Letter

Functionalized Polymer-Supported Pyridine Ligands for Palladium-Catalyzed C(sp3)–H Arylation

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Functionalized Polymer-Supported Pyridine Ligands for Palladium-Catalyzed C(sp^3)–H Arylation

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ABSTRACT: The use of ligands to tune the reactivity and selectivity of transition metal catalysts for C(sp^3)–H bond activation is a current central challenge. One of us previously developed an uncommon example of a homogeneous catalyst that performs controlled C(sp^3)–H arylation using pyridine derivatives as ligands along with Pd in *Science* **2014**, 343, 1216-1220. In this work, we report a functionalizable and tunable polymer support used in the immobilization of pyridine derivatives that yields a soluble, polymeric ligand platform facilitating C(sp^3)–H activation reactions with good yields, selectivities differing from the homogeneous catalyst and recovery of Pd. Unlike the homogeneous system, the supported catalysts in Pd-catalyzed C–H monoarylation reactions respond sensitively to the steric hindrance of the coupling partners.

KEYWORDS: C–H activation , arylation , polymer-supported ligand, immobilized catalyst, palladium

The possibility of direct introduction of a new functionality (or a new C–C bond) via a direct C–H bond transformation is a highly attractive strategy in organic synthesis. The range of substrates has been expanded to simple hydrocarbons, complex organic small molecules, and synthetic and biological polymers.[1-7] Transition metal catalysis has been used extensively in recent years to assist in converting unactivated C–H bonds to more reactive carbon–metal bonds that can subsequently be further functionalized to afford the desired products.[8-15]

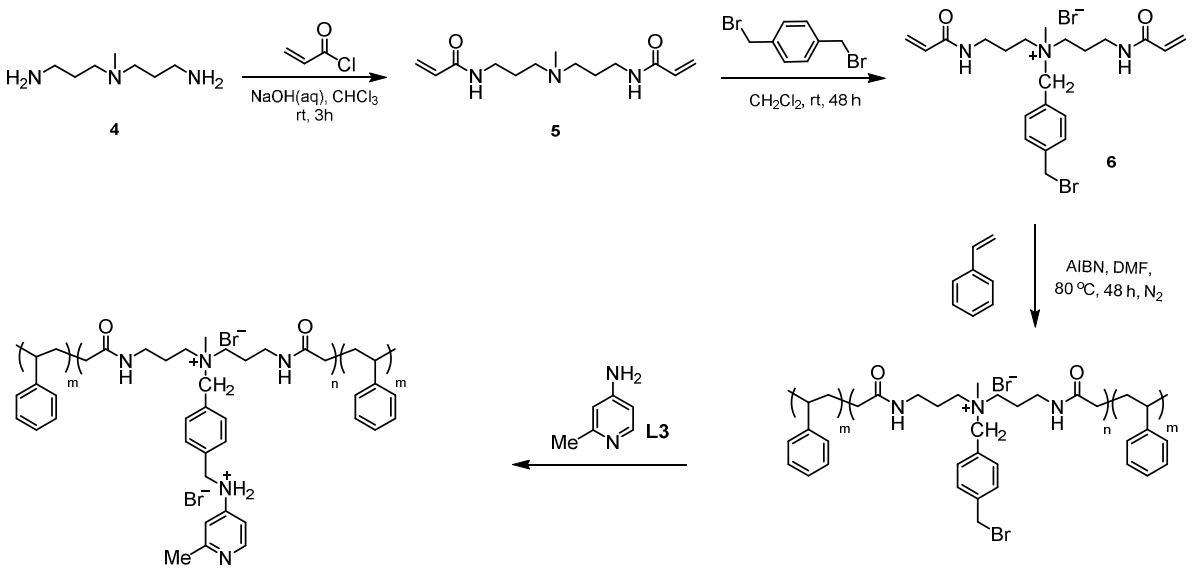
In general, 'inert' C(sp^3)–H bonds possess low reactivity and high thermodynamic stability compared to the C(sp^2)–H and C(sp)–H bonds.[16] This makes C(sp^3)–H activation a more challenging endeavor compared to conventional C–H functionalization routes. A number of catalytic systems have been recently developed for Pd-catalyzed C–H activation.[17-22] In particular, directed Pd-catalyzed C(sp^3)–H arylation reactions have been developed recently. In 2005, the Pd-catalyzed, 8-methylquinoline- and 2-ethylpyridine-directed C(sp^3)–H arylation with aryl iodides was reported by the Daugulis group.[23] A Pd-catalyzed β–C(sp^3)–H arylation of carboxylic acids with aryl iodides was also achieved by the Yu group subsequently.[24]

