JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

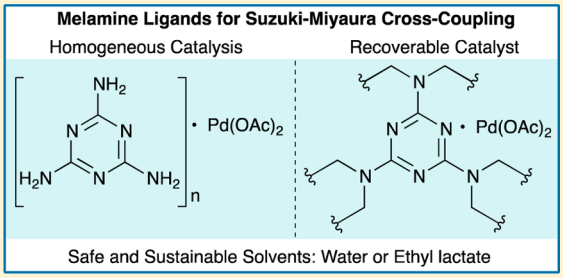
Melamine and Melamine-Formaldehyde Polymers as Ligands for Palladium and Application to Suzuki–Miyaura Cross-Coupling Reactions in Sustainable Solvents

Grant A. Edwards, Mitchell A. Trafford, Alaina E. Hamilton, Audrey M. Buxton, Matthew C. Bardeaux, and Justin M. Chalker*

Department of Chemistry and Biochemistry, The University of Tulsa, Keplinger Hall, 800 South Tucker Drive, Tulsa, Oklahoma 74104, United States.

Supporting Information

ABSTRACT: The Suzuki–Miyaura cross-coupling reaction is a foundation stone of modern organic synthesis, as evidenced by its widespread use in the preparation of pharmaceuticals, agrochemicals, polymers, and other functional materials. With the prevalence of this venerable reaction in industrial synthesis, it is prudent to ensure its application adheres to the tenets of green chemistry. The introduction of cross-coupling catalysts that are active in sustainable solvents is therefore an important endeavor. In this report, a melamine-palladium complex is introduced as a versatile catalyst for the Suzuki–Miyaura cross-coupling reaction. This catalyst is soluble and active in both water and the renewable organic solvent ethyl lactate. The melamine-palladium catalyst can also be cross-linked by reaction with formaldehyde to generate an insoluble polymeric catalyst that can be recovered after the cross-coupling. The melamine-palladium system is inexpensive, easy to handle, bench-stable, and effective in catalysis in the presence of a variety of impurities (high cross-coupling yields were obtained in reactions run in unfiltered river water to illustrate this final point). Additionally, investigations reported herein revealed an intriguing relationship between catalytic efficiency and the base employed in the cross-coupling reaction. Implications for the mechanism of transmetalation in aqueous Suzuki–Miyaura cross-coupling reaction are discussed.



INTRODUCTION

The Suzuki–Miyaura cross-coupling reaction stands as one of the more important carbon–carbon bond-forming reactions in organic synthesis.[1−3] Its widespread use in the synthesis of natural products,[4,5] pharmaceuticals,[6] agrochemicals,[6] and polymers[7] is a testament to its broad impact on the chemical sciences. With an ever-increasing deployment of this reaction in synthesis, the continued development of high performance catalysts is imperative.[8] Moreover, the development of next-generation cross-coupling catalysts should be coordinated with growing commitments to sustainable synthesis and the principles of green chemistry.[9,10] Given that solvent is typically the largest contributor to the waste stream in commercial synthesis,[11] it is critical that novel catalysts are compatible with environmentally benign and renewable reaction media.[11−13] Accordingly, many cross-coupling catalysts have been developed for use in water since this solvent is widely available, nontoxic, and nonflammable.[14−17] Nevertheless, water is not a convenient solvent for nonpolar substrates. While cross-coupling of nonpolar substrates in water has been facilitated by the development of nonionic surfactants,[18] an alternative approach is to engineer catalysts that are broadly compatible with both aqueous and organic reaction media. Herein we report the development of such an ambiphilic catalyst that mediates Suzuki–Miyaura coupling in both water and ethyl lactate,[19] a sustainable organic solvent. The catalyst employs the aminotriazine melamine[20,21] as a ligand for palladium (Scheme 1A). Our interest in melamine as a ligand was motivated in part by its structural similarity to pyrimidine ligands that have proven useful in other Pd-catalyzed coupling reactions.[22−24] In contrast to these previously reported ligands, however, we suspected melamine would confer several important advantages. First, it is very inexpensive (~$0.003 USD/mmol). Second, melamine is soluble in both water and several organic solvents. We envisioned translating this ambiphilic nature to melamine-palladium complexes for homogeneous catalysis in both aqueous and organic reaction media. Third, we suspected that a melamine-palladium complex could be cross-linked by reaction with formaldehyde to form an insoluble palladium-containing polymer that is active as a catalyst and recoverable after the cross-coupling.

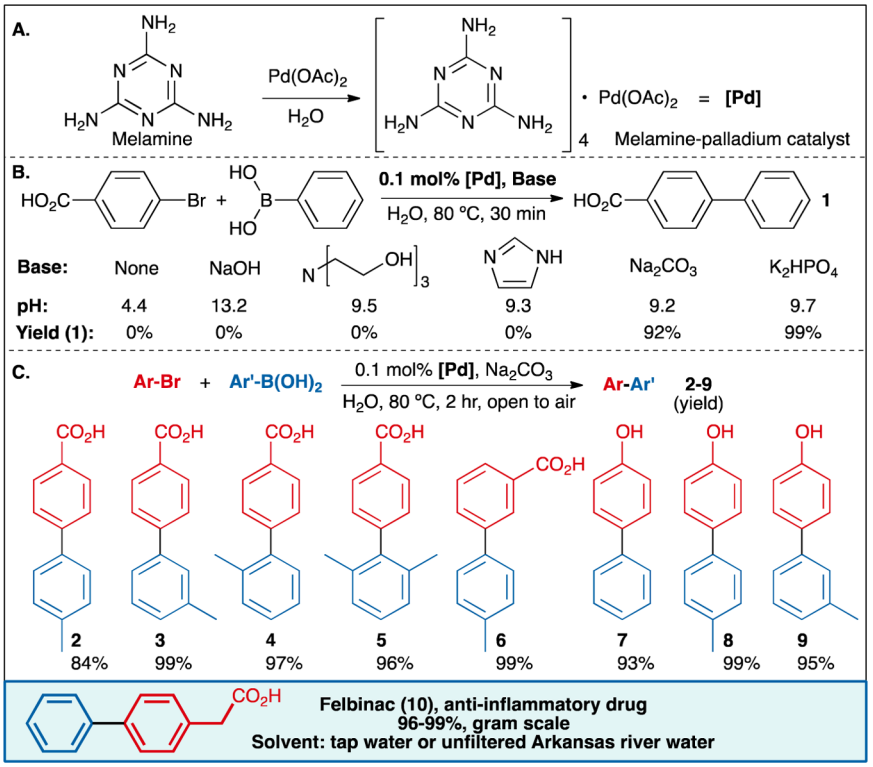
RESULTS AND DISCUSSION

Melamine as a Ligand for Palladium and Cross-Couplings in Water. As a starting point, we prepared a solution of melamine and palladium acetate in water. Simply heating a 4:1 molar ratio of melamine to palladium acetate at 80

Received: December 17, 2013
Published: February 17, 2014

   dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094–2104

Scheme 1. Melamine-Palladium Catalyst and Suzuki–Miyaura Cross-Coupling Reactions in Water



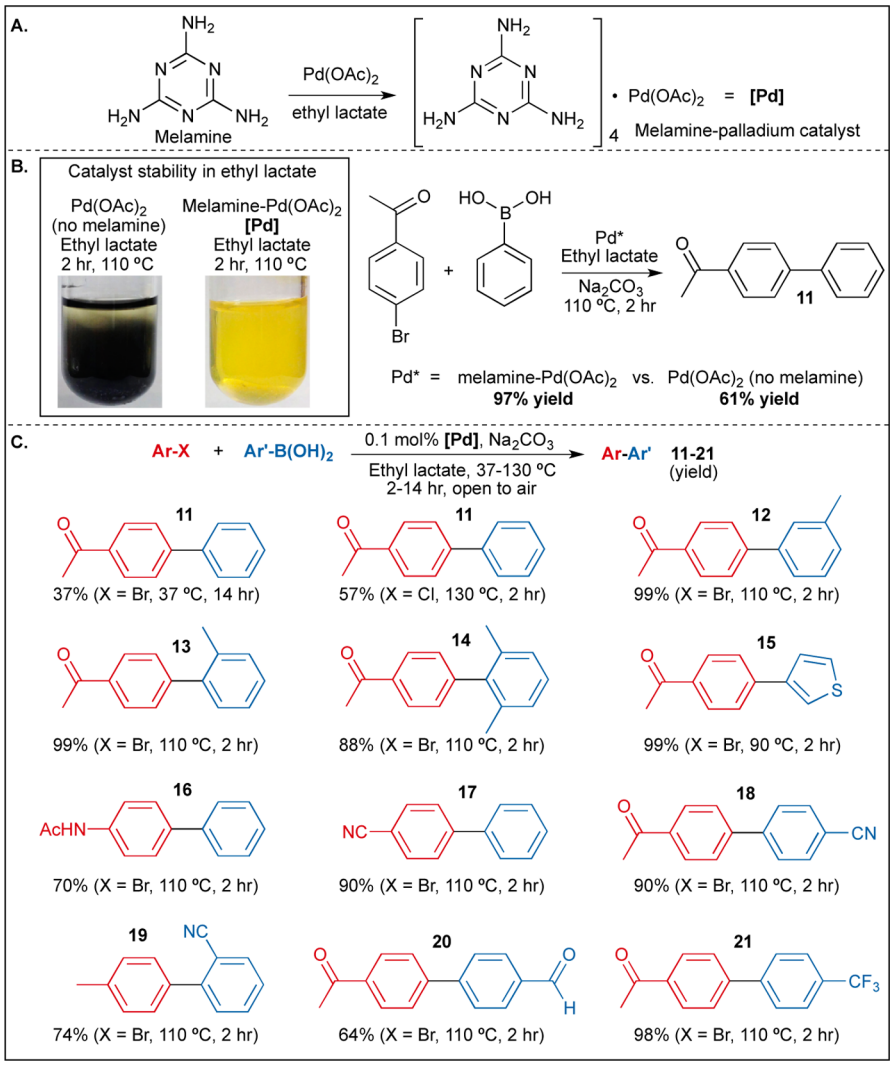
°C resulted in a homogeneous orange solution. This simple experiment established melamine as a ligand for palladium since palladium acetate is insoluble in water. Next, a model cross-coupling was investigated in order to identify an appropriate base for the melamine-palladium system in the Suzuki–Miyaura reaction (Scheme 1B). Five bases were considered: sodium hydroxide, triethanolamine, imidazole, sodium carbonate, and potassium phosphate. These bases were considered here because they are widely available and commonly employed in the preparation of buffers. This latter point is particularly significant with the increasing application of cross-coupling to the covalent modification of biomolecules that require buffered aqueous media.[23−29] Water was the only solvent used in these reactions, and catalyst loading was set at 0.1 mol % palladium for exploratory work. The reactions were carried out for 30 min at 80 °C and then quenched. After extractive workup, the crude products were analyzed directly by ^{1}H NMR. For sodium hydroxide, 3.0 molar equiv was employed: 1 equiv to react with 4-bromobenzoic acid, and the remaining 2 equiv to mediate the cross-coupling.[3] Somewhat surprisingly, no cross-coupling product was observed under these conditions and starting material was recovered. We reasoned that sodium hydroxide alone may result in a pH too high for efficient cross-coupling in this system (the pH of the reaction mixture was 13.2, as measured by a pH meter). This hypothesis was based on recent reports that suggest high concentrations of hydroxide can inhibit the Suzuki–Miyaura cross-coupling reaction by sequestering the arylboronic acid as an arylborate that is unreactive in transmetalation.[30−32] Indeed, a growing body of evidence suggests that in many Suzuki–Miyaura reactions transmetalation can occur most efficiently between the neutral arylboronic acid and a palladium(II) hydroxo complex.[30−35] In these scenarios, the concentration of hydroxide is critical: enough hydroxide is needed to form the key palladium(II) hydroxo species, but excess hydroxide serves an antagonistic role in converting the boronic acid to the unreactive borate.[30−32] In the reactions in Scheme 1B, however, simply lowering the pH is not sufficient, as neither triethanolamine nor imidazole promoted cross-coupling (the pH of these reactions was 9.5 and 9.3, respectively). Fortunately, the use of sodium carbonate or potassium phosphate led to a dramatic increase in yield of cross-coupling product: 92% and 99%, respectively (Scheme 1B). In a control experiment where no base was used, only unreacted starting material was recovered (Scheme 1B).

