JOC The Journal of Organic Chemistry

Article

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A General Suzuki Cross-Coupling Reaction of Heteroaromatics Catalyzed by Nanopalladium on Amino-Functionalized Siliceous Mesocellular Foam

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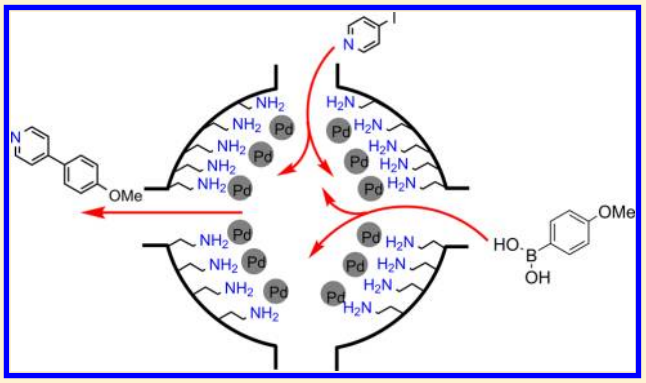
Supporting Information

ABSTRACT: Suzuki–Miyaura cross-coupling reactions of heteroaromatics catalyzed by palladium supported in the cavities of amino-functionalized siliceous mesocellular foam are presented. The nanopalladium catalyst effectively couples not only heteroaryl halides with boronic acids but also heteroaryl halides with boronate esters, potassium trifluoroborates, MIDA boronates, and triolborates, producing a wide range of heterobiaryls in good to excellent yields. Furthermore, the heterogeneous palladium nanocatalyst can easily be removed from the reaction mixture by filtration and recycled several times with minimal loss in activity. This catalyst provides an alternative, environmentally friendly, low-leaching process for the preparation of heterobiaryls.



INTRODUCTION

The Suzuki–Miyaura cross-coupling reaction is one of the most commonly employed transformations for formation of carbon–carbon bonds. Because of the mild reaction conditions, the availability of reagents, and the broad functional group tolerance of this transformation, it has found extensive use in synthetic organic chemistry.[1−3] Heterobiaryls are common structural motifs in biologically active compounds, including drugs in clinical use (Figure 1),[4] and these compounds should be readily available via cross-coupling methodology.

However, there are only a handful of Suzuki–Miyaura procedures that tolerate a wider scope of heterocycles as these cross-coupling reactions typically result in low yields or complete catalyst inhibition.[7−9] A majority of the cross-coupling reactions used in the pharmaceutical industry rely on homogeneous catalysis, which requires recycling of often expensive and toxic catalysts. These catalysts may generate poisonous waste, and there is also a profound risk for metal contamination in the desired product. From a patient safety perspective, removal of toxic metal residues in the pharmaceutically active ingredient is very important.[10,11] The acceptable level of the platinoids (Pt, Pd, Ir, Rh, Ru) in a compound for oral administration is less than 10 ppm.[12,13] For this reason, the development of new techniques and supports for immobilization of the catalytic metal species has gained increased attention.[10,14] Thus, a heterogeneous palladium catalyst where the metal is immobilized to a solid support allows for easier separation of the catalyst from the reaction mixture at the end of the reaction and enables efficient recycling of the catalyst. With ligand-free catalytic systems, the reaction also becomes more environmentally friendly and the work-up is further simplified.[15] Various supports for palladium have been explored,[16−20] such as carbon-based materials,[21,22] metal–organic frameworks (MOF),[23,24] Al_2O_3,[25] and polystyrene.[26] To this end, we decided to investigate a relatively new support, namely, mesocellular foam (MCF), which is a silica-based mesoporous material with a large surface area and a large pore volume, as well as an adjustable pore size.[27,28] The MCF support has the advantage of presenting surface silanol groups that can be functionalized, with a range of diverse ligands, making it a great support for chemical catalysts and biocatalysts.[29−31] Palladium immobilized on aminopropyl (AmP)-functionalized siliceous mesocellular foam (Pd^0-AmP-MCF) is a recently developed heterogeneous catalyst in our laboratories.[32] This catalyst has been used successfully in transfer hydrogenation of alkenes and Suzuki cross-couplings with aryl halides,[33] in racemization of amines,[32] in aerobic oxidation of primary and secondary alcohols,[34] and in selective transfer hydrogenation of nitroarenes to anilines.[35] Recently, both enzyme *Candida antarctica* Lipase B and palladium nanoparticles were immobilized in MCF (in the same cavity) and used for dynamic kinetic resolution (DKR) of amines.[36]

Received: February 20, 2014
Published: March 28, 2014

   dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946–3954

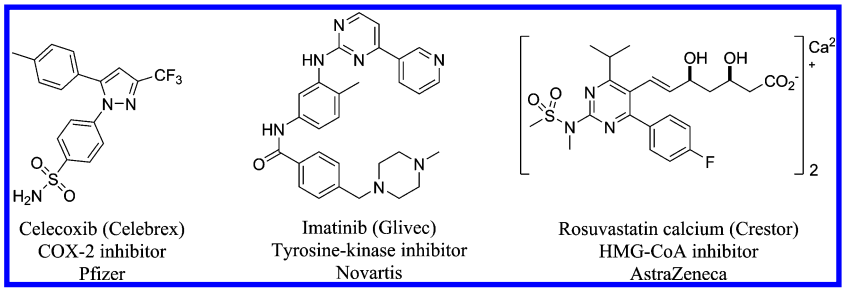
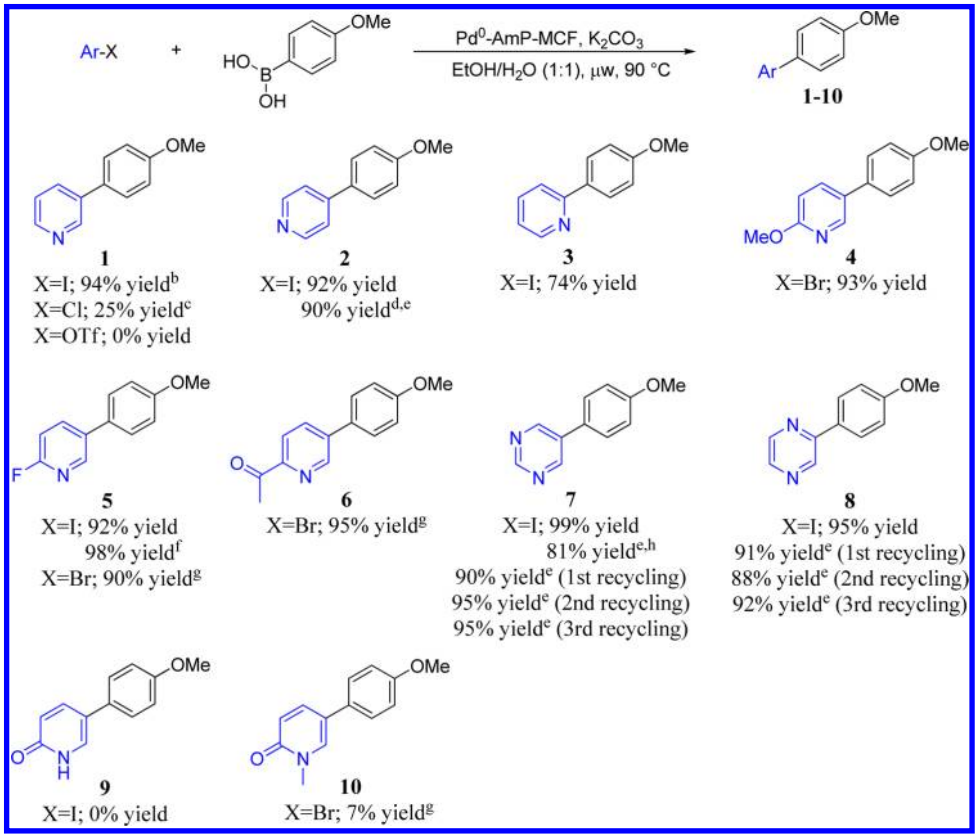