Most compounds contain multiple types of C–H bonds and other functional groups, and controlling site selectivity in C–H activation is necessary to help C–H functionalization methods become widely useful. To this end, the use of ligands to tune the reactivity and selectivity of transition metal catalysts for C(sp^3)–H bond activation has been a key recent focus. Recently, one of us reported the first example of ligand-controlled C(sp^3)–H arylation of an amino acid.[1] Alanine-derived amide **1** bearing a weakly coordinating aniline auxiliary[17,25-27] in conjunction with Pd and various pyridine and quinoline-based ligands were used. We found that pyridine-based ligands were capable of lowering the transition state energy of C(sp^3)–H activation, and promoted the selective monoarylation of a C(sp^3)–H bond with aryl iodides. Among the various pyridine-based ligands tested, 2-methylpyridine provided the optimal balance between yield and mono- versus di-arylation selectivity in these homogeneous reactions.

However, examples exploring the use of heterogeneous catalysts in C–H functionalization reactions are uncommon.[28] In the Son and Shin groups,[29] palladium nanoparticles supported on silica nanotubes have been used to catalyze C(sp^2)–H arylation. Selective heterogeneous C–H halogenation methods using palladium nanoparticles immobilized into porous metal organic frameworks (MOFs) have been reported.[30,31] Impregnated $Pd(OAc)_2$ on the MOF-5 (O_h) has been employed as a heterogenous Pd catalyst with ultrahigh surface area. This supported catalyst was applied in the C–H phenylation of naphthalene.[32] A Pd/C catalyzed arylation of triphenylene with aryiodonium salts has also been reported recently.[33]

Herein, we report a functionalizable and tunable polymer used for the immobilization of pyridine ligands that yields a soluble, polymeric ligand platform that facilitates C(sp^3)–H activation reactions. When substituted for the homogeneous pyridine ligands developed previously under Pd-catalyzed C(sp^3)–H activation conditions,[1] the resulting catalyst not only offers comparable catalytic activity to the unsupported catalyst system, but it allows for catalyst recovery, new catalytic selectivity not observed in the unsupported system, and some catalyst recyclability. To the best of our knowledge, this represents the first C(sp^3)–H activation of an amino acid derivative using a polymer-supported Pd catalyst.

This new polymer was constructed based on monomer **6**, which has two cross-linkable acrylamide and one benzyl bromide functional group (Scheme 1). A low molecular weight polymer backbone was formed by radical polymerization between styrene and monomer **6** (Scheme 1). Based on an investigation of the relative rates of disappearance of monomer **6** and styrene by in situ ^{1}H NMR



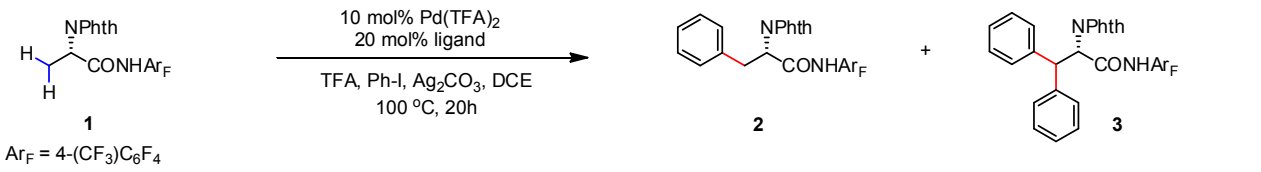
Scheme 1. General preparation of the polymer-supported pyridine derivative used as a ligand for Pd-catalyzed C(sp^3)–H arylation.

