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An efficient and new protocol for phosphine-free Suzuki coupling reaction using palladium-encapsulated and air-stable MIDA Boronates in an aqueous medium

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A simple methodology that uses a system based on polyurea microencapsulated palladium (PdEnCat 30™) and aryl or (2-pyridyl) MIDA boronates for Suzuki–Miyaura cross-coupling reactions of (hetero)aryl halides in water-alcohol under phosphine-free conditions was developed.

Introduction

The palladium catalyzed Suzuki–Miyaura cross-coupling reaction is one of the most powerful and convenient approaches for the synthesis of biaryl compounds.[1] Palladium-catalyzed cross-coupling processes for carbon–carbon bond formation of (het)aryl halides have become an indispensable tool for synthetic and medicinal chemists in their search for new derivatives with wide-ranging therapeutic potential.[2] During the last two decades, there has been an increasing interest in the use of water as solvent for many homogeneously catalyzed reactions.[3] Cost, environmental benefits and safety are among the reasons most often argued to justify the replacement of organic solvents by water in organic transformations. The use of water in Pd-catalyzed cross-coupling reactions goes back to the early development of Suzuki–Miyaura cross-coupling reactions.[4]

On another hand, although boronic acids can serve as excellent building blocks for the synthesis of a wide range of natural products, pharmaceuticals, and materials,[5] some of the potentially most useful boronic acids, including 2-heterocyclic[6-8] derivatives, are inherently unstable, which can significantly limit their benchtop storage and/or efficient cross-coupling. *N*-methyliminodiacetic acid (MIDA) boronates[9,10] represent the first general solution to this problem by virtue of their stability and remarkable capacity for in situ *slow release* of unstable boronic acids. We herein report the use of (aryl) or(2-pyridyl) *N*-methyliminodiacetic acid (MIDA) boronate for Suzuki–Miyaura cross-coupling reactions of highly challenging aryl and heteroarylchlorides, bromides or iodides.

Also, as part of our ongoing interest in palladium-catalyzed reactions, we describe the Suzuki–Miyaura cross-coupling reaction of aryl(heteroaryl)halides with the corresponding MIDA boronates catalyzed by an air-stable and available palladium-encapsulated catalyst (Pd EnCat30™). PdEnCat catalyst significantly facilitates these reactions, benefiting from a much simplified workup procedure: the heterogeneous catalyst is readily removed by filtration.

Therefore, these transformations are often mediated by Pd species in the presence of phosphine ligands, and this may result in difficulties associated with the removal of homogeneous material from reaction mixtures. We have developed an effective methodology that use phosphine-free supported Pd catalyst entrapped in a polyurea matrix, with potential for both economic and environmental advantages. PdEnCat 30™ have proven to be effective as recyclable catalysts for use in Suzuki type cross-coupling reactions and do not require expensive and toxic phosphines as co-ligands.[11-13]

On the other hand, due to their significant and varied biological activities, the design and development of novel methods for the construction of 2-thienyl, 2-pyridil, 3-pyridil, 4-pyridil and 2-phenyl functionalized pyridines have drawn remarkable interest from the synthetic, organic as well as medicinal chemists.[14] 2-(2'-Thienyl)pyridine derivatives have been used frequently to obtain complexes with several transition metals with a wide range of applications in solar energy conversion devices as photocatalysts, photosensitizers and electroluminescent emitters.[15] Also, derivatives of 2-thienylpyridine skeleton exhibited considerable topoisomerase I and II inhibitory activity[16] and are being used in the design of various anticancer agents.[17] Secondly, phenyl pyridines have emerged as the integral backbone of several potent azapeptide HIV protease inhibitors with anti HIV activity such as Atazanavir (BMS-232632), an orally available azapeptide.[18] Bipyridine compounds as α-terpyridine or 4,6-diaryl-2,4'-bipyridine molecule can act as tridentate ligands and form stable complexes by chelating a broad variety of transition metal ions. The numerous reports on DNA binding property and antitumor activity of terpyridine complexes have attracted multiple researchers.[19] (Figure 1)

One of the main objectives of eco-friendly methods in organic chemistry is to develop cost-effective and environmentally benign synthetic protocols which have become one of the main themes of contemporary synthetic chemistry. Thus, we developed a mild, phosphine-free single-step procedure for the Suzuki coupling of readily available hetaryl(aryl)halides in water medium to the corresponding biaryl, bipyridyl and thienylpyridine as a part of our ongoing research in the development of new ecofriendlyprotocols.