Figure 1. Drugs containing heterobiaryl motif.[5,6]

Scheme 1. Suzuki Couplings of Six-Membered Heteroaromatic Halides, Triflates, and 4-Methoxyphenylboronic Acid Using Pd^0-AmP-MCF as Catalyst[a]



[a]Reaction conditions (unless otherwise noted): aryl halide (0.30 mmol), boronic acid (0.39 mmol), K_2CO_3 (0.90 mmol), Pd (1 mol %), EtOH (95% aq):H_2O (1:1, 2 mL, 0.15M), 90 °C, μw, 30 min. [b]Reaction run for 15 min. [c]Reaction run for 1 h at 130 °C, the yield was determined by LCMS. [d]0.1 mol % Pd. [e]The yield was determined by ^{1}H NMR using 1,2,4,5-tetramethylbenzene as internal standard. [f]Reaction conditions: aryl halide (2.0 mmol), boronic acid (2.6 mmol), K_2CO_3 (6.0 mmol), Pd (1 mol %), EtOH (95% aq):H_2O (1:1, 13.3 mL, 0.15M), 90 °C, μw, 30 min. [g]Reaction run for 1 h. [h]Reaction run in EtOH (95% aq), 0.5 M.

Herein, we report on the use of Pd^0-AmP-MCF as a heterogeneous catalyst in Suzuki cross-coupling reactions, using a wide range of heteroaromatic halides and boron derivatives.

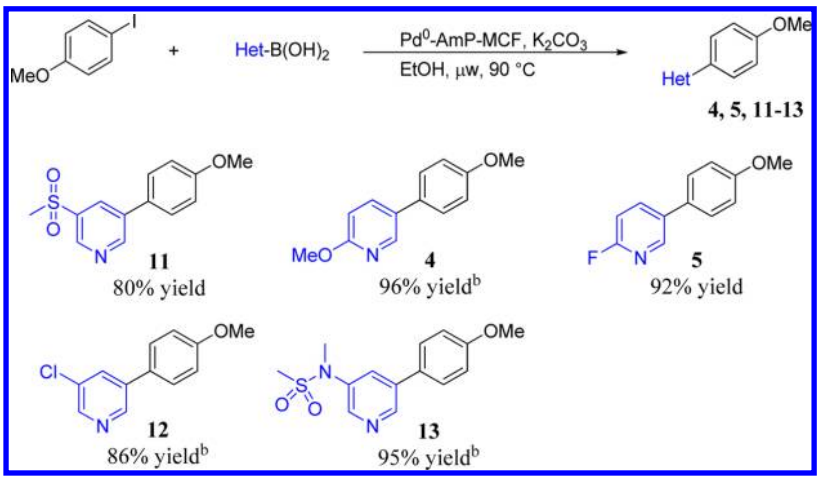
RESULTS AND DISCUSSION

We initially examined the Suzuki cross-coupling of 3-iodopyridine and 4-methoxyphenylboronic acid with potassium carbonate[37] as base, using Pd^0-AmP-MCF (1 mol % palladium) as catalyst in ethanol/water (1:1). The reaction was run at 90 °C for 30 min in a microwave reactor. To our delight, heterobiaryl **1** was obtained in 94% yield.

The same reaction conditions were applied to a range of heteroaromatic halides to investigate the substrate scope. As shown in Scheme 1, the coupled products, **1**–**3**, were obtained in high to excellent yields from the corresponding iodopyridine. Synthesis of **1** using 3-iodopyridine was also evaluated at room temperature and yielded 30% product after 20 h, thus making it impractically slow. Substituting the iodine for chlorine resulted in only 25% yield and a slow reaction even at 130 °C. Furthermore, the corresponding triflate gave no product (**1**), and only hydrolysis of the triflate was observed. Exploring the electronic effect in substituted halopyridines revealed that 5-bromopyridine substituted in the 2-position with an electron-donating group, such as methoxy (**4**), gave the same high yield compared to the unsubstituted pyridine **1**. The yield of **4** could not be improved by prolonged reaction time. Introducing an electron-withdrawing group in the same position, exemplified by products **5** and **6**, afforded the biaryl compound in excellent