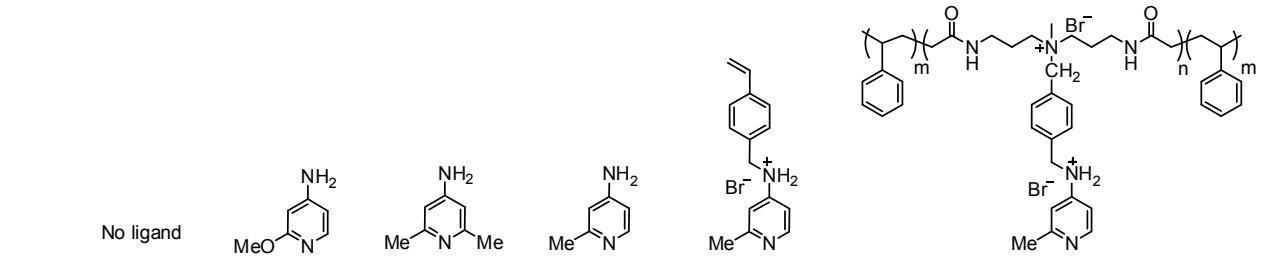
(Figure S3), it is apparent that the polymerization proceeded to form a mostly random copolymer. Figure S4 shows the integration ratios between styrene (H_e) and monomer **6** (H_b) during polymerization, and it was observed that the ratio increased modestly in the first four hours and then remained constant during the rest of the reaction. The amide functional groups within the polymer backbone, based on alanine-derived amide **1**, were specifically included to help concentrate the polar substrates within the polymeric domains, extracting these species from the relatively non-polar reaction solutions,[34] to help accelerate the catalytic reactions. Once the polymeric ligand backbone was prepared, a pyridine-based ligand was post-modified[35] onto the polymer by amination of the benzyl bromide functional group within the polymer using commercially available 4-amino-2-methylpyridine, **L3** (Scheme 1). The completion of the ligand-modification was monitored by ^{1}H NMR (Figure S6). As noted above, the coordination environment of the supported ligand within the polymer and metal was adjusted by tuning the ratios of the functionalized monomer and styrene during polymer preparation, altering the spacing between the ligands within the polymer. In this work, the polymer-support is abbreviated as "**PL**", and the ratio of styrene to monomer is added in parenthesis afterwards.

The Yu group previously developed reaction conditions for the target reaction between alanine-derived amide **1** and iodobenzene: 10 mol% $Pd(TFA)_2$, 20 mol% ligand, 20 mol% TFA, Ag_2CO_3 (1.5 equiv.), iodobenzene (1.5 equiv.) in 1,2-dichloroethane (DCE) at 100 °C to prepare compound **2** in good yield and selectivity.[1] Table 1 reports data under identical reaction conditions from tests of a library of homogeneous pyridine-based ligands that had similar chemical structures to the optimal ligands previously identified by the Yu group,[1] but were also immobilizable via reaction with a benzyl bromide group onto our polymeric support (Scheme 1). Ligands **L1** and **L2** were highly selective for monoarylation, but neither enhanced the conversion substantially relative to the ligand-free catalyst. Ligand **L3** enhanced the reactivity relative to the ligand-free conditions, while offering good selectivity to the monoarylation product. The N-alkylated ligand, **L4**, also showed similar reactivity, suggesting that incorporation of **L3** into a polymer backbone (Scheme S1) would not negatively affect catalytic reactivity from an electronic perspective. Interestingly, the molecular ligands **L3** and **L4**, which had similar chemical structures to the polymer-supported ligand **PL(4)**, showed slightly lower yields of monoarylated product than the polymer-supported ligand. **PL(4)** seemed to possess a useful balance of steric and electronic properties that provided compound **2** in high yield and with excellent selectivity for monoarylation.

We hypothesize that the polar amide functional groups in the polymer backbone helped to accelerate the reaction by concentrating the substrate in the polymer domains, partitioning from the relatively hydrophobic solution, while maintaining high selectivity for monoarylation. An array of polymer-supported ligands were thus prepared to have ratios of styrene to functionalized monomer ranging from 2 to 8 and subsequently the impact of the polymer composition on the performance in the target arylation reaction was evaluated. Figure 1 shows that the polymer supported ligand constructed with a styrene/monomer ratio of 4 ratio yielded the highest reactivity and product selectivity (**PL(4)**). Based on our observations, polymers with a lower ratio of styrene to functionalized monomer

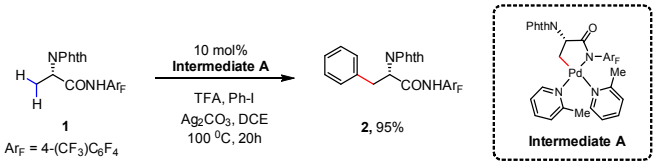
Table 1. Yields obtained during ligand screening in the Pd-catalyzed C(sp^3)–H monoarylation of alanine-derived amide **1** and iodobenzene.[a, b]