The dependence on the pH and identity of base is striking. As suggested previously, sodium hydroxide alone is an inappropriate base for the melamine-palladium system because the equilibrium of the arylboronic acid is shifted to the unreactive arylborate.[30−32] In the case of imidazole and triethanolamine, these bases or their ammonium salts[32] may form a complex with the palladium catalyst that is unreactive in catalysis. These results therefore prompt a cautionary note if either imidazole or triethanolamine is considered as a component of a buffer that will be used in cross-coupling reactions, an increasingly likely scenario with the growing application of palladium mediated cross-coupling on biomolecules.[23−29,36] The effectiveness of carbonate and phosphate is, in part, a consequence of their buffering capacity that maintains a suitable pH for the Suzuki–Miyaura reaction. Another intriguing possibility is that carbonate and phosphate actively promote cross-coupling by serving as ligands for palladium and boron.[37] In any case, carbonate and phosphate were identified as suitable bases for Suzuki–Miyaura cross-coupling reactions catalyzed by the novel melamine-palladium complex. Since carbonate is typically less expensive than phosphate, we used sodium carbonate in subsequent coupling reactions.

A selection of cross-couplings using the melamine-palladium catalyst in water is shown in Scheme 1C. In these cross-

dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094−2104

Scheme 2. Melamine-Palladium Catalyst and Suzuki–Miyaura Cross-Coupling Reactions in Ethyl Lactate

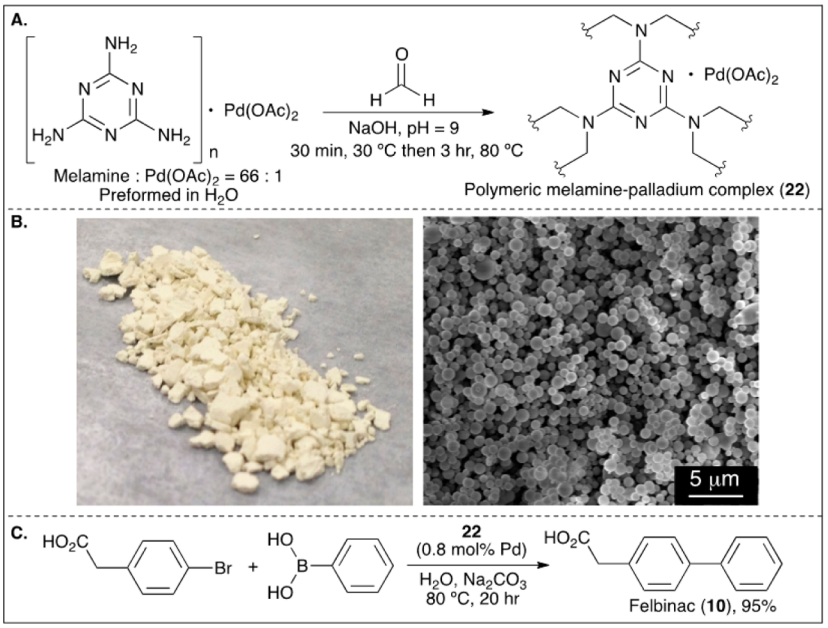


coupling reactions, the substrates and carbonate were typically premixed and heated to 80 °C, at which time the catalyst solution was added to the reaction to give a final loading of 0.1 mol % Pd. All reactions in Scheme 1 were run at 80 °C for 2 h, open to air. A variety of water-soluble benzoates and phenols were obtained in excellent yields under these conditions (**2**–**9**). Notably, the catalyst tolerates a range of substitution patterns, including *ortho*-substitution that can lead to congestion near the forming C–C bond (**4** and **5**). The high yields are a demonstration of the reactivity of the novel melamine-palladium catalyst. The operational ease of these couplings should also be highlighted: all couplings were carried out in reaction vessels open to air, and ultrapure water was not required. To demonstrate this latter point, felbinac (**10**, a topical anti-inflammatory drug)[38] was synthesized on gram-scale in a single step in near-quantitative yield using tap water or even unfiltered Arkansas River water as the solvent (Scheme 1C).[39] Gratifyingly, the melamine-palladium catalyst was compromised by neither the impurities in unfiltered river water nor by molecular oxygen from air, making its use in aqueous cross-coupling reactions a robust and simple operation. To determine if this catalyst system is also applicable to cross-couplings in organic solvents, its reactivity in the renewable organic solvent ethyl lactate was examined next.

Melamine as a Ligand for Palladium and Cross-Couplings in Ethyl Lactate. With the catalytic activity of the melamine-palladium complex established in water, we turned next to cross-coupling reactions in ethyl lactate (Scheme 2). Ethyl lactate has recently emerged as an attractive solvent in synthesis.[19] Ethyl lactate is derived from non-food plant sources and is therefore renewable; it is also fully biodegradable and nontoxic. Despite these advantages, many reactions have yet to be adapted for use in ethyl lactate. In fact, while this work was underway, the first demonstration of Suzuki–Miyaura cross-coupling in ethyl lactate was reported.[40] In this investigation, the authors used palladium acetate as a catalyst at a relatively high loading of 1 mol %. This recent report provided an excellent occasion to investigate what advantages, if any, melamine imparts to the palladium catalyst. Since palladium acetate is fully soluble in ethyl lactate, we first needed to establish that melamine was coordinated to palladium. An examination of the UV–vis spectrum of a solution of palladium acetate in ethyl lactate revealed a shift in λ_{max} from 393 to 353 nm upon the addition of 4 equiv of melamine, suggesting that melamine is coordinating to palladium. Next, we demonstrated that melamine prevents the formation of palladium black when palladium acetate is heated in ethyl lactate for 2 h at 110 °C (Scheme 2B). Finally, the melamine-palladium catalyst was

dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094–2104

Scheme 3. Polymeric Melamine-Palladium Complex As a Recoverable Catalyst



superior to palladium acetate in the synthesis of biaryl **11** (97% yield for the melamine-palladium catalyst vs 61% yield palladium acetate, Scheme 2B).

Motivated by the reactivity of the melamine-palladium complex in ethyl lactate, we examined a variety of cross-coupling reactions (**11**–**21**, Scheme 2C). In these reactions, the melamine-palladium catalyst was added to a mixture of the cross-coupling substrates and sodium carbonate in ethyl lactate before heating to the specified temperature (typically 90–110 °C). All reactions were run in a reaction vessel open to air. Wide tolerance of substitution was again observed (**13** and **14**). Moreover, functional tolerance was demonstrated in the synthesis of ketones, amides, nitriles, and thiophenes (**15**–**17**). The melamine-palladium catalyst also accommodated variation of the arylboronic acid coupling partner, with moderate to excellent cross-coupling yields obtained for arylboronic acids containing electron-withdrawing nitrile, aldehyde, and trifluormethyl functional groups (**18**–**21**). Among these substrates, nitrile **19** is notable in that it is a common intermediate in the industrial syntheses of sartans such as losartan, irbesartan, and valsartan,[41−43] all angiotensin II receptor antagonists used in the treatment of hypertension.[44] The lower yield obtained for aldehyde **20** could not be improved with longer reaction times or excess boronic acid, suggesting that aldehydes may not be optimal substrates for this system. With that said, the wide range of substrates and functionality in Scheme 2 bode well for the general use of the melamine-palladium catalyst and ethyl lactate in sustainable organic synthesis. As a final note on substrate scope and coupling conditions, moderate coupling yields were obtained with aryl chlorides (57% for **11**), albeit at higher temperature (130 °C). Furthermore, while couplings were typically carried out between 90 and 110 °C, the reaction does proceed at lower temperatures (**11** was produced at 37% conversion after 14 h at 37 °C).