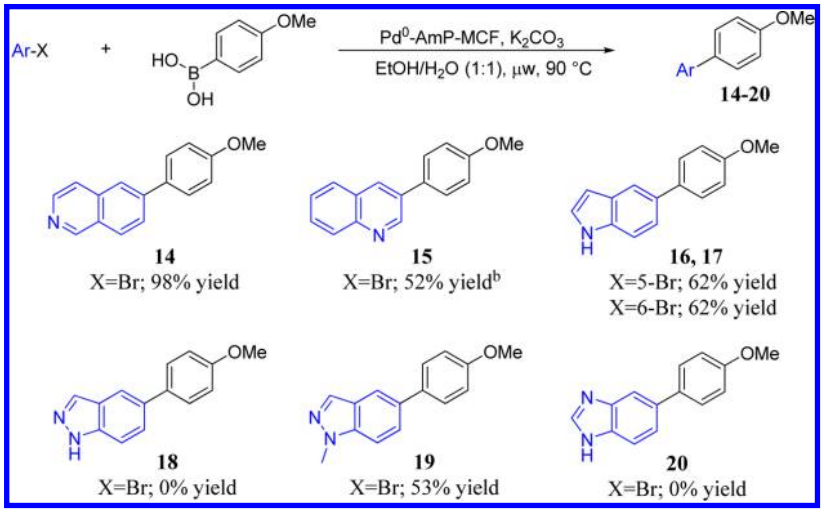
dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946–3954

Scheme 2. Suzuki Couplings of 4-Iodoanisole and Various Heteroaryl Boronic Acids Using Pd^0-AmP-MCF as Catalyst[a]



[a]Reaction conditions (unless otherwise noted): 4-iodoanisole (0.30 mmol), boronic acid (0.39 mmol), K_2CO_3 (0.90 mmol), Pd (1 mol %), EtOH (2 mL, 0.15M), 90 °C, μw, 30 min. [b]Reaction run for 1 h.

Scheme 3. Suzuki Couplings of Fused Heteroaryl Bromides and 4-Methoxyphenylboronic Acid Using Pd^0-AmP-MCF as Catalyst[a]



[a]Reaction conditions (unless otherwise noted): aryl halide (0.30 mmol), boronic acid (0.39 mmol), K_2CO_3 (0.90 mmol), Pd (1 mol %), EtOH/H_2O (1:1, 2 mL), 90 °C, μw, 30 min. [b]Reaction run for 1 h.

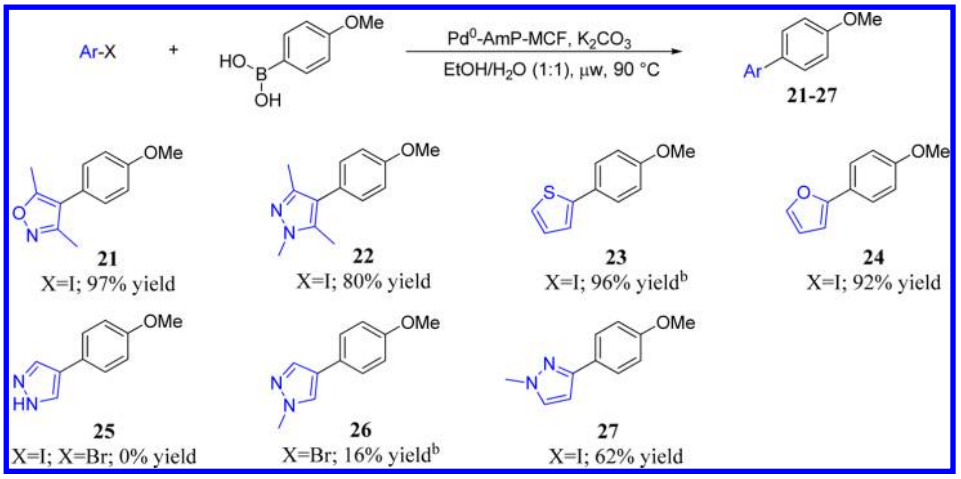
yield for both the bromo and the iodo derivatives, although a longer reaction time, 1 h, was needed for the bromo compounds. To demonstrate the practical utility of this method, a larger scale synthesis of **5** was performed, giving the compound in 98% yield (Scheme 1). In addition, the methodology was found to be efficient also for substrates that contain multiple heteroatoms, such as 5-iodopyrimidine, and 2-iodopyrazine, giving the coupling products, **7** and **8**, respectively, in excellent yields. The reaction of 5-iodopyridone was unsuccessful, but there is ample support in the literature that more basic nitrogens (pK_a = 11 for pyridone[38]) can coordinate to palladium and inhibit the reaction.[7,39] In the above-mentioned reaction, a color change of the palladium from black to transparent was noticed in the end of the reaction, indicating that the palladium may have been deactivated by nitrogen coordination.[7] However, by using the corresponding methylated derivative, the *N*-methyl pyridone, **10**, could be prepared but in a disappointingly low yield. In general, 1 mol % catalyst loading was used for all reactions reported herein. Reduction of the catalyst loading to 0.1 mol % of palladium, under otherwise identical reaction conditions, afforded a 90% yield of biaryl product **2**, whereas, with only 0.01 mol % of palladium, merely 20% conversion to product **2** was observed after 13 h.

With these results, we were encouraged to include a variety of heteroaryl boronic acids. As shown in Scheme 2, the heterobiaryl products, **4**, **5**, **11**−**13**, were obtained in high to excellent yields independently of electronic effects. It is noteworthy that these transformations failed with the previously employed water/ethanol mixture, probably due to the low solubility of 4-iodoanisole. When ethanol (95% aq) was used as the solvent, good to excellent yields were obtained.

To further evaluate the substrate scope, the reaction conditions were applied to a number of fused heteroaromatic ring systems. These type of aromatics, particularly 6,5-fused rings, are very common in drug discovery.[4] As shown in Scheme 3, 6-bromoisoquinoline and 3-bromoquinoline,

dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946−3954

Scheme 4. Suzuki Couplings with Five-Membered Heteroaryl Halides and 4-Methoxyboronic Acid Using Pd^0-AmP-MCF as Catalyst[a]



[a]Reaction conditions (unless otherwise noted): aryl halide (0.30 mmol), boronic acid (0.39 mmol), K_2CO_3 (0.90 mmol), Pd (1 mol %), EtOH/H_2O (1:1, 2 mL), 90 °C, μw, 30 min. [b]The yield was determined by ^{1}H NMR using 1,2,4,5-tetramethylbenzene as internal standard.

coupled with 4-methoxyphenylboronic acid, gave excellent to moderate yields of **14** and **15**, respectively.

The protocol was also found to be efficient for indole substrates, producing **16** and its structual isomer **17** in high yields. Again, with substrates containing slightly acidic N-H, no heterobiaryl products were obtained, as exemplified by **18** and **20**, while the methylated indazole product, **19**, was obtained in moderate yield. According to the recent literature, indazole and benzimidazole, which have pK_a's[40] of 13.8 and 12.9, respectively, can, under the reaction conditions used, coordinate to palladium and deactivate the catalyst.[7] This explanation is supported by our own findings, as evidenced by **18** and **20**. Interestingly, an indole N-H (pK_a[38] = 16.97) was well-tolerated (**16**, **17**).