	No ligand	L1	L2	L3	L4	PL(4)
2:	46 %	21 %	44 %	61 %	61 %	70 %
3:	2 %	0 %	1 %	1 %	2 %	3 %

[a] Substrate (0.1 mmol), $Pd(TFA)_2$ (0.01 mmol), ligand (0.02 mmol), and Ag_2CO_3 (0.15 mmol) were weighed open to air and placed in a pressure tube (5 mL) with a magnetic stir bar. The iodobenzene (0.15 mmol), TFA (0.02 mmol), and DCE (0.5 mL) were added. The reaction vessel was sealed and the mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 20 hours with vigorous stirring. [b] The yield % and ratios of products **2** to **3** were determined by ^{1}H NMR.



Scheme 2. Catalytic reactivity of intermediates in the C(sp^3)–H arylation reaction.

showed poor solubility in dichloroethane, hampering their utility.

Previously, to gain insight into the coordination of the substrate and ligand at the Pd(II) center, the Yu group prepared and characterized a C–H insertion intermediate formed via primary C(sp^3)–H arylation in the absence of aryl iodides.[1] This intermediate was demonstrated to be a viable precatalyst for primary C(sp^3)–H arylation (Scheme 2). We hypothesized that some of the polymers prepared in this work might not easily facilitate the formation of this C–H insertion intermediate due to spatial constraints within the polymer. For example, the polymers that had a lower ligand density (Table S3, styrene/monomer = 8, **PL(8)**) might inhibit the proper coordination between two pyridine ligands and Pd during the reaction, giving lower product yields (Figure 1, styrene/monomer = 8, **PL(8)**). Interestingly, the polymers that had relatively high concentration of ligand (Table S3, styrene/monomer = 2 and 3, **PL(2), PL(3)**), did not as effectively facilitate the reaction either (Figure 1, styrene/monomer = 2 and 3, **PL(2), PL(3)**). These ligands may have dramatically lowered the energy of palladacycle intermediate via chelation effect, thus impeding the subsequent functionalization step of this C(sp^3)–H arylation reaction. We hypothesize that the best polymer provided an optimal balance of solubility and correct spatial coordination with the Pd species.

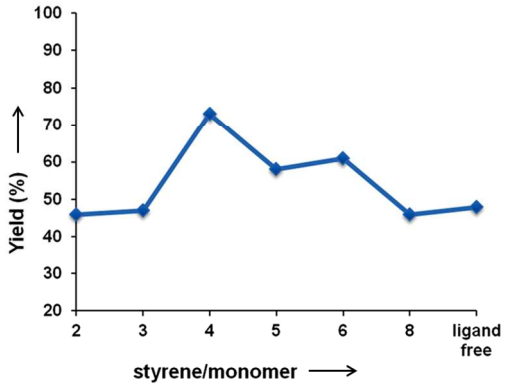


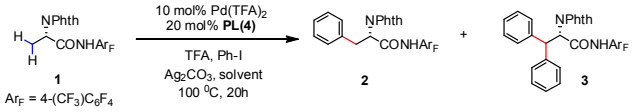
Figure 1. Yield of monoarylation product **2** from reactions using polymers with various ratios of styrene to functional

monomers in the Pd-catalyzed C(sp^3)–H monoarylation. The experimental conditions were the same as in Table 1.

During the reaction, we hypothesize that the polar amide substrate would be concentrated within the polymer due to the relatively polar amide-based backbone when the reactions were conducted in relatively non-polar solvents. In such a scenario, the substrate and Pd-ligand complexes would be in close proximity. This hypothesized preferential interaction of the amide substrate with the functionalized polymer backbone was supported by observed differences in reactivity using various organic solvents (Table 2). The reaction proceeded smoothly in nonpolar solvents (entries1 and 2, Table 2), whereas more polar solvents lowered the reaction yield progressively (entries 5 and 6, Table 2). To obtain the optimal balance of selectivity and yield, we used a cyclohexane/DMF mixed solution as the reaction solvent for further studies. In Figure 2, various volume ratios of cyclohexane and DMF were studied in the monoarylation reaction. When the cyclohexane/DMF volume ratio was 8, both outstanding selectivity (94 %) and yield of the monoarylation product (91 %) were obtained. In Yu's previous work, 2-methylpyridine was successfully used as the ligand in conjunction with Pd to synthesize phenylalanine derivatives (**2a**-**2f**) with electron-rich or electron-poor groups at the *ortho*-, *meta*-, or *para*-positions in high yields.[1]