Polymeric Melamine-Palladium Complexes as Recoverable Catalysts. While the homogeneous catalysis in Schemes 1 and 2 was encouraging, the palladium was not readily recoverable. In an attempt to address this limitation for the reaction in Scheme 1B (using sodium carbonate as the base), the palladium-containing filtrate was recycled as both a catalyst solution and solvent. This is possible since the product of cross-coupling (**1**) precipitates over the course of the coupling. Unfortunately, lower yields (50%) were typically observed in this catalyst recovery strategy. We therefore considered it prudent to evaluate other methods by which the melamine-palladium catalyst could be recovered. Our subsequent approach centered on altering the melamine-palladium complex itself. We reasoned that cross-linking the melamine-palladium complex with formaldehyde would render it insoluble and therefore recoverable. Melamine-formaldehyde polymers have long been employed in the ceramics and coatings industries,[20,21] but use of these polymers as ligands or solid supports for palladium are limited. In these few reports, palladium black was deposited on preformed melamine-formaldehyde polymers and used in catalytic hydrogenations.[45,46] Our strategy differed conceptually since our intention was to preform the melamine-palladium complex used in homogeneous catalysis and then convert it to an insoluble polymer by cross-linking through a condensation with formaldehyde (Scheme 3A). In the event, heating an aqueous solution of the melamine-palladium complex with formaldehyde at pH 9 resulted in the formation of an insoluble material that could be isolated by simple filtration. The isolated polymer is shown in Scheme 3B.

It should be noted that a large molar ratio of melamine to palladium was used in this experiment (66:1). We reasoned that excess melamine could polymerize to form a supporting matrix that serves as both a ligand and a filler that facilitates isolation and handling of the catalyst. It should also be noted that the molar ratio of formaldehyde to melamine used here was 3.0:1.0. This ratio is important since the cross-linking density likely depends on this value. It should also be noted that the structure of the cross-linked melamine shown in Scheme 3A is only a generic structure, and the degree of cross-linking was not confirmed experimentally. The surface characteristics and morphology of the polymer, however, were investigated by scanning electron microscopy (SEM). This analysis revealed a

dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094−2104

microspherical melamine-formaldehyde polymer with diameters ranging from 500 nm to 1.3 μm (Scheme 3B). Importantly, the presence of palladium in these microspheres was verified by energy dispersive X-ray spectroscopy. The amount of palladium was ultimately quantified by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) where the palladium content in the isolated polymer was measured to be 1.12 (±0.02) % by weight, an average of duplicate measurements.

With a candidate polymeric catalyst in hand, its reactivity was investigated in the synthesis of the anti-inflammatory pharmaceutical felbinac (**10**)[38] in water (Scheme 3C). The amount of **22** used in the reaction corresponded to a palladium loading of approximately 0.8−0.9 mol %, based on the weight percentage of the melamine-palladium polymer measured by ICP-AES. Gratifyingly, felbinac (**10**) was obtained in an excellent 95% yield after 20 h of reaction time at 80 °C. Shorter reaction times led to lower conversions, indicating that **22**, while catalytically competent, had a lower turnover frequency than the homogeneous form of the melamine-palladium catalyst. Unlike the homogeneous form of the melamine-palladium catalyst, however, **22** could be recovered by simple filtration. In a typical workup, between 90% and 97% of the polymer was recovered, by mass. The recovered catalyst was also active in cross-coupling, though yields in second and third use of the recovered catalyst were typically about 30% lower than in the first use. For example, recovered **22** was used to provide felbinac (**10**) in 64% yield, under otherwise identical conditions. To determine if palladium leaching from the polymer may account for these lower yields, **22** was subjected to cross-coupling conditions for 24 h at 80 °C (the substrates in Scheme 3C were used in this experiment). After this time, the insoluble polymer was isolated by filtration and dried to provide a 97% recovery of the catalyst by mass. The recovered polymeric catalyst was then analyzed by ICP-AES to determine palladium recovery. The palladium content in the polymer was 1.12% by weight, the same palladium composition of the initial catalyst. The palladium content in the filtrate was only <0.0001% palladium by weight, indicating a negligible amount of palladium is leached into solution under the cross-coupling conditions. Virtually identical results were obtained in a duplication of this leaching experiment. Therefore, while the cross-coupling yields with the recovered catalyst are lower than yields obtained with the catalyst's first use, high palladium recovery is possible with this polymeric system. The lower cross-coupling yields observed for the recovered catalyst may therefore be the result of change in the structure or oxidation state of palladium catalyst over the course of the first cross-coupling.[47] Further investigation of this phenomenon is underway in our laboratory. In any case, it is notable that the polymeric melamine-palladium system (e.g., **22**) can be used in cross-coupling and the palladium can be recovered with high efficiency, a valuable complement to the homogeneous catalysis reported in Schemes 1 and 2. Furthermore, while many ingenious methods have been devised for the preparation of highly active and recyclable palladium catalysts,[48,49] these methods often employ expensive ligands or necessitate relatively complex synthesis of the ligand and solid support.[48,49] In contrast, polymeric melamine-palladium **22** can be formed in short order through an operationally simple condensation of formaldehyde with the preformed melamine-palladium complex. Melamine is also very inexpensive, typically ∼$0.003 USD/mmol from commercial suppliers, further motivating exploration of its use as a ligand in transition metal catalysis. Currently, we are investigating melamine-formaldehyde polymers as ligands not only for palladium but also for other metals such as copper and iron. An account of these polymer-metal complexes and the reactions they catalyze will be reported in due course.

CONCLUSION

In summary, we have demonstrated that melamine is a useful ligand for palladium in Suzuki−Miyaura cross-coupling. Melamine is cheap, commercially available, and easy to handle in a variety of cross-coupling formats. Many cross-coupling catalysts are designed for exclusive use in either water or organic solvents. In contrast, the melamine-palladium catalyst is soluble and active in both aqueous and organic reaction media and therefore applicable to a diverse class of substrates. Ethyl lactate was employed as the organic solvent since it is renewable, nontoxic, and biodegradable. This is only the second report of Suzuki−Miyaura cross-coupling in ethyl lactate, and the melamine ligand was shown to impart superior stability and activity when compared to palladium acetate alone.[40] Water is a useful solvent because it is nonflammable and nontoxic. Palladium-catalyzed cross-coupling in water is also of increasing interest for biological substrates such as nucleic acids,[25] proteins,[23,24,26−29] and even living cells.[36,50−53] We encourage consideration of melamine as a ligand for palladium in these investigations. Complementing the use of the melamine-palladium complex in homogeneous catalysis, we have demonstrated that the melamine-palladium complex can be cross-linked by reaction with formaldehyde to provide a polymeric catalyst that is easily recoverable after cross-coupling reactions. Finally, we have revealed an interesting pH and base dependence in aqueous cross-couplings catalyzed by the melamine-palladium complex. Further exploration of these matters is underway.

EXPERIMENTAL SECTION

General Experimental Methods. Proton nuclear magnetic resonance (^{1}H NMR) and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were assigned as fully as possible using COSY, HSQC, and DEPT-135 experiments. All chemical shifts are quoted on the δ scale in ppm using residual solvent as the internal standard (^{1}H NMR: $CDCl_3$ = 7.26; DMSO-d_6 = 2.50 and ^{13}C NMR: $CDCl_3$ = 77.0; DMSO-d_6 = 39.5). Coupling constants (J) are reported in hertz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad, and a = apparent. Infrared (IR) spectra were recorded on a Fourier transform spectrophotometer using thin films on NaCl plates for liquids and oils and KBr discs for solids and crystals. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were recorded on a electrospray ionization mass spectrometer with atmospheric pressure chemical ionization (APCI) capability and an orbitrap mass analyzer. Accurate mass (m/z) values are reported in daltons. Thin layer chromatography (TLC) was carried out using aluminum-backed 200 μm silica plates impregnated with a UV_{254} fluorophore. Visualization of the silica plates was achieved using a UV lamp (λ_{max} = 254 nm), and/or ammonium molybdate (5% in 2 M H_2SO_4), and/or potassium permanganate (5% $KMnO_4$ in 1 M NaOH with 5% potassium carbonate). Flash column chromatography was carried out using 60 Å, 40−63 μm silica gel. All solvents were used as received from commercial suppliers. Deionized water was used for chemical reactions unless otherwise indicated. Reagents purchased from commercial suppliers were used as received, unless otherwise indicated. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40−

dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094−2104

60 °C. Brine refers to a saturated solution of sodium chloride. Anhydrous magnesium sulfate ($MgSO_4$) was used as a drying agent after reaction workup, as indicated. For compounds that have been previously synthesized, references are provided for purposes of comparison.

Preparation of Melamine-Palladium Catalyst in Water for Homogeneous Catalysis in Aqueous Media. *Method A.* Palladium acetate (2.2 mg, 0.010 mmol) and melamine (5.5 mg, 0.044 mmol) were added to a 10.0 mL volumetric flask. Deionized H_2O was added to the flask, and the mixture was stirred at 80 °C for 2 h until the palladium had dissolved. After this time, the stir bar was removed, and the solution was diluted to 10.0 mL with deionized H_2O to provide a catalyst solution that is 1 mM in palladium. This catalyst solution was stored for months in a capped vial at room temperature with no discernible change in activity.

Method B. Palladium acetate (2.2 mg, 0.010 mmol) and melamine (5.5 mg, 0.044 mmol) were placed in a 10.0 mL volumetric flask followed by 9.0 mL of deionized H_2O. The suspension was placed in an ultrasonication bath and incubated for 1 h at 60 °C. The solution was then cooled to room temperature and diluted to 10.0 mL to provide a catalyst solution that is 1 mM in palladium. This catalyst solution was stored for months in a capped vial at room temperature with no discernible change in activity.