We then went on to prove the generality of this protocol by including five-membered heteroaryl halides. To our surprise, the steric hindrance of the substrates, 4-iodo-3,5-dimethylisoxazole and 4-iodo-1,3,5-trimethyl-1*H*-pyrazole, did not appreciably affect the yield of the products **21** and **22**, which were both coupled in high yields (Scheme 4). Furthermore, 2-iodothiophene and 2-iodofurane were both successfully coupled to produce **23** and **24**, again in excellent yield. In accordance with the indazole and benzimidazole substrates, 4-iodopyrazole failed to give the desired product (pK_a[38] = 14.2 for pyrazole), while the methylated pyrazole derivatives were coupled with 4-methoxy boronic acid to generate the biaryl products **26** and **27** in 16% and 62% yield, respectively.

Finally, we wanted to evaluate if we could use the same reaction conditions with other boron derivatives, such as boronate esters, potassium trifluoroborates, MIDA boronates, and triolborates.

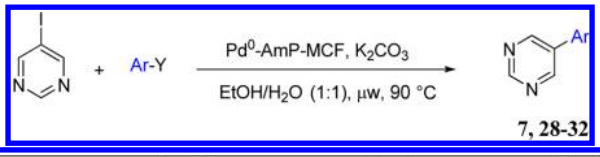
Gratifyingly, the pinacol ester worked perfectly and gave **7** in 93% yield (Table 1, entry 1). Running this reaction at room temperature for 24 h gave, to our surprise, the heterobiaryl in an excellent yield of 90% (entry 1). Continuing with the phenyl and methoxyphenyl potassium trifluoroborates, as well as the MIDA boronate, the corresponding products **7** and **28** were generated in excellent yield (entries 2−4). Boronic acids possessing different functional groups (entries 5−7) were well-tolerated and coupled nicely with 5-iodopyrimidine to give **29**−**31** in excellent yield. Cyclic triolborates are air- and water-stable and are at present an alternative to some boronic acids, especially heteroaromatic substrates, where there is a risk of hydrolytic cleavage of the carbon−boron bond under basic aqueous conditions.[41,42] The lithium salt of 3-pyridyl triolborate coupled in high yield to give the heterobiaryl product **32** (entry 8).

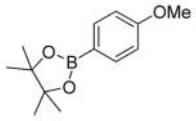
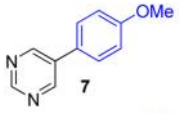
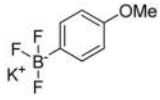
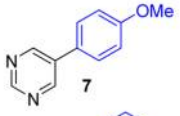
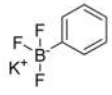
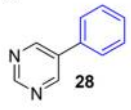
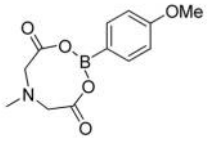
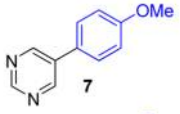
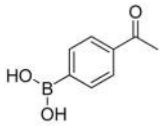
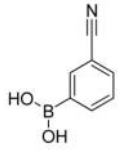
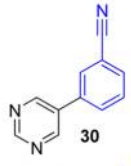
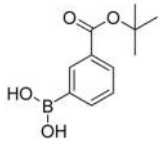
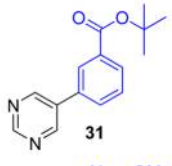
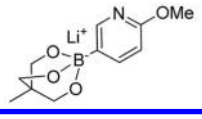
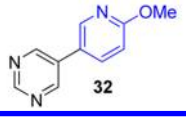
As recently reported by us, the nanocatalyst shows excellent reusability for Suzuki couplings with aryl halides.[33] To ensure that this was also true for heteroaromatics, which potentially may act as ligands for palladium, the Pd^0-AmP-MCF was recycled several times. To our satisfaction, the catalyst could be recycled at least three times without any loss of activity (see Scheme 1, products **7** and **8**, respectively). Interestingly, analysis of the reused MCF catalyst by transmission electron microscopy (TEM) revealed that the palladium nanoparticles had aggregated to larger particles (Figure 2) compared with the unused Pd(0)-AmP-MCF where the palladium was well-distributed across the support. This agglomeration was not found to have any observable effect on the outcome of the first three reactions of the recycling study; however, it is expected that the Pd(0)-AmP-MCF will gradually exhibit reduced catalytic efficiency over the next cycles due to increased agglomeration of the Pd nanoparticles that lead to a decreased surface-to-volume ratio.

To investigate whether any palladium had leached from the MCF, a leaching test of the MCF particles was performed. The filtrates from two different coupling reactions producing heterobiaryl **1** and **7**, respectively, were analyzed with inductively coupled plasma atomic emission spectroscopy (ICP-AES). Using this technique, we could demonstrate that only small amounts, 2.5 and 5.7 ppm, respectively, of palladium had leached out into solution. A hot filtration test was also performed by using the coupling reaction with 5-bromo-2-methoxypyridine, biaryl **4**, as a representative case. After 10 min of reaction, the catalyst was filtered off and the yield was determined to be 57% by LCMS (with anisole as internal standard). The filtrate was further stirred under the same reaction conditions for 23 h, and according to LCMS, the yield was still 57%. The fact that the yield has not increased shows that there is no active palladium in solution and hence confirms that the catalyst is a truly heterogeneous catalyst.

dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946−3954

Table 1. Suzuki Couplings with Boronate Esters, Potassium Trifluoroborates, MIDA Boronates, and Triolborate[a]



Entry	Ar-Y	Product	Yield (%)
1			93 90[b,c]
2			98
3			98
4			93
5			94
6			86
7			99
8			68[d]

[a]Reaction conditions (unless otherwise noted): aryl halide (0.30 mmol), boronic acid (0.39 mmol), K_2CO_3 (0.90 mmol), Pd (1 mol %), EtOH/H_2O (1:1, 2 mL), 90 °C, μw, 30 min. [b]Reaction run at room temperature for 24 h. [c]The yield was determined by ^{1}H NMR using 1,2,4,5-tetramethylbenzene as internal standard. [d]Reaction was run for 1 h at 90 °C.