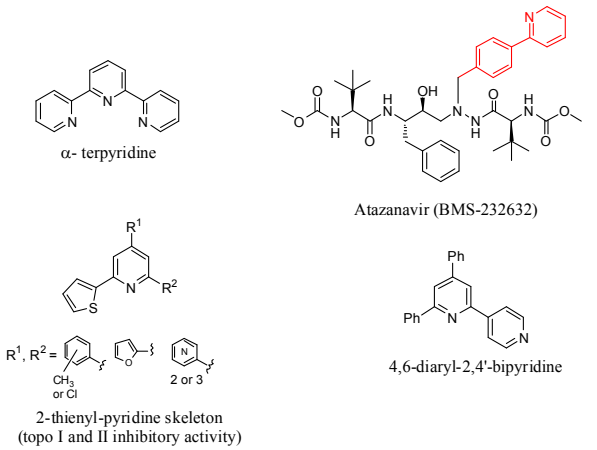
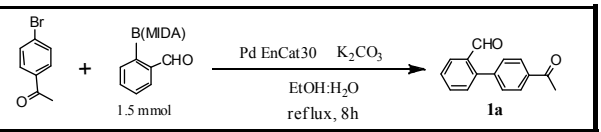


Figure 1. Structure of 2-thienylpyridines, α-terpyridine and 4,6-diaryl-2,4'-bipyridine derivatives.

Results and discussion

In order to optimize the reaction conditions for the Suzuki–Miyaura synthesis we studied the coupling reaction of 4-bromoacetophenone with 2-formylphenylboronic acid MIDA or 6-methoxypiridylboronic acid MIDA ester (1.5 equiv) in the presence of K_2CO_3 (3.0 equiv) as a model.

Two parameters were investigated: (1) optimal ratio of aqueous solvent used and (2) palladium catalyst concentration. (Table 1)



Entry[a]	Volumetric ratios EtOH:H_2O	Catalyst Loading (mol%)	Suzuki-coupling product **(1a)** yield[b] (%)
1	1:1	10 %mol	(51%)
2	2:1	10 %mol	(56%)
3	3:1	10 %mol	(60%)
4	4:1	10 %mol	(76%)
5	4:1	8 %mol	(77%)
6	**4:1**	**6 %mol**	**(80%)**
7	4:1	2.5 %mol	(70 %)
8	4:1	1 %mol	(67%)
9	6:1	10 %mol	(61%)
10	8:1	10 %mol	(63%)

[a]3.0equiv of K_2CO were used [b] isolated yield

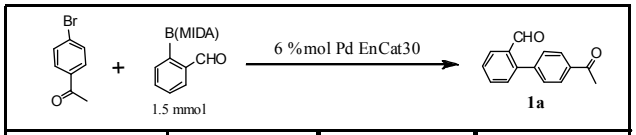
Table 1 Suzuki-Miyaura reaction of 4-bromoacetophenone with 2-formylphenylboronic acid MIDA ester as a model to optimize the conditions.

Initially, the reaction was carried out using only ethanol as solvent, PdEnCat30 (10 mol%) as the catalyst and K_2CO_3 (3 eq) as base, heating under reflux for 3-9 h, when we isolated the Suzuki product in very low yields, the majors products being the homocoupling and the dehalogenation products, alongside with the formation of black palladium. However, yields increased substantially when significant volumes of water were added to the reaction. Then, we tested several volumetric ratios of ethanol: H_2O (1:1, 2:1, 3:1, 4:1, 6:1, 8:1) and we found that in the reaction conditions used, the highest conversion to **1** was observed when the volumetric ratio of ethanol:H_2O was 4:1, together with the lowest occurrence of the debrominated or homocoupling side products, while the formation of black palladium was not observed. In the other ratios tested, the coupling reactions were accompanied by different extents of hydrodehalogenation or homocoupling, which were isolated always as major products in these cases where formation of black palladium was observed.