Base and pH Profile for Aqueous Cross-Couplings in the Synthesis of 4-Phenylbenzoic Acid (1) (Scheme 1B). *Sodium Carbonate (pH 9.2).* 4-Bromobenzoic acid (200 mg, 1.0 mmol), phenylboronic acid (146 mg, 1.2 mmol), and sodium carbonate (212 mg, 2.0 mmol) were added to a 25 mL round-bottom flask and dissolved in deionized H_2O (4.0 mL). The melamine-palladium catalyst solution (1 mL of a 1 mM solution in water, 0.001 mmol Pd) was then added at room temperature. The pH of this solution was 9.21 (pH meter). The reaction was then placed in an oil bath preheated to 80 °C. The reaction was stirred, open to air, at 80 °C for 30 min. After this time, the product had precipitated as a white solid. The reaction was then cooled to room temperature and transferred to a separatory funnel along with EtOAc (50 mL) and 1 M HCl (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid was recrystallized (EtOH/1 M HCl) to provide the cross-coupled product as white crystals (182 mg, 92% yield). Spectroscopic data was consistent with that previously reported.[23] Mp = 222−225 °C. IR (υ_{max}, KBr): 3000, 2550, 1680, 1650, 1608, 1560, 1420, 1317, 1287, 1192, 1129, 1007, 938, 861, 751, 696. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (1H, t, J = 7.3), 7.51 (2H, t, J = 7.3), 7.73 (2H, d, J = 7.3), 7.80 (2H, d, J = 8.8), 8.02 (2H, d, J = 8.8), 12.97 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.2, 127.4, 128.7, 129.5 (4 × CH_{Ar}), 130.0 (4°$_{Ar}$), 130.4 (CH_{Ar}), 139.4, 144.7 (2 × 4°$_{Ar}$), 167.6 (C═O). HRMS m/z (ESI$^-$): found 197.0606 $[M - H]^-$; $C_{13}H_9O_2$ requires 197.0608.

Sodium Hydroxide (pH 13.2). 4-Bromobenzoic acid (200 mg, 1.0 mmol), phenylboronic acid (146 mg, 1.2 mmol), and sodium hydroxide (120 mg, 3.0 mmol) were added to a 25 mL round-bottom flask and dissolved in deionized H_2O (4.0 mL). The melamine-palladium catalyst solution (1 mL of a 1 mM solution, 0.001 mmol Pd) was then added at room temperature. The pH of this solution was 13.2 (pH meter). The reaction was then placed in an oil bath preheated to 80 °C. The reaction was stirred, open to air, at 80 °C for 30 min. After this time, no product had crystallized from the reaction mixture. The reaction was then cooled to room temperature and transferred to a separatory funnel along with EtOAc (50 mL) and 1 M HCl (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was analyzed directly by ^{1}H NMR. No cross-coupled product (**1**) was observed; only unreacted starting materials were detected.

Potassium Phosphate (pH = 9.72). 4-Bromobenzoic acid (204 mg, 1.01 mmol), phenylboronic acid (140 mg, 1.15 mmol), and potassium phosphate monobasic (KH_2PO_4, 289 mg, 2.13 mmol) were added to a round-bottom flask and suspended in 4.0 mL of H_2O. The pH was then adjusted to 9.72 by the addition of KOH (236 mg, 4.21 mmol). The resulting solution was then heated to 80 °C. Then 1.0 mL of the melamine-palladium catalyst solution (1 mM in H_2O, 0.001 mmol Pd) was added in a single portion, and the mixture was vigorously stirred for 2 h open to air. Over the course of the reaction, a white solid precipitated from solution. The reaction was subsequently cooled to room temperature, placed in an ice bath, and quenched with 2 M HCl (10 mL). The mixture was then transferred to a separatory funnel, diluted with 100 mL of EtOAc, and washed with sequentially with 2 M HCl (2 × 50 mL) and finally with brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting white solid was purified by flash chromatography, eluting with 5% methanol in DCM. The purified product (**1**) was isolated as white prisms (200 mg, 99%). Analytical data was identical to that obtained using carbonate as base.

Triethanolamine (pH = 9.54). 4-Bromobenzoic acid (201 mg, 1.00 mmol), phenylboronic acid (146 mg, 1.20 mmol), and triethanolamine (0.27 mL, 2.00 mmol) were dissolved in 4.0 mL of H_2O by stirring in an oil bath at 80 °C. The pH was then adjusted to pH = 9.54 by the addition of NaOH (39 mg, 1.00 mmol). Then 1.0 mL of the melamine-palladium catalyst solution (1.0 mM in H_2O, 0.001 mmol Pd) was added in one portion, and the mixture was stirred vigorously for 30 min open to air. No precipitate was observed. The reaction was subsequently cooled to room temperature and quenched with 1 M HCl (10 mL). The reaction mixture was then transferred to a separatory funnel, diluted with 100 mL of EtOAc, washed with 1 M HCl (2 × 50 mL) and then brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude mixture was analyzed directly by ^{1}H NMR. No cross-coupled product (**1**) was observed; only unreacted starting materials were detected.

Imidazole (pH = 9.3). 4-Bromobenzoic acid (202 mg, 1.01 mmol), phenylboronic acid (147 mg, 1.21 mmol), and imidazole (137 mg, 2.02 mmol) were dissolved in 4.0 mL of H_2O by stirring in an oil bath at 80 °C. The pH was then adjusted to pH = 9.3 by the addition of NaOH (48 mg, 1.2 mmol). Then 1.0 mL of the melamine-palladium catalyst solution (1.0 mM in H_2O, 0.001 mmol Pd) was added in one portion, and the mixture was stirred vigorously for 30 min open to air. No precipitate was observed. The reaction was subsequently cooled to room temperature and quenched with 1 M HCl (10 mL). The reaction mixture was then transferred to a separatory funnel, diluted with 100 mL of EtOAc, and washed with 1 M HCl (2 × 50 mL) and then brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude mixture was analyzed directly by ^{1}H NMR. No cross-coupled product (**1**) was observed; only unreacted starting materials were detected.

No Base (pH = 4.4). 4-Bromobenzoic acid (201 mg, 1.00 mmol) and phenylboronic acid (148 mg, 1.21 mmol) were suspended in 4.0 mL of H_2O. The stirred mixture was then heated to 80 °C. Then 1.0 mL of the melamine-palladium catalyst solution (1.0 mM in H_2O, 0.001 mmol Pd) was added in one portion, and the mixture was stirred vigorously for 30 min open to air. The pH of this mixture was 4.4, as measured by a pH meter. After the 30 min of reaction time, the mixture was cooled to room temperature and quenched with 2 M HCl (5 mL). The mixture was then transferred to a separatory funnel, diluted with EtOAc (50 mL), and washed sequentially with 2 M HCl (2 × 30 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was analyzed directly by ^{1}H NMR, which revealed only unreacted 4-bromobenzoic acid and phenylboronic acid. 4-Phenylbenzoic acid (**1**) was not observed, indicating that base is necessary for this cross-coupling reaction.

General Cross-Coupling Procedure for Melamine-Palladium Catalyst in Homogeneous Aqueous Media (Substrates 2−9, Scheme 1). The aryl halide (1.0 mmol), arylboronic acid (1.1 mmol), and sodium carbonate (2.1 mmol) were added to a reaction vial and suspended in H_2O (4.0 mL). The stirred mixture was placed in an oil bath that was preheated to 80 °C. After all material had dissolved, a 1.0 mL aliquot of the 1 mM aqueous melamine-palladium catalyst solution (0.001 mmol Pd) was added to give catalyst loading of 0.1 mol % Pd. The reaction was stirred vigorously for 2 h, open to air. After this time, the reaction was cooled to 0 °C and quenched with 2 M HCl (10 mL). The reaction mixture was then transferred to a separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was washed

dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094−2104

sequentially with 2 M HCl (2 × 50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting product was typically analyzed directly. If necessary, the product was further purified by column chromatography, as indicated.

4′-Methylbiphenyl-4-carboxylic Acid (2).[54] 178 mg isolated, 84% yield, no purification was required. Mp = 250−252 °C. IR (ν_{max}, KBr) = 3431, 2919, 1680, 1301, 768. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (3H, s, CH_3), 7.30 (2H, d, J = 8.0, CH_{Ar}), 7.63 (2H, d, J = 8.0, CH_{Ar}), 7.75 (2H, d, J = 8.4, CH_{Ar}), 8.00 (2H, d, J = 8.4, CH_{Ar}), 12.94 (1H, s, CO_2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.7 (CH_3), 126.4, 126.7 (CH_{Ar}), 129.3 (4°$_{Ar}$), 129.7, 129.9 (CH_{Ar}), 136.1, 137.7, 144.2 (3 × 4°$_{Ar}$), 167.1 (C═O). HRMS m/z (ESI$^-$): found 211.0766 $[M - H]^-$; $C_{14}H_{11}O_2$ requires 211.0765.

3′-Methylbiphenyl-4-carboxylic Acid (3).[55] 210 mg isolated, 99% yield, no purification was required. Mp = 198−200 °C. IR (ν_{max}, KBr) = 3436, 2914, 1685, 1284, 770. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 7.23 (1H, d, J = 7.5, CH_{Ar}), 7.37 (1H, t, J = 7.4, CH_{Ar}), 7.51 (1H, d, J = 7.7, CH_{Ar}), 7.55 (1H, s, CH_{Ar}), 7.77 (2H, d, J = 6.1, CH_{Ar}), 8.01 (2H, d, J = 6.1, CH_{Ar}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1 (CH_3), 124.1, 126.8, 127.6, 128.89, 128.94, 129.6, 129.9 (6 × CH_{Ar} and 1 × 4°$_{Ar}$), 138.3, 139.0, 144.4 (3 × 4°$_{Ar}$), 167.2 (C═O). HRMS m/z (ESI$^-$): found 211.0768 $[M - H]^-$; $C_{14}H_{11}O_2$ requires 211.0765.

2′-Methylbiphenyl-4-carboxylic Acid (4).[23] 206 mg isolated after purification by flash column chromatography (5% methanol in dichloromethane), 97% yield. A 2.0 mmol portion of *o*-tolylboronic acid was used in this reaction, along with 3.2 mmol of sodium carbonate. All other conditions are prescribed in the general protocol. Mp = 186−188 °C. IR (ν_{max}, KBr) = 3368, 1597, 1455, 1237, 782. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 7.17−7.27 (4H, m, CH_{Ar}), 7.42 (2H, d, J = 8.5, CH_{Ar}), 7.97 (2H, d, J = 8.5, CH_{Ar}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.5 (CH_3), 126.5, 128.3 (CH_{Ar}), 129.64, 129.67, 129.76, 129.78 (3 × CH_{Ar} and 1 × 4°$_{Ar}$), 130.90 (CH_{Ar}), 135.1, 140.7, 146.1 (3 × 4°$_{Ar}$), 167.6 (C═O). HRMS m/z (ESI$^-$): found 211.0764 $[M - H]^-$; $C_{14}H_{11}O_2$ requires 211.0765.