This reaction was also demonstrated to be tolerant of halide substituents and a wide range of polar functional groups. Herein, we evaluated the catalytic activity of **PL(4)** with aryl iodides bearing both mono- and di-substituted electron-donating or electron withdrawing groups under our optimized reaction conditions. Overall, the electron withdrawing substituted aryl iodides were less

Table 2. Solvent effect in Pd-catalyzed C(sp^3)–H monoarylation of alanine-derived amide **1** and iodobenzene.[a, b]



Entry	Solvent	Yield (%)[b]	**2:3**[b]
1	Cyclohexane	77	68:9
2	DCE	73	70:3
3	Toluene	57	56:1
4	1,4-Dioxane	55	54:1
5	DMF	40	40:0
6	CH_3CN	7	7:0

[a] Substrate (0.1 mmol), Pd(TFA)$_2$ (0.01 mmol), **PL(4)** (0.02 mmol), and Ag_2CO_3 (0.15 mmol) were weighed out open to air and placed in a pressure tube (5 mL) with a magnetic stir bar. The iodobenzene (0.15 mmol), TFA (0.02 mmol), and solvent (0.5 mL) were added. The reaction vessel was sealed and the mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 20 hours with vigorous stirring. [b] The yield % and ratios of products **2** to **3** were determined by ^{1}H NMR.

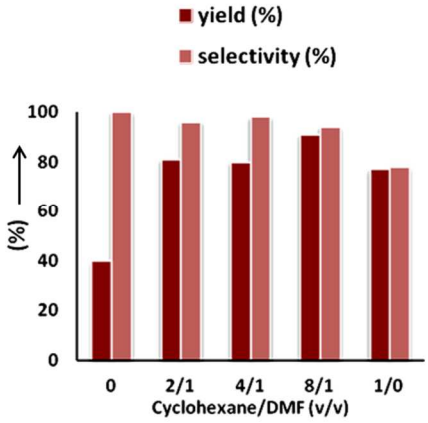
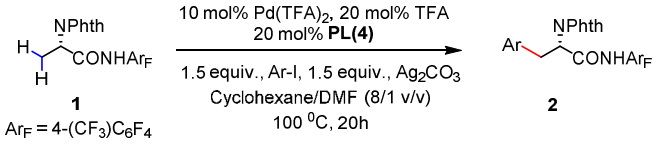


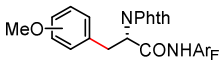
Figure 2. Pd-catalyzed C(sp^3)–H monoarylation selectivity and yield in cyclohexane/DMF mixed solutions. The experimental conditions are the same as in Table 2.

reactive compared to the electron-donating substituted aryl iodides. Interestingly, the polymer-supported ligand showed steric selectivity of aryl iodide partners in monoarylation reactions, which has not been observed in the previous homogeneous Pd-ligand catalyzed reaction.[1] With the supported catalyst, the yields were decreased significantly when the substituents on the aromatic ring were close to the active site (**2a**, **2b**, and **2e**, Table 3). Apparently, Pd ligated to the immobilized ligand was impacted by steric constraints associated with the polymer support. For example, when methoxy substituted iodobenzenes were used as the coupling partners in this C(sp^3)–H monoarylation, *ortho*-methoxyiodobenzene showed significantly lower conversion than *para*-methoxyiodobenzene (**2a$_1$** and **2a$_3$**, Table 3). This phenomenon was also observed in ester and fluoro-substituted iodobenzenes as well (**2b$_1$** and **2b$_3$**; **2e$_1$** and **2e$_3$**, Table 3), where iodobenzenes bearing substituents at the *meta*-position– showed more moderate conversions (**2a$_2$**, **2b$_2$** and **2e$_2$**, Table 3). This unique property could be potentially exploited in protocols aimed at selective C(sp^3)–H monoarylation with aryl iodides that contain multiple iodides.

