive amounts of copper, elevated reaction temperatures, large excesses of heavy base, and use of DMF as solvent are literature reaction parameters that have all been favorably mitigated. Most notably, the need for a copper salt as an additive in these reactions has been eliminated by altering the substituent at the 6-position of the pyridine ring to slow the rate of protodeboronation under basic conditions. Key to this success was the judicious choice of either fluorine or chlorine on the pyridyl ring. This approach adds considerable flexibility for secondary same-pot (1) facile removal via a newly developed hydrodehalogenation based on

DOI: 10.1021/acscatal.7b03241
ACS Catal. 2017, 7, 8331–8337

Ni nanoparticles, (2) S_NAr reactions with a 6-fluoro group, and (3) Suzuki–Miyaura coupling with products bearing a 6-chloro moiety. The electron-withdrawing substituents act primarily by mimicking the effect of copper, which functions by slowing the rates of protodeboronation of intermediate 2-pyridylboronic acids. This strategy may prove to be general in other transition-metal-catalyzed reactions using 2-pyridyl organometallic reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b03241.

Experimental procedures, analytical data, copper release rate studies, and NMR spectra (PDF)

Computational and mechanistic results (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by Novartis and the NSF (SusChEM 1561158) is warmly acknowledged. We are also grateful for support by the NIH in the form of a Shared Instrument Grant (1S10OD012077-01A1) and by the Center for Scientific Computing at the CNSI and MRL (NSF MRSEC (DMR-1121053) and NSF CNS-0960316) as well as the use of CYLview version 1.0b software for 3D drawings (C. Y. Legault, Université de Sherbrooke, 2009; http://www.cylview.org). Salts of palladium provided by Johnson Matthey (Dr. Thomas Colacot) and selected chemicals supplied by MilliporeSigma are gratefully acknowledged.

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DOI: 10.1021/acscatal.7b03241
ACS Catal. 2017, 7, 8331−8337