2′,6′-Dimethylbiphenyl-4-carboxylic Acid (5). 217 mg isolated, 96% yield, no purification was required. Mp = 255−260 °C. IR (ν_{max}, KBr) = 3385, 2909, 1685, 1060, 753. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (6H, s, 2 × CH_3), 6.91 (2H, d, J = 7.8, CH_{Ar}), 7.06 (1H, t, J = 7.8, CH_{Ar}), 7.71 (2H, d, J = 6.8, CH_{Ar}), 7.88 (2H, d, J = 6.8, CH_{Ar}), 8.16 (1H, s, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4 (CH_3), 126.0 (CH_{Ar}), 127.3 (4°$_{Ar}$), 127.7 (CH_{Ar}), 130.5 (4°$_{Ar}$), 131.7 (CH_{Ar}), 132.1 (CH_{Ar}), 138.8 (4°$_{Ar}$) 167.08 (C═O). HRMS m/z (ESI$^-$): found 225.0916 $[M - H]^-$; $C_{15}H_{13}O_2$ requires 225.0921.

4′-Methylbiphenyl-3-carboxylic Acid (6). 210 mg isolated, 99% yield, no purification was required. Mp = 181−184 °C. IR (ν_{max}, KBr) = 3448, 2922, 1696, 1309, 753.^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (3H, s, CH_3), 7.30 (2H, d, J = 7.8, CH_{Ar}), 7.59−7.61 (3H, m, CH_{Ar}), 7.90 (1H, d, J = 7.6, CH_{Ar}), 7.97 (1H, d, J = 7.6, CH_{Ar}), 8.22 (1H, s, CH_{Ar}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1 (CH_3), 127.0, 127.5, 128.4, 129.7, 130.1, 131.2, 131.9, 136.8, 137.7, 140.8 (10 × Ar), 167.7 (C═O). HRMS m/z (ESI$^-$): found 211.0761 $[M - H]^-$; $C_{14}H_{11}O_2$ requires 211.0765.

4-Phenylphenol (7).[23] 158 mg isolated, 93% yield, no purification was required. Mp = 157−158 °C. IR (ν_{max}, KBr): 3396, 3032, 2925, 2848, 1486, 748. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.83 (2H, d, J = 7.0), 7.23 (1H, t, J = 5.9), 7.35 (2H, t, J = 7.0), 7.44 (2H, d, J = 7.0), 7.53 (2H, d, J = 7.8), 9.53 (1H, s, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 116.2, 126.4, 126.8, 128.2, 129.4 (5 × CH_{Ar}), 131.4, 140.7, 157.6 (3 × 4°$_{Ar}$). HRMS m/z (ESI$^-$): found 169.0655 $[M - H]^-$; $C_{12}H_9O$ requires 169.0659.

4′-Methylbiphenyl-4-ol (8).[56] 182 mg isolated after purification by flash column chromatography (5% methanol in dichloromethane), 99% yield. Mp = 143−145 °C. IR (ν_{max}, KBr) = 3422, 1615, 1500, 1264, 807. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (3H, s, CH_3), 5.22 (1H, s, OH), 6.90 (2H, d, J = 8.6, CH_{Ar}), 7.23 (2H, d, J = 8.6, CH_{Ar}), 7.43−7.47 (4H, m, CH_{Ar}).^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1 (CH_3), 115.6, 126.6, 128.2, 129.4 (4 × CH_{Ar}), 133.9, 136.4, 137.9, 154.8 (4 × 4°$_{Ar}$). HRMS m/z (ESI$^-$): found 183.0812 $[M - H]^-$; $C_{13}H_{11}O$ requires 183.0815.

3′-Methylbiphenyl-4-ol (9).[56] 175 mg isolated after purification by flash column chromatography (5% methanol in dichloromethane), 95% yield. Mp = 52−54 °C. IR (ν_{max}, KBr) = 3368, 1597, 1455, 1237, 782. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (3H, s, CH_3), 5.67 (1H, s, OH), 6.93 (2H, d, J = 8.6, CH_{Ar}), 7.16 (1H, d, J = 7, CH_{Ar}), 7.31−7.40 (3H, m, CH_{Ar}), 7.50 (2H, d, J = 8.6, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_3), 115.7, 123.9, 127.50, 127.57, 128.43, 128.68 (6 × CH_{Ar}), 134.1, 138.3, 140.8, 155.0 (4 × 4°$_{Ar}$). HRMS m/z (ESI$^-$): found 183.0814 $[M - H]^-$; $C_{13}H_{11}O$ requires 183.0815.

Synthesis of Felbinac (10) in Unpurified Tap Water. 4-Bromophenylacetic acid (1.00 g, 4.70 mmol) and phenylboronic acid (680 mg, 5.58 mmol) were added to a 125 mL conical flask. City of Tulsa tap water (10 mL) was added to the reaction vessel along with sodium carbonate (1.10 g, 10.4 mmol). The resulting mixture was stirred until all material had dissolved. After this time, 4.7 mL of the palladium-melamine catalyst solution was added in a single portion. This aqueous catalyst solution was 1 mM in Pd, resulting in a catalyst loading of 0.1 mol % (0.0047 mmol Pd). The reaction was then placed in an oil bath preheated to 80 °C and stirred (open to air) for 2 h. After this time, the reaction was removed from heat and cooled to 0 °C. Then 1 M HCl was added to the reaction mixture (15 mL), and the organic material was extracted with ethyl acetate (100 mL). The organic layer was then washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide felbinac as an analytically pure white solid (998 mg, 99% yield). Spectroscopic data was consistent with that previously reported.[57] Mp = 155−158 °C. IR (ν_{max}, KBr) = 2955, 1685, 1250, 732. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.63 (2H, s, CH_2), 7.35−7.37 (3H, m, CH_{Ar}), 7.46 (2H, t, J = 7.7, CH_{Ar}), 7.61 (2H, d, J = 8.1, CH_{Ar}), 7.66 (1H, d, J = 8.1, CH_{Ar}), 12.40 (1H, bs, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 40.21 (CH_2), 126.47, 126.49, 127.23, 128.82 (4 × CH_{Ar}), 134.20, 138.45, 139.87 (3 × 4°$_{Ar}$), 172.60 (C═O). HRMS m/z (ESI$^-$): found 211.0763 $[M - H]^-$; $C_{14}H_{11}O_2$ requires 211.0765.

Gram-Scale Synthesis of Felbinac (10) in Unpurified Arkansas River Water. 4-Bromophenylacetic acid (1.00 g, 4.70 mmol), phenylboronic acid (626 mg, 5.14 mmol), and sodium carbonate (1.06 g, 9.81 mmol) were dissolved in 5.4 mL of unfiltered Arkansas River water by stirring in an oil bath at 80 °C for several minutes. A 4.7 mL aliquot of the melamine-palladium catalyst solution was added in one portion, and the mixture was vigorously stirred for 2 h open to air. The aqueous catalyst solution was 1 mM in Pd, resulting in a catalyst loading of 0.1 mol % (0.0047 mmol Pd). The reaction was subsequently cooled to room temperature, placed in an ice bath and quenched with 2 M HCl (10 mL). The reaction mixture was transferred to a separatory funnel, diluted with 100 mL of EtOAc, and washed with 2 M HCl (2 × 50 mL) and then with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting product (feblinac) was isolated as a white solid and did not require further purification (951 mg, 96% yield). Spectroscopic data was consistent with that obtained in the felbinac synthesis described in the previous experiment.

Catalyst Recovery under Homogeneous Conditions in Water. 4-Bromobenzoic acid (200 mg, 1.0 mmol), phenylboronic acid (145 mg, 1.19 mmol), and sodium carbonate (238 mg, 2.25 mmol) were added to a 25 mL round-bottom flask. H_2O (4.0 mL) was added to the reaction flask, and the stirred mixture was heated to 80 °C to dissolve. The melamine-palladium catalyst solution (1 mL of a 1 mM solution in water, 0.001 mmol Pd) was then added, and the reaction was stirred, open to air, at 80 °C for 30 min. After this time, the reaction was cool to 0 °C, the precipitated product was isolated by filtration, and the filtrate was saved for a subsequent reaction (see below). The solid product was transferred to a 50 mL beaker, suspended in 2 M HCl (10 mL), and then transferred into a separatory funnel along with EtOAc (35 mL). The organic layer was separated and then washed with brine (50 mL) before drying ($MgSO_4$), filtering, and concentrating under reduced pressure. The product, 4-phenylbenzoic acid (**1**), was spectroscopically identical to the compound synthesized in Scheme 1 (185 mg isolated, 93% yield). The filtrate

isolated after the cross-coupling was then used as a catalyst solution for the same cross-coupling. Accordingly, 4-bromobenzoic acid (200 mg, 1.0 mmol), phenylboronic acid (145 mg, 1.19 mmol), and sodium carbonate (238 mg, 2.25 mmol) were added to a 25 mL round-bottom flask and then dissolved in the filtrate from the first cross-coupling. The mixture was heated at 80 °C for 30 min, open to air. After this time, the reaction was cooled to 0 °C and quenched with 2 M HCl (5 mL). The mixture was then transferred to a separatory funnel, diluted with EtOAc (50 mL), and washed sequentially with 2 M HCl (2 × 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and isolated under reduced pressure. The crude product was analyzed directly by ^{1}H NMR (DMSO-d_6), which revealed 50% conversion to the cross-coupled product **1** and unreacted 4-bromobenzoic acid and phenylboronic acid. (The ^{1}H NMR spectrum in this experiment was compared to spectra of the unreacted starting materials and purified **1** for peak assignments in conversion analysis.) This experiment indicates that the palladium-melamine catalyst in water can be recovered in reactions where the product precipitates, but the catalytic activity of the filtrate is diminished relative to the original homogeneous solution.

Preparation of Melamine-Palladium Catalyst in Ethyl Lactate for Homogeneous Catalysis in Organic Media. Palladium acetate (56 mg, 0.25 mmol) and melamine (126 mg, 1.00 mmol) were added to a 25.0 mL volumetric flask. Ethyl lactate (20 mL) was added, and the resulting mixture was stirred at 60 °C to dissolve (~10 min). The stir bar was then removed, and the resulting dark yellow solution was diluted to 25.0 mL to give a catalyst solution that is 10 mM in palladium. The solution was stored for months in a capped vial at room temperature with no discernible change in activity.