CONCLUSION

In summary, we have shown that the heterogeneous nanoparticle catalyst Pd^0-AmP-MCF is very efficient in Suzuki cross-coupling reactions with heteroaromatic halides with a practical and simple reaction procedure to provide nitrogen-containing biaryls in good to excellent yields. The procedure is efficient for a range of heteroaromatic iodides and bromides with various boronic acids; however, it is not efficient when triflates and heteroaryl chlorides are employed as starting materials. In addition, this protocol is effective not only for heteroarylboronic acids but also for the corresponding boronate esters, potassium trifluoroborates, MIDA boronates, and triolborates. The Pd nanocatalyst can easily be removed from the product by filtration and leaves very low amounts of residual palladium in the product. Repeated recycling of catalyst revealed minimal loss in activity, despite alteration of the overall morphology of the nanoparticles toward larger agglomerates. The procedure reported herein provides an alternative, environmentally friendly process for the preparation of nitrogen-containing biaryls using a heterogeneous palladium nanocatalyst.

EXPERIMENTAL SECTION

General Information. All solvents and reagents were obtained from commercially available sources and used without further purification. The microwave syntheses were performed in a Biotage initiator with an external surface IR probe. Flash chromatography was carried out on prepacked silica gel columns and used on automated flash instruments. ^{1}H NMR and ^{13}C NMR spectra were generated on a 500 MHz cryo instrument. Chemical shifts (δ) are given in parts per million (ppm), with the residual solvent signal used as a reference. Coupling constants (J) are reported as Hz. NMR abbreviations are used as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Analytical HPLC/MS was conducted on a QTOF mass spectrometer using a UV detector monitoring either at (a) 210 nm with a BEH C18 column (2.1 × 100 mm, 1.7 μm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium carbonate buffer pH10) to 98% v/v CH_3CN in H_2O or at (b) 230 nm with an HSS C18 column (2.1 × 100 mm, 1.8 μm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium formate buffer pH3) to 98% v/v CH_3CN in H_2O. Preparative HPLC was conducted on a C18 column (10 μm 250 × 50 ID mm) using a gradient of 20 → 60% acetonitrile in H_2O/ACN/NH_3 95/5/0.2 buffer over 20 min with a flow of 100 mL/min. HRMS data were recorded using TOF ESI detection. Transmission electron miscroscopy (TEM) was used for analyzing the palladium nanoparticles after the recycling study. The amount of palladium leaching into the reaction was measured with inductively coupled plasma-atomic emission spectroscopy (ICP-AES). The palladium(0) nanoparticles immobilized in aminopropyl-functionalized mesocellular foam were synthesized as previously described.[34]

General Procedure for the Preparation of Biaryls 1−10 and 14−32. Heteroaryl halide (0.30 mmol), (4-methoxyphenyl)boronic acid (0.39 mmol), potassium carbonate (0.90 mmol), and Pd^0-AmP-MCF (3.99 mg, 0.003 mmol) were suspended in a 1:1 mixture of ethanol (95% aq)/water (2 mL) in a microwave vial. The sealed vial was heated at 90 °C (fixed hold time, normal absorption) for an appropriate time in a microwave reactor. The mixture was diluted with dichloromethane and washed with water. The phases were separated. The organic phase was run through a phase separator and purified by flash chromatography using a gradient of ethyl acetate/heptane to give the desired product after evaporation of solvent. All compounds were characterized by high-resolution MS, ^{1}H NMR, and ^{13}C NMR.

General Procedure for the Preparation of Biaryls 4, 5, 11−13. The same procedure as above, but with ethanol (95% aq, 2 mL) as solvent.

Procedure for the Recycling Study. 2-Iodopyrazine (0.063 g, 0.31 mmol), (4-methoxyphenyl)boronic acid (0.085 g, 0.39 mmol), potassium carbonate (0.124 g, 0.90 mmol), and Pd^0-AmP-MCF (3.99 mg, 0.003 mmol) were suspended in a 1:1 mixture of ethanol/water (2 mL) in a microwave vial. The sealed vial was heated at 90 °C (fixed hold time, normal absorption) for 30 min in a microwave oven. The catalyst was separated by centrifugation, and the supernatant was collected. The solid material was washed with ethyl acetate three times, and the organic layers were pooled with the supernatant. The catalyst was further washed with water three times. The water phases were combined with the organic phases. The organic phase was separated, filtered through a small silica plug, and concentrated. The catalyst was used in another cycle under identical conditions. This procedure was

dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946−3954

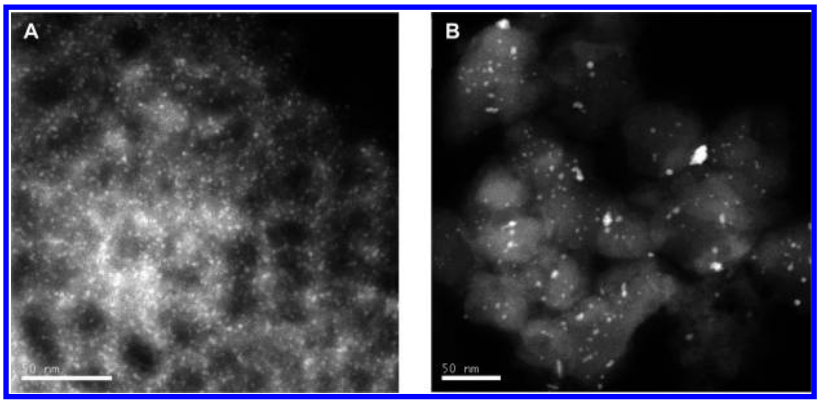


Figure 2. TEM images of unused Pd(0)-AmP-MCF catalyst. **A** shows the nanopalladium well-distributed in MCF. **B** shows the catalyst after being reused three times.

repeated twice. The palladium catalyst was then collected and analyzed with TEM.

Procedure for the Leaching Study. 3-Iodopyridine (0.102 g, 0.50 mmol), (4-methoxyphenyl)boronic acid (0.141 g, 0.65 mmol), potassium carbonate (0.207 g, 1.50 mmol), and Pd^0-AmP-MCF (6.65 mg, 5.00 μmol) were suspended in a 1:1 mixture of ethanol/water (3.4 mL) in a sealed microwave vial. The capped vial was heated at 90 °C (fixed hold time, normal absorption) for 30 min in a microwave oven. The mixture was filtered through a small silica plug, and the mother liquor was sent for ICP analysis.