Heterocyclic compounds are of particular interest to the pharmaceutical industry,[20]but the application of heterocyclic compounds in cross-coupling reactions remains a challenge.[21] To the best of our knowledge, only a few successful examples of aqueous-phase Suzuki–Miyaura cross-coupling reactions of heteroaryl chlorides are known.[22]

Thus, there is a need for the development of efficient procedures for the cross-coupling reactions of heteroaryl chlorides with arylboronic acids in water. To carry out an economical large-scale synthesis of pharmaceutical intermediates or other bulk fine chemicals, a low loading catalyst is needed. So then, we finally investigated the minimum quantity of catalyst required to achieve a fast and complete conversion. We compared three conditions with decreasing amounts of Pd EnCat30(without phosphine) and using K_2CO_3 as base and ethanol:H_2O (4:1) as solvent. Then, carrying out the coupling reaction at palladium loadings of 10, 8, 6, 2.5 or 1mol% always led to the desired coupling product in similar yields after 8 h at reflux. The best results were obtained in the presence of a 6 mol% catalyst concentration.

Additionally, we performed a study of the catalytic activity of Pd EnCat30 for our reaction under the best conditions found using the reaction of 4-bromoacetophenone with 2-formylphenylboronic acid MIDA ester as model. The results showed that when the catalyst was recycled 3 times at the reaction conditions established no significant loss of activity or yield occurred. During these reactions, the formation of black palladium was not observed. (Table 2)

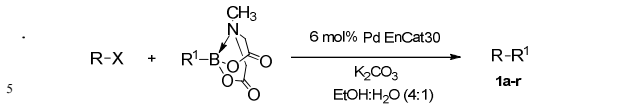


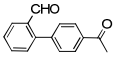
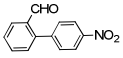
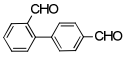
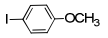
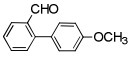
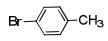
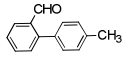
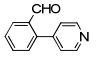
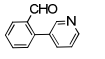
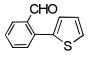
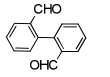
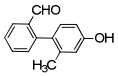
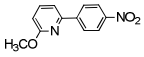
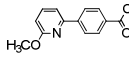
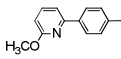
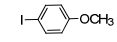
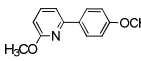
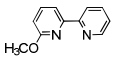
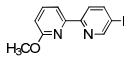
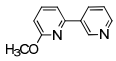
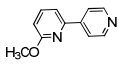
	1st recycle	2nd recycle	3rd recycle
% Yield **1a**	78	77	74

Conditions: K_2CO_3 (3.0 mmol), EtOH:H_2O (4:1), reflux, 8h

Table 2 Reuse of Pd-catalyst in the Suzuki-Miyaura reaction of 4-bromoacetophenone with 2-formylphenylboronic acid MIDA ester

Under the optimized reaction conditions, we investigated the reaction of some aryl halides with 2-formylphenylboronic and 6-methoxy-2-pyridylboronic acids MIDA esters.This investigation showed that the reaction successfully occurred without any phosphine ligand to give the corresponding Suzuki-coupling products **1a-t** in good to excellent yields. (Table 3)



Entry[c]	R-X	R^1	Reaction time (h)	Suzuki-coupling product (1) yield[b] (%)
1			(8)	 **1a** (80%)
2			(5)	 **1b** (90%)
3			(3)	 **1c** (98%)
4			(9)	 **1d** (78%)
5			(8)	 **1e** (80%)
6[e]			(8)	 **1f** (91%)
7			(9)	 **1g** (97%)
8			(8)	 **1h** (85%)
9			(5)	 **1i** (84%)
10			(9)	 **1j** (81%)
11			(3)	 **1k** (82%)
12			(8)	 **1l** (84%)
13			(8)	 **1m** (96%)
14			(9)	 **1n** (91%)
15			(9)	 **1o** (72%)
16			(3)	 **1p** (76%)
17			(8)	 **1q** (85%)
18			(8)	 **1r** (76%)
19			(3)	**1s** (80%)
20			(8)	**1t** (75%)

[a] Reaction conditions: 1 equiv of aryl halide (1 mmol), 1.5 equiv of MIDA boronate, 6 mol % Pd EnCat30, 3 equiv of K_2CO_3, 0.1 M in 4:1 ethanol/H_2O. [b] isolated yield. [c]Cross-couplings were run at reflux. [d]4-bromopyridine hydrochloride was used.