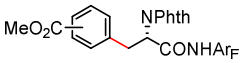
The supported ligand, when combined with Pd, yielded a highly effective catalyst, providing altered selectivities and improved yield of the monoarylated product compared to the homogeneous catalyst under identical reaction conditions, which is by itself a useful advance. Supported catalysts offer the potential to also recover and recycle the valuable and expensive Pd. To investigate the potential recyclability of the polymer-supported ligand in Pd-catalyzed C(sp^3)–H monoarylation reactions, we used **PL(4)** and iodobenzene as the model ligand and substrate with DCE as the reaction solvent for ligand recovery and recycle studies (Table 4). As expected, as a control, it was noted that the C(sp^3)–H monoarylation reaction failed in

Table 3. Substrate effects in the Pd-catalyzed C(sp^3)–H monoarylation using **PL(4)**

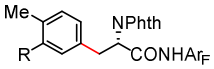




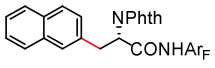
2a₁ *o*-OMe, 48%
2a₂ *m*-OMe, 77%
2a₃ *p*-OMe, 89%



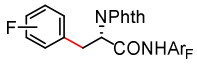
2b₁ *o*-CO_2Me, 25%
2b₂ *m*-CO_2Me, 85%
2b₃ *p*-CO_2Me, 88%



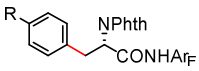
2c₁ R = H, 84%
2c₂ R = Me, 77%



2d, 70%

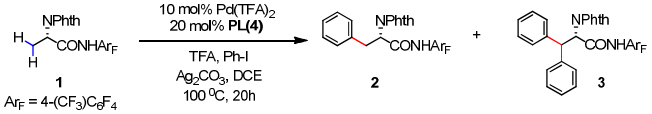


2e₁ *o*-F, 26%
2e₂ *m*-F, 52%
2e₃ *p*-F, 80%



2f₁ R = Cl, 81%
2f₂ R = Br, 59%
2f₃ R = CF_3, 68%
2f₄ R = NO_2, 50%
2f₅ R = CN, 50%

Table 4. Recycling **PL(4)** in Pd-catalyzed C(sp^3)–H monoarylation [a, b, c]



Run	Ligand	$Pd(TFA)_2$	Yield(%)[b]	**2** : **3**[b]
1	**PL(4)**	0	N.R.[c]	N.D.[c]
1*		10 mol%	73	70:3
2	Recycled **PL(4)**	0	72	70:2
2*	from run 1*	10 mol%	73	71:2
3	Recycled **PL(4)**	0	<5	N.D.[c]
3*	from run 2	10 mol%	40	40:0

[a] Substrate (1.0 equiv.), $Pd(TFA)_2$ (0.1 equiv.), **PL(4)** (0.2 equiv.), and Ag_2CO_3 (1.5 equiv.) were weighed out open to air and placed in a pressure tube (5 mL) with a magnetic stir bar. The iodobenzene (1.5 equiv.), TFA (0.2 equiv.), and DCE were added. The reaction vessel was sealed and the mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 20 hours with vigorous stirring. [b] The yield % and ratios of products **2** to **3** were determined by ^{1}H NMR [c] N.R. means no reaction; N.D. means not determined

the absence of Pd[1] (Run 1, Table 4). Subsequently, the reaction was run under standard conditions, using the polymeric ligand **PL(4)** in conjunction with Pd. Interestingly, the used **PL(4)** that was collected after the first run reaction gave an identical yield of the coupled product as the fresh **PL(4)** in the absence of additional Pd in a recycle test (Run 1* and 2, Table 4). Based on the elemental analysis and ^{1}H NMR of the reused material, we verifed that we successfully recycled **PL(4)** and Pd with high conversion (Table 4, Figure S7) after recovery from the first reaction. This is thus an uncommon example of ligand and metal recycling in a C(sp^3)–H functionalization reaction. Although the recovered **PL(4)** catalyst was not robust after multiple runs (Run 3 and 3*, Table 4), the recovery of the ligands and Pd metal is attractive and the potential of developing more robust recyclable systems is being explored.

In conclusion, a functionalizable and tunable polymer was synthesized and used in immobilization of pyridine ligands for use in an important Pd-catalyzed C(sp^3)–H monoarylation reaction. Such C(sp^3)–H activation reactions have the potential to become useful tools to construct and functionalize complex organic molecules. Notably, this is the first example of polymer-supported catalyst that selectively promotes C(sp^3)–H monoarylation. The immobilized ligand showed selectivity towards less hindered aryl iodides, and was reusable with an identical catalytic yield in a second cycle.

ASSOCIATED CONTENT

Supporting Information. Supporting Information Available: [Experimental procedures, ^{1}H, ^{13}C NMR spectra and other characterization data for the materials, reaction yields under additional reaction conditions.] This material is available free of charge via the Internet at http://pubs.acs.org.

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