Procedure for the Hot Filtration Study. 5-Bromo-2-methoxypyridine (0.056 g, 0.30 mmol), (4-methoxyphenyl)boronic acid (0.085 g, 0.39 mmol), potassium carbonate (0.124 g, 0.90 mmol), and Pd^0-AmP-MCF (3.99 mg, 0.003 mmol) were suspended in ethanol (1 mL) and water (1 mL) in a sealed microwave vial. Anisole was added as an internal standard.

The capped vial was heated at 90 °C in a metal block for 10 min. The mixture was filtered directly through a plug of Celite. Potassium carbonate was added to the mother liquor, and the mixture was heated at 90 °C in a metal block for 23 h in a sealed microwave vial. The reaction was analyzed by LCMS against the internal standard.

3-(4-Methoxyphenyl)pyridine[43] ***(1)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 52 mg (94%) of **1** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02−9.11 (m, 1H), 8.79 (d, J = 4.3 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.58 (dd, J = 7.8, 4.8 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 4.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 148.0, 147.9, 136.2, 133.8, 130.3, 128.2, 123.5, 114.5, 55.4; HRMS (ESI+) m/z calculated for $[C_{12}H_{11}NO + H^+]$: 186.0919, found 186.0918.

4-(4-Methoxyphenyl)pyridine[44] ***(2)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate afforded 51 mg (92%) of **2** as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55−8.73 (m, 2H), 7.55−7.70 (m, 2H), 7.42−7.53 (m, 2H), 6.98−7.09 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 150.2, 147.8, 130.4, 128.1, 121.0, 114.5, 55.4; HRMS (ESI+) m/z calculated for $[C_{12}H_{11}NO + H^+]$: 186.0919, found 186.0921.

2-(4-Methoxyphenyl)pyridine[44] ***(3)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 41 mg (74%) of **3** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64−8.70 (m, 1H), 7.92−8.02 (m, 2H), 7.65−7.77 (m, 2H), 7.18 (ddd, J = 7.2, 4.8, 1.2 Hz, 1H), 6.98−7.06 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 157.1, 149.5, 136.6, 132.04, 128.1, 121.4, 119.8, 114.1, 55.3; HRMS (ESI+) m/z calculated for $[C_{12}H_{11}NO + H^+]$: 186.0919, found 186.0923.

2-Methoxy-5-(4-methoxyphenyl)pyridine[40] ***(4)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 60 mg (93%) of **4** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, J = 2.5, 0.7 Hz, 1H), 7.75 (dd, J = 8.6, 2.6 Hz, 1H), 7.42−7.49 (m, 2H), 6.96−7.03 (m, 2H), 6.81 (dd, J = 8.6, 0.7 Hz, 1H), 3.98 (s, 3H), 3.86 (s, 3H), 1.57 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 159.2, 144.5, 137.2, 130.4, 129.8, 127.7, 114.4, 110.7, 55.4, 53.5; HRMS (ESI+) m/z calculated for $[C_{13}H_{13}NO_2 + H^+]$: 216.1025, found 216.1014.

2-Fluoro-5-(4-methoxyphenyl)pyridine[45] ***(5)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 56 mg (92%) of **5** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 2.5 Hz, 1H), 7.93 (ddd, J = 8.4, 7.7, 2.6 Hz, 1H), 7.44−7.51 (m, 2H), 6.95−7.05 (m, 3H), 3.87 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.7, 162.2, 159.9, 145.6, 145.5, 139.5, 139.4, 134.7, 134.7, 129.3, 128.3, 114.8, 109.7, 109.4, 55.6; HRMS (ESI+) m/z calculated for $[C_{12}H_{10}FNO + H^+]$: 204.0825, found 204.0814.

1-(5-(4-Methoxyphenyl)pyridin-2-yl)ethanone[46] ***(6)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 65 mg (95%) of **6** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.98 (dd, J = 8.2, 2.3 Hz, 1H), 7.55−7.64 (m, 2H), 7.00−7.10 (m, 2H), 3.89 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 160.4, 151.7, 146.9, 139.4, 134.3, 129.2, 128.5, 121.8, 114.8, 55.4, 25.8; HRMS (ESI+) m/z calculated for $[C_{14}H_{13}NO_2 + H^+]$: 228.1025, found 228.1023.

5-(4-Methoxyphenyl)pyrimidine[40] ***(7)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate to give 56 mg (99%) of **7** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.93 (s, 2H), 7.51−7.57 (m, 2H), 7.03−7.10 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4, 156.9, 154.4, 133.9, 128.1, 126.5, 114.9, 55.4; HRMS (ESI+) m/z calculated for $[C_{11}H_{10}N_2O + H^+]$: 187.0871, found 187.0877.

2-(4-Methoxyphenyl)pyrazine[47] ***(8)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 53 mg (95%) of **8** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, J = 1.5 Hz, 1H), 8.59 (dd, J = 2.5, 1.6 Hz, 1H), 8.45 (d, J = 2.5 Hz, 1H), 7.9−8.06 (m, 2H), 7.00−7.11 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 152.5, 142.0, 142.1, 141.6, 128.9, 128.3, 114.5, 55.4; HRMS (ESI+) m/z calculated for $[C_{11}H_{10}N_2O + H^+]$: 187.0871, found 187.0860.

5-(4-Methoxyphenyl)-1-methylpyridin-2(1H)-one[48] ***(10)***. Purified by preparative HPLC on a XBridge C18 column (10 μm 250 × 50 ID mm) using a gradient of 20 → 60% acetonitrile in H_2O/ACN/NH_3 95/5/0.2 buffer over 20 min with a flow of 100 mL/min to give 18 mg (7%) of **10** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 9.4, 2.6 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.29−7.36 (m, 2H), 6.92−6.99 (m, 2H), 6.66 (d, J = 9.4 Hz, 1H), 3.85 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 159.1, 139.4, 134.9, 129.0, 127,0, 120.6, 120.0, 114.5, 55.4, 37.9. HRMS (ESI+) m/z calculated for $[C_{13}H_{13}NO_2 + H^+]$: 216.1024, found 216.1013.