UV−vis Analysis of Palladium-Melamine Complex in Ethyl Lactate. Palladium acetate (2.2 mg, 0.010 mmol) and melamine (5.0 mg, 0.040 mmol) were added to a 2.0 mL volumetric flask and dissolved in ethyl lactate. Diluting the total volume to 2.0 mL with ethyl lactate provided a 5 mM solution of the palladium-melamine catalyst in ethyl lactate. As a control, a 5 mM solution of palladium acetate in ethyl lactate (no melamine) was also prepared in the same fashion. As another control, a 20 mM solution of melamine in ethyl lactate was also prepared (no palladium). UV−vis analysis revealed a λ_{Max} = 393 nm for $Pd(OAc)_2$ in ethyl lactate; λ_{Max} = 353 nm for $Pd(OAc)_2$ and melamine in ethyl lactate. The shift in λ_{Max} is evidence for melamine coordination to palladium. The solution of melamine alone is clear and does not absorb in the visible region. UV−vis spectra are shown in the Supporting Information.

Stability Studies of Palladium-Melamine Complex in Ethyl Lactate (Scheme 2B). The stability of the melamine-palladium catalyst in ethyl lactate was compared to that of palladium acetate in ethyl lactate at 110 °C. Accordingly, three solutions were prepared. Solution 1, melamine only: melamine (2.3 mg, 18 μmol) was added to a reaction 10 mL reaction tube and dissolved in 2 mL ethyl lactate. Solution 2, palladium only: $Pd(OAc)_2$ (1.0 mg, 4.5 μmol) was added to a 10 mL reaction tube and dissolved in 2 mL ethyl lactate. Solution 3, palladium and melamine: melamine (2.3 mg, 18 μmol) and $Pd(OAc)_2$ (1.0 mg, 4.5 μmol) were both added to a 10 mL reaction tube and dissolved in 2 mL of ethyl lactate. All three reaction tubes were placed in an oil bath that was preheated to 110 °C. Within 10 min the Solution 2 (palladium only) turned black. After 2 h, Solution 3 (both melamine and palladium) was still homogeneous. No visible change was observed for the Solution 1 negative control (melamine only). Photographs of the solutions before and after heating are available in the Supporting Information.

Comparison of Catalytic Activity of Palladium Acetate and Palladium-Melamine in Ethyl Lactate in the Synthesis of 4-Phenylacetophenone (11) (Scheme 2B). *Without Melamine.* 4-Bromoacetophenone (202 mg, 1.01 mmol), phenylboronic acid (149 mg, 1.22 mmol), and sodium carbonate (221 mg, 2.08 mmol) were combined in a 10 mL reaction tube followed by ethyl lactate (0.40 mL). The tube was placed in an oil bath preheated to 110 °C, and the mixture was stirred vigorously. Then 100 μL of catalyst solution (10 mM $Pd(OAc)_2$ in ethyl lactate, no melamine, 0.001 mmol Pd) was added in 1 portion, and the reaction mixture was stirred vigorously open to air at 110 °C for 2 h. The reaction mixture turned black within 15 min. After 2 h of reaction time, the mixture was cooled to room temperature and diluted with 1 mL of EtOAc and 1 mL of H_2O. Flash chromatography was performed directly on this mixture, eluting with 10% EtOAc in petrol, providing **11** as white needles (120 mg isolated, 61% yield).

With Melamine. 4-Bromoacetophenone (202 mg, 1.01 mmol), phenyl boronic acid (149 mg, 1.22 mmol), and sodium carbonate (221 mg, 2.08 mmol) were added to a 10 mL reaction tube followed by ethyl lactate (0.40 mL). The tube was placed in an oil bath preheated to 110 °C, and the mixture was stirred vigorously. Then 100 μL of melamine-palladium catalyst solution (10 mM in Pd and 40 mM in melamine, prepared in ethyl lactate according to the general procedure described previously, 0.001 mmol Pd) was added in one portion, and the reaction mixture was stirred vigorously, open to air, at 110 °C for 2 h. The reaction mixture was subsequently cooled to room temperature and diluted with 1 mL of EtOAc and 1 mL of H_2O. Flash chromatography was performed directly on this mixture, eluting with 10% EtOAc in petrol, providing **11** as white needles (192 mg isolated, 97% yield).

Data for **11**:[58] mp = 105−106 °C. IR (υ_{max}, KBr): 3057, 2917, 1681, 1403, 1358, 764. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (3H, s, CH_3), 7.37 (1H, t, J = 7.4), 7.46 (2H, t, J = 7.4), 7.61 (2H, d, J = 7.4), 7.67 (2H, d, J = 8.4), 8.02 (2H, d, J = 8.4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6 (CH_3), 127.19, 127.24, 128.22, 128.89, 128.94 (5 × CH_{Ar}), 135.8, 139.8, 145.7 (3 × 4°$_{Ar}$), 197.7 (C═O). HRMS m/z (ESI$^+$): found 197.0962 $[M + H]^+$; $C_{14}H_{13}O$ requires 197.0961.

General Cross-Coupling Procedure for Melamine-Palladium Catalyst in Ethyl Lactate (Substrates 12−21, Scheme 2C). The aryl bromide (1.00 mmol), arylboronic acid (1.20 mmol), and sodium carbonate (2.00 mmol) were added to a 10 mL reaction tube. Ethyl lactate (0.4 mL) was added to the mixture followed by 100 μL of the melamine-palladium catalyst solution (10 mM in Pd and 40 mM in melamine, prepared in ethyl lactate according to the general procedure described previously, 0.001 mmol Pd) to give a catalyst loading of 0.1 mol %. The stirred reaction mixture was then placed in an oil bath preheated to 110 °C and stirred, open to air, for 2 h. After this time, the reaction mixture was cooled to room temperature and then diluted with water (0.5 mL) and ethyl acetate (0.5 mL). The resulting solution was purified directly by flash column chromatography (5−10% ethyl acetate in petrol). In the preparation of **15**, 2.00 mmol of 3-thienylboronic acid was employed, and the reaction was instead run for 2 h at 90 °C. In the preparation of **16**, the reaction was run at a 2.4 mmol scale where all reaction components were scaled accordingly. After the reaction, **16** was extracted into dichloromethane after the reaction and then purified by recrystallization (dichloromethane/petrol).

1-(3′-Methyl-[1,1′-biphenyl]-4-yl)ethanone (12).[59] 208 mg isolated, 99% yield. Mp = 72−73 °C. IR (υ_{max}, KBr): 3035, 3017, 2922, 1683, 1602, 1585, 1421, 1397, 1358, 1272, 1114, 1025. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (3H, s, CH_3), 2.61 (3H, s, $COCH_3$), 7.20 (1H, d, J = 7.5), 7.34 (1H, t, J = 7.5), 7.40−7.42 (2H, m), 7.65 (2H, d, J = 8.4), 8.0 (2H, d, J = 8.4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 26.7 (2 × CH_3), 124.4, 127.2, 128.0, 128.9 (2 × C, 2 cross-peaks in HSQC), 129.0 (6 × CH_{Ar}), 135.7, 138.6, 139.8, 145.9 (4 × 4°$_{Ar}$), 197.7 (C═O). HRMS m/z (ESI$^+$): found 211.1116 $[M + H]^+$; $C_{15}H_{15}O$ requires 211.1117.

1-(2′-Methyl-[1,1′-biphenyl]-4-yl)ethanone (13).[60] 209 mg isolated, 99% yield, clear oil. IR (υ_{max}, film): 3061, 3018, 2956, 2924, 2856, 1686, 1606, 1557, 1483, 1401, 1358, 1267, 1181, 1110, 1006, 957, 843, 763. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (3H, s, CH_3), 2.64 (3H, s, $COCH_3$), 7.20−7.30 (4H, m, CH_{Ar}), 7.42 (2H, d, J = 8.0, CH_{Ar}), 8.01 (2H, d, J = 8.0, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (CH_3), 26.6 ($CO\underline{C}H_3$), 125.8, 127.8, 128.1, 129.35, 129.39, 130.4 (6 × CH_{Ar}), 135.0, 135.5, 140.6, 146.8 (4 × 4°$_{Ar}$), 197.7 (C═O). HRMS m/z (ESI$^+$): found 211.1116 $[M + H]^+$; $C_{15}H_{15}O$ requires 211.1117.

1-(2′,6′-Dimethyl-[1,1′-biphenyl]-4-yl)ethanone (14).[61] 197 mg isolated, 88% yield. Mp = 58−59 °C. IR (υ_{max}, KBr): 3019, 2955, 2933, 2856, 1685, 1580, 1511, 1463, 1441, 1425, 1264, 1179,

dx.doi.org/10.1021/jo402799t | J. Org. Chem. 2014, 79, 2094−2104

1018. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (6H, s, 2 × CH_3), 2.65 (3H, s, $COCH_3$), 7.11 (2H, d, J = 7.7), 7.19 (1H, t, J = 7.7), 7.26 (2H, d, J = 8.0), 8.04 (2H, d, J = 8.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8 (CH_3), 26.6 ($COCH_3$), 127.45, 127.53, 128.6, 129.4 (4 × CH_{Ar}), 135.5, 135.6, 140.7, 146.5 (4 × 4°$_{Ar}$), 197.8 (C═O). HRMS m/z (ESI$^+$): found 225.1275 $[M + H]^+$; $C_{16}H_{17}O$ requires 225.1274.

1-(4-(Thiophen-3-yl)phenyl)ethanone (15).[62] 164 mg isolated, 81% yield. Mp = 136−138 °C. IR (υ_{max}, KBr): 3099, 2922, 1676, 1423, 1361, 1274, 1206, 853, 834, 784. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (3H, s, CH_3), 7.40−7.43 (2H, m, $CH_{thiophene}$), 7.55−7.58 (1H, m, $CH_{thiophene}$), 7.66 (2H, d, J = 8.3, CH_{Ar}), 7.97 (2H, d, J = 8.3, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6 (CH_3), 122.0 ($CH_{thiophene}$), 126.1 ($CH_{thiophene}$), 126.3 (CH_{Ar}), 126.8 ($CH_{thiophene}$), 129.0 (CH_{Ar}), 135.6, 140.2, 141.0 (4°$_{Ar}$), 197.6 (C═O). HRMS m/z (ESI$^+$): found 203.0526 $[M + H]^+$; $C_{12}H_{11}OS$ requires 203.0525.