Table 3 Suzuki-Miyaura reaction of aryl (hetaryl) halides with 2-formylphenylboronic acid MIDA ester and two 2-pyridyl boronic acid MIDA ester [a]

Then, a wide array of aryl halides reacted efficiently with 2-formylphenylboronic acid MIDA ester and 6-methoxy-2-pyridylboronic acid MIDA ester respectively to provide the corresponding products **1a-t**. For example, 4-bromobenzaldehyde and 4-iodonitrobenzene reacted with 2-formylphenylboronic acid MIDA ester to yield in 90% and 98% respectively, the coupling products **1b** and **1c**.

The coupling reactions of representative heteroaromatic halides were also effective with this protocol. Under the same conditions, 3-bromopyridine reacted efficiently with 6-methoxypyridylboronic acid MIDA ester within 8 h, providing 85% yield of the desired product **1q**, while, the quinoline **1s** was prepared by the reaction of 2-bromoquinoline with 6-methoxypyridylboronic acid MIDA ester to give the desired product in good yield (80%). The 2,2'-bipyridine unit is a key structural feature found in some important natural products that show antibiotic and cytotoxic activities.[23]

The feasibility of our strategy was demonstrated in the synthesis of thio-derivatives, when 2-bromothiophene was treated with 2-formylphenylboronic acid MIDA ester or 6-methoxypyridylboronic acid MIDA ester (1.5 equiv) under the conditions already established. The reaction proceeded well to give 2-(thiophen-2-yl)benzaldehyde (**1h**) and 2-methoxy-6-(thiophen-2-yl)pyridine (**1t**) respectively, in good yields via C–C bond formation. Since most of the strategies for the synthesis of these phenyl-pyridines or thienylpyridines by condensation and substitution reactions frequently afford the desired products in low yields and with low regioselectivity towards the 2-position, our synthetic strategy allows the effective construction of large libraries of 2-thienyl and 2-phenylpyridinederivatives in an efficient and eco-friendly method.

Conclusions

In conclusion, a convenient methodology was developed for the palladium catalyzed Suzuki–Miyaura reaction in water. The reaction is catalyzed by a system based on Pd- microencapsulated in a polyurea matrix (Pd EnCat30), through a simple and efficient protocol for the phosphine-free Suzuki coupling of aryl (hetaryl) halides with arylboronic acids MIDA esters. The advantages of this procedure are simple operation, good to excellent yields, short reaction time, absence of phosphine-ligands and mild and environmentally friendly conditions. A great diversity of substrates was tolerated for this method.

Experimentalprocedure

General information

All reagents were purchased from Sigma Aldrich and used without further purification. Ethanol were purchased from local suppliers. The analyses by Gas Chromatography–Mass Spectrometry (CG-MS) were performed on a Shimadzu GCMS-QP2010S with a RTX-5MS capillary column (30 m x 0.25 mm x 0.25 µm, with the stationary phase 5% diphenyl and 95% dimethylpolysiloxane), mass detector in mode electron ionization (EI) standard (70 eV), with helium as a carrier gas.The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AMX-200 spectrometer operating at 200 MHz (^{1}H) and 50 MHz (^{13}C) in $CDCl_3$ with TMS as an internal standard. The ^{1}H- and ^{13}C-NMR spectra were processed using MESTREC/NMR.

General Method for Carrying out the Suzuki-Coupling (Table 3)

Under ambient atmosphere, to a 15 mL vial equipped with a stir bar was added the halide (1.0 mmol), 2-formylphenyl or 2-pyridyl MIDA boronate (1.5 mmol), K_2CO_3 (3.0 mmol), Pd enCat30 (6 mol %) and ethanol:H_2O (4:1 v/v). The reaction mixture was stirred at reflux for 3-9 h. The mixture was cooled to room temperature and then was transferred to a 60 mL separatory funnel and was added brine (10 mL). The mixture was extracted with AcOEt (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The organic residue was adsorbed onto silica gel, and then purified by column flash chromatography (hexane/ethyl acetate as eluent) to afford the desired product **1a-t**. All the compounds prepared are known compounds.[24-42] The products were confirmed by comparing the ^{1}H NMR and mass spectral data with authentic samples reported in the literature.