3-(4-Methoxyphenyl)-5-(methylsulfonyl)pyridine ***(11)***. Purification by flash chromatography using a gradient of ethyl acetate/heptane, 40 → 60% ethyl acetate gave 63 mg (80%) of **11** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (t, J = 2.4, 2.4 Hz, 2H), 8.36 (t, J =

dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946−3954

2.2, 2.2 Hz, 1H), 7.49−7.67 (m, 2H), 6.97−7.14 (m, 2H), 3.89 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 152.2, 146.1, 137.0, 132.4, 128.4, 127.8, 114.9, 55.5, 44.9; HRMS (ESI+) m/z calculated for $[C_{13}H_{13}NO_3S + H^+]$: 264.0694, found 264.0692.

3-Chloro-5-(4-methoxyphenyl)pyridine (**12**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate afforded 57 mg (86%) of **12** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 1.9 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 7.83 (t, J = 2.1, 2.1 Hz, 1H), 7.46−7.56 (m, 2H), 7.03 (dd, J = 9.2, 2.4 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 146.5, 145.7, 137.5, 133.5, 132.1, 128.7, 128.3, 114.7, 55.4; HRMS (ESI+) m/z calculated for $[C_{12}H_{10}ClNO + H^+]$: 220.0529, found 220.0524.

N-(5-(4-Methoxyphenyl)pyridin-3-yl)-N-methylmethanesulfonamide (**13**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 40% ethyl acetate gave 83 mg (95%) of **13** as a yellow solid. ^{1}H NMR (500 MHz, CDCl3) δ 8.74 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 7.90 (t, J = 2.3, 2.3 Hz, 1H), 7.51−7.58 (m, 2H), 6.99−7.06 (m, 2H), 3.88 (s, 3H), 3.43 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 160.2, 146.4, 144.2, 138.1, 136.9, 131.9, 129.2, 128.9, 128.4, 114.7, 55.4, 38.0, 35.8; HRMS (ESI+) m/z calculated for $[C_{14}H_{16}N_2O_3S + H^+]$: 293.0960, found 293.0959.

6-(4-Methoxyphenyl)isoquinoline (**14**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 10 → 40% ethyl acetate gave 69 mg (98%) of **14** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.54 (d, J = 5.7 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.96 (s, 1H), 7.85 (dd, J = 8.5, 1.7 Hz, 1H), 7.64−7.73 (m, 3H), 7.02−7.09 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 152.2, 143.4, 142.6, 136.2, 132.6, 128.7, 128.1, 127.5, 126.7, 123.3, 120.5, 114.4, 55.4; HRMS (ESI+) m/z calculated for $[C_{16}H_{13}NO + H^+]$: 236.1075, found 236.1070.

3-(4-Methoxyphenyl)quinoline[49] (**15**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 10 → 40% ethyl acetate gave 37 mg (52%) of **15** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.84−7.91 (m, 1H), 7.64−7.77 (m, 3H), 7.54−7.63 (m, 1H), 7.04−7.12 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 149.9, 147.0, 133.5, 132.4, 130.3, 129.2, 129.0, 128.5, 128.1, 127.9, 126.9, 114.7, 55.4, 41.0; HRMS (ESI+) m/z calculated for $[C_{16}H_{13}NO + H^+]$: 236.1075, found 236.1072.

5-(4-Methoxyphenyl)-1H-indole[35] (**16**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 20 → 60% ethyl acetate afforded 42 mg (62%) of **16** as a light beige solid. ^{1}H NMR (500 MHz, CDCl3) δ 8.16 (s, 1H), 7.78−7.86 (m, 1H), 7.56−7.63 (m, 2H), 7.38−7.49 (m, 2H), 7.24−7.26 (m, 1H), 6.96−7.05 (m, 2H), 6.61 (ddd, J = 2.9, 2.0, 0.7 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 158.5, 135.2, 135.0, 133.1, 128.4, 128.3, 124.7, 121.7, 118.7, 114.1, 111.1, 102.9, 55.3; HRMS (ESI+) m/z calculated for $[C_{15}H_{13}NO + H^+]$: 224.1075, found 224.1072.

6-(4-Methoxyphenyl)-1H-indole[35] (**17**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 10 → 40% ethyl acetate gave 42 mg (62%) of **17** as a light beige solid. ^{1}H NMR (500 MHz, CDCl3) δ 8.19 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.54−7.63 (m, 3H), 7.36 (dd, J = 8.2, 1.6 Hz, 1H), 7.24 (dd, J = 3.2, 2.4 Hz, 1H), 6.96−7.04 (m, 2H), 6.58 (ddd, J = 3.1, 2.0, 1.0 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 136.6, 135.5, 135.1, 128.5, 127.0, 124.7, 121.0, 119.9, 114.3, 109.2, 102.7, 55.6; HRMS (ESI+) m/z calculated for $[C_{15}H_{13}NO + H^+]$: 224.1075, found 224.1052.

5-(4-Methoxyphenyl)-1-methyl-1H-indazole (**19**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 10 → 40% ethyl acetate gave 38 mg (53%) of **19** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 0.9 Hz, 1H), 7.86 (dd, J = 1.6, 0.8 Hz, 1H), 7.62 (dd, J = 8.7, 1.7 Hz, 1H), 7.54−7.60 (m, 2H), 7.45 (dt, J = 8.7, 0.8, 0.8 Hz, 1H), 6.98−7.04 (m, 2H), 4.11 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (151 MHz, CDCl3) δ 159.0, 139.3, 134.3, 133.9, 133.2, 128.5, 126.5, 124.8, 118.7, 114.4, 109.3, 55.6, 35.8; HRMS (ESI+) m/z calculated for $[C_{15}H_{14}N_2O + H^+]$: 239.1184, found 239.1176.

4-(4-Methoxyphenyl)-3,5-dimethylisoxazole[50] (**21**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 10 → 40% ethyl acetate afforded 60 mg (97%) of **21** as a transparent oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.22 (m, 2H), 6.95−7.02 (m, 2H), 3.86 (s, 3H), 2.39 (s, 3H), 2.26 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 159.0, 158.8, 130.3, 122.6, 116.2, 114.2, 55.3, 11.5, 10.8; HRMS (ESI+) m/z calculated for $[C_{12}H_{13}NO_2 + H^+]$: 204.1025, found 204.1033.

4-(4-Methoxyphenyl)-1,3,5-trimethyl-1H-pyrazole[51] (**22**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 20 → 60% ethyl acetate gave 22 mg (80%) of **22** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11−7.23 (m, 2H), 6.9−7.02 (m, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.23 (d, J = 4.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 145.0, 136.0, 130.5, 126.6, 118.8, 113.9, 55.3, 36.0, 12.4, 10.2; HRMS (ESI+) m/z calculated for $[C_{13}H_{16}N_2O + H^+]$: 217.1341, found 217.1338.