***N*-Biphenyl-4-yl-acetamide (16).**[63] 148 mg isolated, 70% yield. Mp = 158−160 °C. IR (υ_{max}, KBr): 3247, 3175, 3105, 3051, 2372, 1663, 1540, 1488, 1320, 760. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04 (3H, s, CH_3), 7.27 (1H, t, J = 7.4), 7.39 (2H, t, J = 7.8), 7.55 (4H, t, J = 8.6), 7.64 (2H, d, J = 8.6), 10.00 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.47 (CH_3), 119.76, 126.62, 127.29, 127.36, 129.29 (5 × CH_{Ar}), 135.07, 139.25, 140.18 (3 × 4°$_{Ar}$), 168.76 (C═O). HRMS m/z (ESI$^+$): found 212.1067 $[M + H]^+$; $C_{14}H_{14}NO^+$ requires 212.1070.

4-Cyanobiphenyl (17).[64] 161 mg isolated, 90% yield. Mp = 80−82 °C. IR (υ_{max}, KBr): 3076, 3030, 2926, 2854, 2253, 2227, 1606, 1485, 1448, 1397. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (1H, t, J = 7.3), 7.48 (2H, t, J = 7.3), 7.58 (2H, d, J = 7.0), 7.66−7.72 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.9, 118.9 (2 × 4°), 127.2, 127.7 128.6, 129.1, 132.6 (5 × CH_{Ar}), 139.1, 145.6 (2 × 4°).

4′-Acetyl-(1,1′-biphenyl)-4-carbonitrile (18).[59] 199 mg isolated, 90% yield. Mp = 110−111 °C. IR (υ_{max}, KBr): 3036, 2996, 2227, 1686, 1603, 1396, 1359, 815. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (3H, s, CH_3), 7.64−7.71 (6H, m), 8.03 (2H, d, J = 8.6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7 (CH_3), 111.8, 118.6 (2 × 4°), 127.4, 127.9, 129.1, 132.7 (4 × CH_{Ar}), 136.9, 143.4, 144.2 (3 × 4°), 197.4 (C═O).

4′-Methyl-(1,1′-biphenyl)-2-carbonitrile (19).[57] 143 mg isolated, 74% yield. IR (υ_{max}, film): 3053, 2986, 2305, 1421, 1265,738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (3H, s, CH_3), 7.29 (2H, d, J = 8.1), 7.40 (1H, td, J = 7.7, 1.4), 7.45 (2H, d, J = 8.1), 7.49 (1H, d, J = 7.9), 7.6 (1H, td, J = 1.4, 7.7), 7.73 (1H, d, J = 7.8). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (CH_3), 111.1, 118.8 (2 × 4°), 127.2, 128.6, 129.4, 129.9, 132.7, 133.7 (6 × CH_{Ar}), 135.2, 138.7, 145.5 (3 × 4°).

4′-Acetyl-(1,1′-biphenyl)-4-carbaldehyde (20). 143 mg isolated, 64% yield. Mp = 83−85 °C. IR (υ_{max}, KBr): 2919, 1683, 1675, 1266, 1218, 812. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (3H, s, CH_3), 7.68 (2H, d, J = 8.2), 7.74 (2H, d, J = 8.1), 7.93 (2H, d, J = 8.1), 8.02 (2H, d, J = 8.2) (CH_{Ar}) 10.02 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7 (CH_3), 127.5, 127.8, 129.0, 130.3 (4 × CH_{Ar}), 135.8, 136.7, 144.0, 145.6 (4 × 4°$_{Ar}$), 191.7, 197.5 (2 × C═O). HRMS m/z (ESI$^+$): found 225.0906 $[M + H]^+$; $C_{15}H_{13}O_2^+$ requires 225.0910.

1-(4′-(Trifluoromethyl)-[1,1′-biphenyl]-4-yl)ethanone (21).[65] 259 mg isolated, 98% yield. Mp = 118−119 °C. IR (υ_{max}, KBr): 3052, 2929, 1685, 1322, 1159, 1122, 1069, 823. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (3H, s, CH_3), 7.67 (2H, d, J = 8.6), 7.70 (br. s, 4H), 8.04 (2H, d, J = 8.6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6 (CH_3), 122.7, 125.4, 125.79, 125.83, 125.87, 125.91, 127.4, 127.6, 128.15, 129.0, 129.7, 130.0, 130.3, 130.7, 136.6, 143.3, 144.1, 197.5 (C═O) (q, J_{CF} = 32.6, CF_3) (note all peaks in multiplets due to C−F spin coupling are listed; these peaks are consistent with those previously reported for this compound[65]). HRMS m/z (ESI$^+$): found 265.0831 $[M + H]^+$; $C_{15}H_{12}F_3O^+$ requires 265.0835.

Synthesis of 4-Phenylacetophenone (11) at 37 °C. 4-Bromoacetophenone (199 mg, 1.00 mmol), phenyl boronic acid (147 mg, 1.21 mmol), and sodium carbonate (212 mg, 2.00 mmol) were added to a 10 mL reaction tube followed by ethyl lactate (0.40 mL). The tube was placed in an oil bath preheated to 37 °C, and the mixture was stirred vigorously. Then 100 μL of the melamine-catalyst solution (10 mM in Pd and 40 mM in melamine, prepared in ethyl lactate according to the general procedure described previously, 0.001 mmol Pd) was added in one portion, and the reaction mixture was stirred vigorously open to air at 37 °C for 14 h. The reaction mixture was subsequently cooled to room temperature, diluted with 100 mL of EtOAc, and washed sequentially with H_2O (3 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was analyzed directly by ^{1}H NMR, which revealed 37% conversion to the cross-coupled product (conversion was based on the relative integration of the CH_3 peaks of the starting material and product). The ^{1}H NMR of the product was consistent with the purified sample obtained in the previous experiment. HRMS m/z (ESI$^+$) also corroborated the formation of the cross-coupled product: found 197.0953 $[M + H]^+$; $C_{14}H_{13}O^+$ requires 197.0961. This experiment demonstrates that the melamine-palladium complex can catalyze cross-coupling at physiological temperature, albeit with relatively low turn over frequency.

Synthesis of 4-Phenylacetophenone (11) from an Aryl Chloride. 4-Chloroacetophenone (200 mg, 1.30 mmol), phenyl boronic acid (192 mg, 1.58 mmol, 1.2 equiv), and sodium carbonate (176 mg, 1.67 mmol) were added to a 10 mL reaction tube followed by ethyl lactate (0.40 mL). The tube was placed in an oil bath that was preheated to 130 °C, and the mixture was stirred vigorously. Then 130 μL of melamine-palladium catalyst solution (10 mM in Pd and 40 mM in melamine, prepared in ethyl lactate according to the general procedure described previously, 0.0013 mmol Pd) was added in 1 portion, and the reaction mixture was stirred vigorously open to air at 130 °C for 2 h. After this time, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed sequentially with H_2O (3 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product then analyzed by ^{1}H NMR, which revealed 57% conversion of starting material to product (conversion was based on the relative integration of the CH_3 peaks of the starting material and product). The ^{1}H NMR spectrum of the product was consistent with the purified sample obtained previously. HRMS m/z (ESI$^+$) also corroborated the formation of the cross-coupled product: found 197.0955 (product) $[M + H]^+$; $C_{14}H_{14}O^+$ requires 197.0961.

Preparation of Polymeric Melamine-Palladium Catalyst (22). Melamine (5.00 g, 39.7 mmol) and palladium acetate (134 mg, 0.598 mmol) were added to a 500 mL round-bottom flask and dissolved in 250 mL of deionized water. The resulting mixture was stirred in an oil bath at 80 °C for 2 h to ensure all solids dissolved. The bath temperature was then reduced to 30 °C, and 1 M NaOH was added dropwise to adjust the pH to 9.3 (approximately 3.5 mL of 1 M NaOH was added in this step). Next, 8.90 mL (119 mmol) of formalin (37% formaldehyde in H_2O) was added in one portion, and the oil bath was reheated to 80 °C. The reaction flask was stoppered, and the mixture was stirred vigorously at 80 °C for 3 h. After this time, the resulting cloudy suspension was cooled to room temperature and then to 0 °C. The solid palladium-melamine polymer was isolated by filtration and dried for several hours under vacuum. The final polymeric catalyst was obtained as a light yellow solid (3.14 g).

SEM Analysis of Melamine Formaldehyde Polymeric Catalyst 22. The polymeric melamine-palladium catalyst (**22**) was dusted onto a scanning electron microscope stud coated in a carbon-based adhesive. The sample was then sputter-coated with a 30 nm conductive layer of gold particles and analyzed using a field emission scanning electron microscope (FESEM). SEM images revealed the polymer to be microspherical in nature with typical diameters from 500 nm to 1.3 μm. Representative SEM images are shown in Scheme 3 and in the Supporting Information.

Energy-Dispersive X-ray (EDX) Spectroscopy of Polymeric Catalyst 22. The polymeric melamine-palladium catalyst (**22**) was dusted onto a scanning electron microscope stud coated in a carbon-based adhesive. EDX analysis revealed the presence of palladium, as indicated by the detection of the Pd Lα_1, Lβ_1, and Lβ_2 X-ray emissions at 3 keV. The EDX spectrum is provided in the Supporting Information.

Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) Analysis. ICP-AES analysis was preformed using bomb

digestion for **22** (approximately 1 g of polymer per sample was employed) and an argon gas nebulizer for aqueous samples. Samples were run in duplicate, and average values are reported. The palladium content was measured to be 1.12 (±0.02) wt % for the melamine-palladium polymeric catalyst **22**.