4'-Acetyl-[1,1'-biphenyl]-2-carbaldehyde (1a).[24] Following the general procedure for Table 3, using 4-bromoacetophenone (70mg, 0.351 mmol), 2-formylphenylboronic acid MIDA ester (110mg, 0.422 mmol), potassium carbonate (145mg, 1.054 mmol), Pd EnCat30 (53mg, 0.021 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1a** as a colorless oil (63 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ2.67 (s, 3H), 7.43-7.61 (m, 3 H), 7.63-7.72 (m, 2 H), 8.02-8.09 (m,3 H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 128.3, 128.6, 128.7, 129.7, 130.0,130.3, 130.5,130.8, 133.9, 136.8, 142.9, 144.7, 191.9, 197.7.

4'-Nitro-[1,1'-biphenyl]-2-carbaldehyde (1b).[25] Following the general procedure for Table3, using 4-iodonitrobenzene (70 mg, 0.281 mmol), 2-formylphenylboronic acid MIDA ester (88 mg, 0.337 mmol), potassium carbonate (117 mg, 0.843 mmol), Pd EnCat30 (43 mg, 0.017 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 5 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide**1b** as a light yellow solid (54 mg, 90% yield), mp 118-120 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ7.43 (d, *J* = 7.6 Hz, 1 H), 7.57-7.67 (m, 4 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 8.04 (d, *J* = 7.6 Hz, 1 H), 8.34 (d, *J* = 8.3 Hz, 1 H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.8, 129.1, 129.3, 130.8, 131.0, 133.8, 134.1, 143.2, 145.0, 147.9, 191.2.

[1,1'-Biphenyl]-2,4'-dicarbaldehyde(1c).[26] Following the general procedure for Table 3, using 4-bromobenzaldehyde (80 mg, 0.432 mmol), 2-formylphenylboronic acid MIDA ester (170 mg, 0.648 mmol), potassium carbonate (180 mg, 1.30 mmol), Pd EnCat30 (64.8 mg, 0.026 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 3 h. After work-up the residue was purified by flash column chromatography (SiO_2, 7:1 hexane:ethyl acetate) to provide **1c** as a white solid (87 mg, 98% yield), mp 94-96 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.74 (m, 5 H), 7.98-8.08 (m, 3 H), 9.98 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.4, 128.8, 129.8, 130.7, 130.8, 133.8, 133.9, 136.0, 144.3, 144.4, 191.6, 191.8.

4'-Methoxy-[1,1'-biphenyl]-2-carbaldehyde (1d).[27] Following the general procedure for Table 3, using 4-iodoanisol (85 mg, 0.363 mmol), 2-formylphenylboronic acid MIDA ester (142 mg, 0.540 mmol), potassium carbonate (151 mg, 1.09 mmol), Pd EnCat30 (54 mg, 0.022 mmol), 4:1 aq. ethanol (11 mL) were heated under reflux for 9 h. After work-up the residue was purified by flash column chromatography (SiO_2, 15:1 hexane:ethyl acetate) to provide **1d** as a colorless oil (60 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ3.88 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.42-7.46 (m, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 10.0 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ55.6, 114.2, 127.6, 127.8, 130.3, 131.0, 131.5, 133.7, 134.0, 145.9, 159.9, 192.9.

4'-Methyl-[1,1'-biphenyl]-2-carbaldehyde (1e).[28] Following the general procedure for Table 3, using 4-bromotoluene (75 mg, 0.44 mmol), 2-formylphenylboronic acid MIDA ester (171 mg, 0.657 mmol), potassium carbonate (181 mg, 1.31 mmol), Pd EnCat30 (66 mg, 0.026 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate) to provide **1d** as a light yellow oil (68 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ2.40 (s, 3H), 7.22-7.30 (m, 4H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H), 8.00 (dd, *J* = 8.2, 1.2 Hz, 1H), 9.97 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 114.4, 127.3, 127.6, 130.6, 130.9, 131.5, 133.9, 134.1, 146.0, 159.8, 192.8.

2-(Pyridin-4-yl)benzaldehyde (1f).[29] Following the general procedure for Table 3, using 4-bromopyridine hydrochloride (95 mg, 0.49 mmol), 2-formylphenylboronic acid MIDA ester (192 mg, 0.734 mmol), potassium carbonate (203 mg, 1.47mmol), Pd EnCat30 (74 mg, 0.029 mmol), 4:1 aq. ethanol (12 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 3:2 hexane:ethyl acetate) to provide **1f** as a light orange solid (80 mg, 91% yield); mp 64-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.32-7.35 (m, 2 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.73 (dt, *J* = 7.5, 1.5 Hz, 1 H), 8.07 (d, *J* = 7.5 Hz, 1 H), 8.72 (dd, *J* = 6.2, 1.1 Hz, 2 H), 9.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ124.9, 128.6, 129.2, 130.5, 133.6, 134.0, 142.9, 146.1, 150.0, 191.3.