2-(4-Methoxyphenyl)thiophene[52] (**23**). After extraction, the crude product was run through a small silica plug and the solid was evaporated. Gave 55 mg (96%) of **23** as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 7.51−7.58 (m, 2H), 7.20−7.24 (m, 2H), 7.06 (dd, J = 5.1, 3.6 Hz, 1H), 6.90−6.95 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 144.3, 127.9, 127.7, 127.3, 127.2, 123.8, 122.1, 114.3, 114.1, 55.4; HRMS (ESI+) m/z calculated for $[C_{11}H_{10}OS + H^+]$: 191.0530, found 191.0529.

2-(4-Methoxyphenyl)furan[53] (**24**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 0 → 30% ethyl acetate gave 48 mg (82%) of **24** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.65 (m, 2H), 7.44 (dd, J = 1.8, 0.7 Hz, 1H), 6.90−6.96 (m, 2H), 6.52 (dd, J = 3.3, 0.7 Hz, 1H), 6.45 (dd, J = 3.3, 1.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 154.0, 141.4, 125.2, 124.0, 114.2, 114.1, 111.5, 103.3, 55.3, 55.3.

4-(4-Methoxyphenyl)-1-methyl-1H-pyrazole[54] (**26**). After extraction, the crude product was run through a small silica plug and the solid was evaporated. Gave 9 mg (16%) of **26** as a light beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.72 (m, 1H), 7.54 (s, 1H), 7.36−7.43 (m, 2H), 6.88−6.95 (m, 2H), 3.94 (s, 2H), 3.83 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 136.5, 126.7, 126.3, 125.3, 123.0, 114.3, 55.3, 39.0; HRMS (ESI+) m/z calculated for $[C_{11}H_{12}N_2O + H^+]$: 189.1028, found 189.1021.

3-(4-Methoxyphenyl)-1-methyl-1H-pyrazole (**27**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 20 → 50% ethyl acetate afforded 40 mg (62%) of **27** as a light beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.77 (m, 2H), 7.36 (d, J = 2.2 Hz, 1H), 6.90−6.97 (m, 2H), 6.47 (d, J = 2.3 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 151.5, 131.2, 126.7, 126.6, 126.5, 126.4, 114.0, 102.3, 55.3, 38.9.; HRMS (ESI+) m/z calculated for $[C_{11}H_{12}N_2O+H^+]$: 189.1028, found 189.1038.

5-Phenylpyrimidine[55] (**28**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 40 → 70% ethyl acetate afforded 46 mg (98%) of **28** as a transparent oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.97 (s, 2H), 7.57−7.62 (m, 2H), 7.51−7.57 (m, 2H), 7.46−7.51 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.7, 155.1, 134.5, 134.4, 129.6, 129.2, 127.2. HRMS (ESI+) m/z calculated for $[C_{10}H_8N_2 + H^+]$: 157,0765, found 157,0759.

1-(4-(Pyrimidin-5-yl)phenyl)ethanone[56] (**29**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 40 → 60% ethyl acetate gave 56 mg (94%) of **29** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 9.01 (s, 2H), 8.11−8.14 (m, 2H), 7.68−7.74 (m, 2H), 2.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 158.2, 155.0, 138.7, 137.2, 133.3, 129.4, 127.2, 26.7; HRMS (ESI+) m/z calculated for $[C_{12}H_{10}N_2O + H^+]$: 199.0871, found 199.0869.

3-(Pyrimidin-5-yl)benzonitrile (**30**). Purification by flash chromatography using a gradient of ethyl acetate/heptane, 40 → 60% ethyl acetate gave 47 mg (86%) of **30** as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 9.30 (s, 1H), 8.97 (s, 2H), 7.89 (t, J = 1.5, 1.5 Hz, 1H), 7.83 (ddd, J = 7.8, 1.8, 1.2 Hz, 1H), 7.79 (dt, J = 7.8, 1.3, 1.3 Hz, 1H), 7.65−7.71 (m, 1H); ^{13}C NMR (126 MHz, CDCl3) δ 158.4, 154.9, 135.8, 132.4, 131.3, 130.5, 130.4, 118.0, 113.9; HRMS (ESI+) m/z calculated for $[C_{11}H_7N_3 + H^+]$: 182.0718, found 182.0713.

dx.doi.org/10.1021/jo500409r | J. Org. Chem. 2014, 79, 3946−3954

*tert-Butyl 3-(pyrimidin-5-yl)benzoate (**31**).* Purification by flash chromatography using a gradient of ethyl acetate/heptane, 20 → 50% ethyl acetate afforded 76 mg (99%) of **31** as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 9.25 (s, 1H), 9.00 (s, 2H), 8.22 (t, J = 1.6, 1.6 Hz, 1H), 8.10 (dt, J = 7.8, 1.3, 1.3 Hz, 1H), 7.75 (ddd, J = 7.7, 1.9, 1.2 Hz, 1H), 7.59 (t, J = 7.8, 7.8 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (126 MHz, CDCl3) δ 165.0, 157.8, 155.0, 134.4, 133.7, 133.3, 130.7, 129.9, 129.4, 127.9, 81.7, 28.2, 28.0; HRMS (ESI+) m/z calculated for $[C_{15}H_{16}N_2O_2 + H^+]$: 257.1290, found 257.1301.

5-(6-Methoxypyridin-3-yl)pyrimidine[57] *(**32**).* Purification by flash chromatography using a gradient of ethyl acetate/heptane, 40 → 80% ethyl acetate afforded 38 mg (68%) of **32** as a light beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.92 (s, 2H), 8.41 (d, J = 2.5 Hz, 1H), 7.80 (dd, J = 8.6, 2.6 Hz, 1H), 6.91 (dd, J = 8.6, 0.5 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 157.5, 154.4, 145.2, 137.0, 131.5, 123.3, 111.7, 53.8; HRMS (ESI+) m/z calculated for $[C_{10}H_9N_3O + H^+]$: 188.0824, found 188.0811.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Berzelii Center EXSELENT is gratefully acknowledged. We thank Ms. A. Nagendiran (Stockholm University) and Dr. O. Karlsson (AstraZenceca) for helpful discussions, Dr. A. Gill (AstraZeneca) for his generous support, and Dr. C.-W. Tai (Stockholm University) for TEM analyses.

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