Synthesis of Felbinac (10) Using Polymeric Melamine-Palladium Catalyst 22. 4-Bromophenylacetic acid (101 mg, 0.47 mmol), phenylboronic acid (143 mg, 1.17 mmol), and sodium carbonate (101 mg, 0.955 mmol) were added to a 10 mL reaction vial followed by deionized water (1 mL). The reaction vial was placed in an oil bath preheated to 80 °C and stirred until all solids were dissolved. After this time, the cross-linked melamine-palladium complex **22** (40 mg melamine-palladium polymer, approximately 0.45 mg Pd or 0.0042 mmol Pd, based on ICP-AES) was added to the reaction vial (resulting in ∼0.8−0.9 mol % Pd catalyst loading). The vial was then capped and stirred for 20 h at 80 °C. After this time, the vial was cooled to room temperature. The solid catalyst was then recovered by with vacuum filtration (37 mg after drying on high vacuum, 91% catalyst recovery by mass). Next, the filtrate was acidified with 2 M HCl (50 mL) and extracted with ethyl acetate. The organic layer was then dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The final product was purified by column chromatography (10% methanol in dichloromethane) to provide the felbinac product as white crystals (94 mg isolated, 95%). Spectroscopic data was identical to the felbinac synthesized using homogeneous catalysis.

Cross-Coupling Using Recovered Cross-Linked Melamine-Palladium Complex 22. The recovered melamine-palladium catalyst was dried thoroughly under high vacuum before use. The felbinac cross-coupling was then carried out on the same scale as described in the previous experiment with the entirety of the recovered melamine-palladium polymer. Again, the catalyst was recovered and the mixture was purified by column chromatography (10% methanol in dichloromethane) to provide felbinac (136 mg isolated, 64% yield).

Pd Leaching from Polymeric Melamine-Palladium Catalyst 22. 4-Bromophenylacetic acid (215 mg, 1.00 mmol), phenyl boronic acid (146 mg, 1.20 mmol), and sodium carbonate (249 mg, 2.34 mmol) were dissolved in 5.0 mL of H_2O at 80 °C. The melamine-palladium polymeric catalyst (**22**) (1.00 g) was added in a single portion, and the mixture was stirred vigorously for 24 h, open to air. After this time, the reaction was cooled to 0 °C, and the polymer was isolated by filtration and dried for several hours under vacuum to provide 970 mg of recovered catalyst. This experiment was then repeated so that duplicate samples of both recovered polymer and filtrate could be analyzed by ICP-AES. Accordingly, both the filtrate and the recovered catalyst were analyzed by ICP-AES to determine the degree of palladium leaching. Bomb digestion was employed for recovered **22**, and an argon gas nebulizer was used for aqueous filtrate sample. The recovered polymer (**22**) was measured to be 1.12 (±0.06) wt % Pd and the filtrate was <0.0001 wt % Pd. Since the original catalyst was 1.12 (±0.02) wt % Pd, this experiment indicates that essentially no palladium was leached from the melamine-formaldehyde polymer under the cross-coupling reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for compounds **1**−**21**, UV−vis spectra for the melamine-palladium complex in ethyl lactate, further details on stability analysis of palladium in ethyl lactate, supplemental SEM images of catalyst **22**, and EDX spectra of catalyst **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: justin-chalker@utulsa.edu.

Notes

The authors declare no competing financial interest.

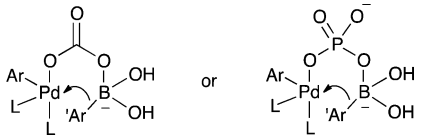
■ ACKNOWLEDGMENTS

We thank The University of Tulsa for start-up funds (J.M.C.) and financial support through the Student Research Grant Program (M.A.T., M.C.B.), the Tulsa Undergraduate Research Challenge (M.A.T., A.E.H.), and the Chemistry Summer Undergraduate Research Program (M.A.T., A.E.H., M.C.B.). We thank Paige Johnson and Jennifer Holland for technical assistance.

■ REFERENCES

(1) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.
(2) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.
(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(4) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
(5) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
(6) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027.
(7) Schlüter, A. D. *J. Polym. Sci., Part A: Polym. Chem* **2001**, *39*, 1533.
(8) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. *ACS Catal.* **2012**, *2*, 1147.
(9) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
(10) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.
(11) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. *Green Chem.* **2011**, *13*, 854.
(12) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31.
(13) Curzons, A. D.; Constable, D. C.; Cunningham, V. L. *Clean Prod. Processes* **1999**, *1*, 82.
(14) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305.
(15) Franzén, R.; Xu, Y. *Can. J. Chem.* **2005**, *83*, 266.
(16) Shaughnessy, K. H. *Eur. J. Org. Chem.* **2006**, 1827.
(17) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643.
(18) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333.
(19) Pereira, C. S. M.; Silva, V. M. T. M.; Rodrigues, A. E. *Green Chem.* **2011**, *13*, 2658.
(20) Singh, M. *Int. J. Chem. Sci.* **2005**, *3*, 1.
(21) Bretterbauer, K.; Schwarzinger, C. *Curr. Org. Synth.* **2012**, *9*, 342.
(22) Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Eur. J. Org. Chem.* **2005**, 4256.
(23) Chalker, J. M.; Wood, C. S. C.; Davis, B. G. *J. Am. Chem. Soc.* **2009**, *131*, 16346.
(24) Li, N.; Lim, R. K. V.; Edwardraja, S.; Lin, Q. *J. Am. Chem. Soc.* **2011**, *133*, 15316.
(25) Lercher, L.; McGouran, J. F.; Kessler, B. M.; Schofield, C. J.; Davis, B. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 10553.
(26) Spicer, C. D.; Davis, B. G. *Chem. Commun.* **2011**, *47*, 1698.
(27) Wang, Y.-S.; Russell, W. K.; Wang, Z.; Wan, W.; Dodd, L. E.; Pai, P.-J.; Russell, D. H.; Liu, W. R. *Mol. BioSyst.* **2011**, *7*, 714.
(28) Dumas, A.; Spicer, C. D.; Gao, Z.; Takehana, T.; Lin, Y. A.; Yasukohchi, T.; Davis, B. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 3916.
(29) Gao, Z.; Gouverneur, V.; Davis, B. G. *J. Am. Chem. Soc.* **2013**, *135*, 13612.
(30) Amatore, C.; Jutand, A.; Le Duc, G. *Chem.—Eur. J.* **2011**, *17*, 2492.
(31) Amatore, C.; Jutand, A.; Le Duc, G. *Chem.—Eur. J.* **2012**, *18*, 6616.
(32) Amatore, C.; Le Duc, G.; Jutand, A. *Chem.—Eur. J.* **2013**, *19*, 10082.
(33) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116.
(34) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362.
(35) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412.

(36) Li, J.; Chen, P. R. *ChemBioChem* **2012**, *13*, 1728.
(37) For instance, both carbonate and phosphate may promote rate-determining transmetalation as a bridging ligand. We are currently pursuing this hypothesis both for the melamine-palladium system as well as for other palladium catalysts used in aqueous Suzuki−Miyaura reactions.



(38) Hosie, G.; Bird, H. *Eur. J. Rheumatol. Inflamm.* **1994**, *14*, 21.
(39) We do not advocate using river water as a standard medium for synthesis. The purpose of this experiment was to demonstrate that the melamine-palladium catalyst is robust, easy to handle, and generally compatible with unpurified water.
(40) Wan, J.-P.; Wang, C.; Zhoua, R.; Liu, Y. *RSC Adv.* **2012**, *2*, 8789.
(41) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.
(42) Bühlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29.
(43) Amatore, M.; Gosmini, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2089 and references therein.
(44) Muszalska, I.; Sobczak, A.; Dołhań, A.; Jelińska, A. *J. Pharm. Sci.* **2014**, *103*, 2.
(45) Cao, S.; Xu, S.; Xu, S. *Polym. Adv. Technol.* **1999**, *10*, 43.
(46) Liu, P.; Zhu, W. *Polym. Adv. Technol.* **2004**, *15*, 214.
(47) The reducing agent in these cross-couplings is thought to be the arylboronic acid by way of two transmetalations to the $Pd^{(II)}$ precatalyst followed by a reducitve elimination to generate a biphenyl byproduct and the $Pd^{(0)}$ catalyst. In **22**, β-hydrides are also available on the melamine-formaldehyde polymer and may therefore play a role in the reduction of $Pd^{(II)}$ to $Pd^{(0)}$ that is not possible in the homogeneous form of the melamine-palladium catalyst.
(48) Molnár, Á. *Chem. Rev.* **2011**, *111*, 2251.
(49) Nasir Baig, R. B.; Varma, R. S. *Chem. Commun.* **2013**, *49*, 752.
(50) Yusop, R. M.; Unciti-Broceta, A.; Johansson, E. M. V.; Sánchez-Martín, R. M.; Bradley, M. *Nat. Chem.* **2011**, *3*, 239.
(51) Spicer, C. D.; Triemer, T.; Davis, B. G. *J. Am. Chem. Soc.* **2012**, *134*, 800.
(52) Spicer, C. D.; Davis, B. G. *Chem. Commun.* **2013**, *49*, 2747.
(53) Li, J.; Lin, S.; Wang, J.; Jia, S.; Yang, M.; Hao, Z.; Zhang, X.; Chen, P. R. *J. Am. Chem. Soc.* **2013**, *135*, 7330.
(54) Nemoto, K.; Yoshida, H.; Egusa, N.; Morohashi, N.; Hattori, T. *J. Org. Chem.* **2010**, *75*, 7855.
(55) Korolev, D. N.; Bumagin, N. A. *Tetrahedron Lett.* **2006**, *47*, 4225.
(56) Moteki, S. A.; Takacs, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 894.
(57) Alacid, E.; Nájera, C. *Org. Lett.* **2008**, *10*, 5011.
(58) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435.
(59) Kuroda, J.-i.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, 2251.
(60) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701.
(61) Li, G.-Q.; Yamamoto, Y.; Miyaura, N. *Synlett* **2011**, 1769.
(62) Bernini, R.; Cacchi, S.; Fabrizi, G.; Forte, G.; Petrucci, F.; Prastaro, A.; Niembro, S.; Shafir, A.; Vallribera, A. *Green Chem.* **2010**, *12*, 150.
(63) Bai, L.; Wang, J.-X. *Adv. Synth. Catal.* **2008**, *350*, 315.
(64) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189.
(65) Lipshutz, B. H.; Nihan, D. M.; Vinogradova, E.; Taft, B. R.; Bošković, Ž. V. *Org. Lett.* **2008**, *10*, 4279.