2-(Pyridin-3-yl)benzaldehyde (1g).[30] Following the general procedure for Table 3, using 3-bromopyridine (70 mg, 0.44 mmol), 2-formylphenylboronic acid MIDA ester (139 mg, 0.531 mmol), potassium carbonate (184 mg, 1.33 mmol), Pd EnCat30 (66 mg, 0.026 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 9 h. After work-up the residue was purified by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate) to provide **1g** as a colorless oil (80 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.46 (m, 2 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.73 (d, *J* = 7.5 Hz, 1 H), 8.06 (d, *J* = 7.5 Hz, 1 H), 8.70 (dd, *J* = 6.4, 1.5 Hz, 2 H), 9.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.3, 128.7, 128.9, 131.2, 133.8 133.9, 134.1, 137.4, 142.0, 149.5, 150.3, 191.5.

2-(Thiophen-2-yl)benzaldehyde (1h).[30] Following the general procedure for Table 3, using 2-bromothiophene (100 mg, 0.61 mmol), 2-formylphenylboronic acid MIDA ester (240 mg, 0.92 mmol), potassium carbonate (253 mg, 1.83 mmol), Pd EnCat30 (92 mg, 0.036 mmol), 4:1 aq. ethanol (13 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 30:1 hexane:ethyl acetate) to provide **1h** as a light yellow oil (98 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.14 (m, 1 H), 7.15-7.18 (m, 1 H), 7.46-7.49 (m, 3 H), 7.60 (d, *J* = 8.2 Hz, 1 H), 8.01 (d, *J* = 7.5 Hz, 1 H), 10.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.5, 127.9, 128.0, 128.4, 129.7, 131.5, 133.7, 134.4, 138.2, 138.9, 192.2.

[1,1'-Biphenyl]-2,2'-dicarbaldehyde (1i).[31] Following the general procedure for Table 3, using 2-bromobenzaldehyde (60 mg, 0.324 mmol), 2-formylphenylboronic acid MIDA ester (127 mg, 0.49 mmol), potassium carbonate (134 mg, 0.972 mmol), Pd EnCat30 (48 mg, 0.020 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 5 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1i** as a light yellow oil (56 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.34 (dd, J = 1.0, 7.8 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.66 (dt, *J* = 1.2, 7.6 Hz, 2H), 8.06 (dd, *J* = 1.0, 7.8 Hz, 2H), 9.83 (s, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 141.3, 134.7, 133.5, 131.8, 128.9, 128.7.

4'-Hydroxy-2'-methyl-[1,1'-biphenyl]-2-carbaldehyde (1j).[32] Following the general procedure for Table 3, using 4-chloro-3-methylphenol (70 mg, 0.491 mmol), 2-formylphenylboronic acid MIDA ester (192 mg, 0.73 mmol), potassium carbonate (203 mg, 1.47 mmol), Pd EnCat30 (73 mg, 0.0294 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 1:1 hexane:ethyl acetate) to provide **1j** as a white solid (81 mg, 81% yield), mp 148-150 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ2.51 (s, 3H), 7.27-7.17 (m, 2H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.60-7.55 (m, 2H), 7.87-7.90 (m, 2H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 114.1, 121.4, 128.6, 128.7, 132.3, 133.3, 133.6, 133.7, 134.8, 135.4, 139.7, 155.6, 195.9.

2-Methoxy-6-(4-nitrophenyl)pyridine (1k).[33] Following the general procedure for Table 3, using 4-iodonitrobenzene (85 mg, 0.34 mmol), 6-

methoxypyridylboronic acid MIDA ester (135 mg, 0.51 mmol), potassium carbonate (142 mg, 1.02 mmol), Pd EnCat30 (51 mg, 0.020 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 3 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1k** as a light yellow solid (64 mg, 82% yield); mp104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ4.05 (s, 3H), 6.80 (d, J = 8.0 Hz, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.69 (t, J = 8.0 Hz, 1 H), 8.18-8.32 (m,4 H).^{13}C NMR (100 MHz, $CDCl_3$) δ53.6, 111.5, 114.0, 124.1, 127.5, 139.6, 145.2, 148.2, 152.2, 164.2.

4-(6-Methoxypyridin-2-yl)acetophenone (1l).[34] Following the general procedure for Table 3, using 4-bromoacetophenone (50 mg, 0.25 mmol), 6-methoxypyridylboronic acid MIDA ester (99 mg, 0.38 mmol), potassium carbonate (104 mg, 0.75 mmol), Pd EnCat30 (38 mg, 0.015 mmol), 4:1 aq. ethanol (8 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1l** as a white solid (48 mg, 84% yield); mp73-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 4.05 (s, 3H), 6.75 (d, J = 8.0 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.66 (t, J = 8.0 Hz, 1 H), 8.01-8.16 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ26.9, 53.5, 110.6, 113.7, 126.9, 128.9, 137.2, 139.5, 143.5, 153.4, 164.1, 198.0.

4-(6-Methoxypyridin-2-yl)benzaldehyde (1m).[35] Following the general procedure for Table 3, using 4-bromobenzaldehyde (60 mg, 0.32 mmol), 6-methoxypyridylboronic acid MIDA ester (128 mg, 0.48 mmol), potassium carbonate (134 mg, 0.96 mmol), Pd EnCat30 (49 mg, 0.019 mmol), 4:1 aq. ethanol (8 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1m** as a white solid (66 mg, 96% yield); mp 74-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3H), 6.77 (d, J = 7.6 Hz, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.67 (t, J = 7.6 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 2 H), 8.22 (d, J = 7.6 Hz, 2 H), 10.07 (s, 1H) .^{13}C NMR (100 MHz, $CDCl_3$) δ 53.5, 110.9, 113.9, 127.3, 130.2, 136.5, 139.5, 144.8, 153.2, 164.1, 192.1.

2-Methoxy-6-(4-methoxyphenyl)pyridine (1n).[36] Following the general procedure for Table 3, using 4-iodoanisol (50 mg, 0.21 mmol), 6-methoxypyridylboronic acid MIDA ester (84 mg, 0.32 mmol), potassium carbonate (89 mg, 0.63 mmol), Pd EnCat30 (32 mg, 0.013 mmol), 4:1 aq. ethanol (8 mL) were heated under reflux for 9 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1n** as a colorless oil (42 mg, 91% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ3.85 (s, 3H), 4.02 (s, 3H), 6.63 (d, J = 7.8 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.55 (t, J = 8.0 Hz, 1 H),7.98-8.02 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ53.3, 55.5, 108.5, 112.1, 114.2, 114.4, 127.9, 128.2, 132.0, 139.3, 154.6, 160.6, 163.9.

6-Methoxy-2,2'-bipyridine (1o).[37] Following the general procedure for Table 3, using 2-bromopyridine (60 mg, 0.38 mmol), 6-methoxypyridylboronic acid MIDA ester (150 mg, 0.57 mmol), potassium carbonate (157 mg, 1.14 mmol), Pd EnCat30 (57 mg, 0.023 mmol), 4:1 aq. ethanol (8 mL) were heated under reflux for 9 h. After work-up the residue was purified by flash column chromatography (SiO_2, 15:1 hexane:ethyl acetate) to provide **1o** as a colorless oil (51 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ4.05 (s, 3H), 6.76 (d, J = 8.0 Hz, 1 H), 7.28-7.33 (m, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.80 (td, J = 7.4, 1.0 Hz, 1 H), 8.00 (d, J = 7.4 Hz, 1 H), 8.41 (d, J = 7.5 Hz, 1 H), 8.65 (dd, J = 7.4, 1.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.4, 111.2, 113.9, 121.2, 123.7, 136.9, 139.6, 149.3, 153.7, 156.3, 163.7.

6'-Methoxy-5-nitro-2,2'-bipyridine (1p).[38]Following the general procedure for Table3, using 2-chloro-4-nitropyridine (65 mg, 0.41 mmol), 6-methoxypyridylboronic acid MIDA ester (163 mg, 0.62 mmol), potassium carbonate (170 mg, 1.23 mmol), Pd EnCat30 (62 mg, 0.025 mmol), 4:1 aq. ethanol (10mL) were heated under reflux for 3 h. After work-up the residue was purified by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate) to provide **1p** as a white solid (72 mg, 76% yield); mp 114-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 3H), 6.88 (d, J = 7.8 Hz, 1 H), 7.76 (t, J = 7.6 Hz, 1 H), 8.13 (d, J = 7.4 Hz, 1 H), 8.57-8.64 (m, 2 H), 9.45 (s, 1 H).^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 113.4, 115.7, 121.0, 132.0, 139.8, 144.0, 144.9, 151.3, 161.1, 164.0.

6-Methoxy-2,3'-bipyridine (1q).[39] Following the general procedure for Table 3, using 3-bromopyridine (60 mg, 0.38 mmol), 6-methoxypyridylboronic acid MIDA ester (150 mg, 0.57 mmol), potassium carbonate (157 mg, 1.14 mmol), Pd EnCat30 (57 mg, 0.023 mmol), 4:1 aq. ethanol (8 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate) to provide **1q** as a colorless oil (60 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 6.74 (d, J = 8.0 Hz, 1 H), 7.35-7.41 (m, 2 H), 7.66 (t, J = 8.0 Hz, 1 H), 7.80 (dt, J = 8.0, 1.0 Hz, 1 H), 8.62 (dd, J = 8.0, 1.0 Hz, 1 H), 9.25 (s, 1 H).^{13}C NMR (100 MHz, $CDCl_3$) δ 53.5, 110.4, 114.0, 123.6, 134.1, 134.7, 139.5, 148.4, 149.8, 152.1, 164.2.

6-Methoxy-2,4'-bipyridine (1r).[40] Following the general procedure for Table 3, using 4-bromopyridine hydrochloride (80 mg, 0.41 mmol), 6-methoxypyridylboronic acid MIDA ester (163 mg, 0.61 mmol), potassium carbonate (170 mg, 1.23 mmol), Pd EnCat30 (62 mg, 0.025 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) to provide **1r** as a colorless oil (58 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ3.97 (s, 3H), 6.72 (dd, J = 8.3, 0.6 Hz, 1 H), 7.34 (dd,J = 7.4, 0.6 Hz,1 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.81-7.87 (m, 2 H), 8.59-8.66 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.5, 111.7, 113.6, 121.0, 139.5, 146.3, 140.4, 151.9, 164.2.

2-(6-Methoxypyridin-2-yl)quinoline (1s).[41] Following the general procedure for Table 3, using 2-bromoquinoline (70 mg, 0.33 mmol), 6-methoxypyridylboronic acid MIDA ester (133 mg, 0.50 mmol), potassium carbonate (139 mg, 1.00 mmol), Pd EnCat30 (50 mg, 0.020 mmol), 4:1 aq. ethanol (10 mL) were heated under reflux for 3 h. After work-up the residue was purified by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate) to provide **1s** as a white solid (63 mg, 80% yield); mp 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 6.83 (d, J = 8.1 Hz, 1 H), 7.54 (t, J = 7.4 Hz, 1 H), 7.68-7.80 (m, 2H), 7.84 (d, J = 8.1Hz, 1 H), 8.17 (d, J = 8.5 Hz, 1H), 8.17-7.30 (m, 2H), 8.57 (d, J = 8.5 Hz, 1H).^{13}C NMR (100 MHz, CDCl3) δ 53.5, 111.5, 114.7, 119.2, 126.8, 127.7, 128.4, 129.6, 130.0, 136.7, 139.6, 148.1, 153.9, 156.3, 163.8.

2-Methoxy-6-(thiophen-2-yl)pyridine (1t).[42] Following the general procedure for Table 3, using 2-bromothiophene (100 mg, 0.61 mmol), 6-methoxypyridylboronic acid MIDA ester (240 mg, 0.92 mmol), potassium carbonate (253 mg, 1.83 mmol), Pd EnCat30 (91 mg, 0.036 mmol), 4:1 aq. ethanol (13 mL) were heated under reflux for 8 h. After work-up the residue was purified by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate) to provide **1t** as a light yellow oil (88 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3H), 7.23 (dd, J = 3.6, 0.9 Hz, 1 H), 7.69 (dd, J = 5.1, 0.9 Hz, 1 H), 7.92 (dd, J = 5.1,0.6 Hz, 1 H), 8.02 (dd, J = 8.0, 1.2 Hz, 1 H), 8.04 (t, J = 8.0, 1.2 Hz, 1 H), 8.49 (dd, J = 7.8, 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl3) δ 53.4, 108.9, 111.3, 124.3, 127.1, 127.9, 139.1, 144.9, 150.0, 163.5.

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