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Chelation-directed C–H activation/C–C bond forming reactions catalyzed by Pd(II) nanoparticles supported on multiwalled carbon nanotubes†

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Chelation-directed C–H activation/C–C bond forming reactions utilizing homogeneous palladium(II) and the Pd(II)/Pd(IV) catalytic cycle have been previously reported. Here we report the first use of a solid-supported Pd(II) catalyst [Pd(II) nanoparticles on multiwalled carbon nanotubes, Pd(II)/MWCNT] to carry out C–H activation/C–C bond forming reactions. The results presented demonstrate that the solid-supported Pd(II)/MWCNT catalyst can effectively catalyze these arylation reactions using the Pd(II)/Pd(IV) catalytic cycle. We also show that the solid-supported catalyst is recyclable, has turnover frequencies up to 2.9-fold higher than the homogeneous catalyst, and results in low levels of residual palladium contamination in the products.

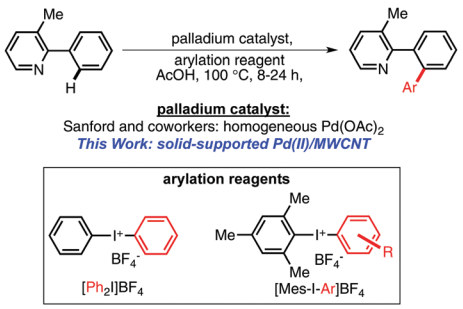

Fig. 1 Chelation-directed C–H activation/C–C bond forming reactions catalyzed by Pd(II).

Development of methodologies for the formation of carbon–carbon bonds has been an active area of investigation in organic chemistry for decades. Many of the latest innovations in carbon–carbon bond forming reactions currently come from the C–H activation field, which seeks to selectively and directly functionalize unreactive C–H bonds. C–H activation/C–C bond forming reactions are highly sought for their atom economy, synthetic utility, and cost savings because they reduce the need for multi-step pre-functionalization of substrates.[1]

One methodology for selective C–H activation/C–C bond forming reactions is the use of palladium(II) catalysts in combination with intramolecular directing groups such as basic, heteroaromatic nitrogens or sp^2 hybridized oxygens in amides. Examples of selective, oxidative chelation-directed C–H activation/C–C bond forming reactions catalyzed by $Pd(OAc)_2$ have been reported by Sanford[2] (Fig. 1) and others.[3] In contrast to the traditional cross-coupling reactions that utilize Pd(0)/Pd(II) cycle, these C–H activation reactions utilize Pd(II)/Pd(IV) catalytic cycle (Scheme 1).[2b]

While there are examples of chelation-directed C–H activation/C–C bond forming reactions using homogeneous Pd(II) sources, to our knowledge, there are no examples of this reaction that utilize a solid-supported Pd(II) catalyst. To date, there are only a few examples of the use of solid-supported catalysts in direct arylation or C–H activation/C–C bond forming reactions of any type.[4] Solid-supported catalysts have several advantages including: (1) ease of catalyst recovery, (2) reducing or eliminating palladium contamination in the products following the reaction, and (3) the ability to recycle the catalyst and reuse it multiple times.[5]

We have previously reported the use of a solid-supported Pd(II)/MWCNT catalyst in *N*-chelation directed C–H activation reactions, including alkoxylation (C–OAc, C–OMe) and halogenation (C–Cl, C–Br) reactions.[6] Our previous findings demonstrated that these reactions occur with higher rates compared to the homogenous Pd(II) catalyst and that our Pd(II)/MWCNT catalyst also had the advantages of recyclability and negligible Pd contamination in the products.[6]

Encouraged by our previous results, the goal of this current work is to test the hypothesis that the solid-supported Pd(II)/MWCNT nanoparticle catalyst can be used to catalyze chelation-directed

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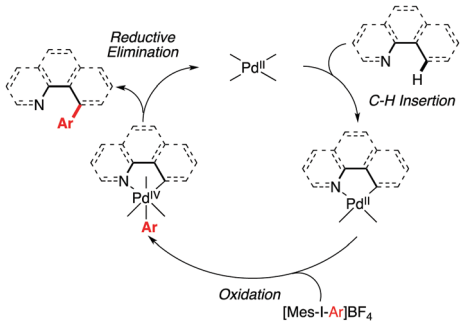
† Electronic supplementary information (ESI) available: Experimental details and spectal data. See DOI: 10.1039/c7cc02122d

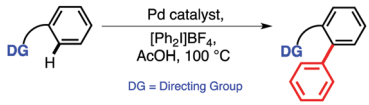


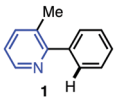
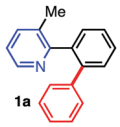
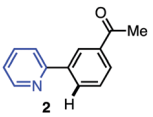
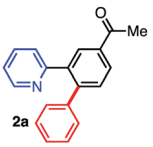
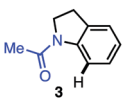
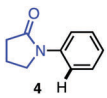
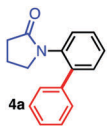
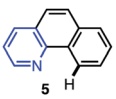
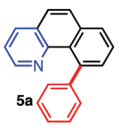
Scheme 1 Pd(II)/Pd(IV) catalytic cycle for chelation-directed C–H activation/C–C bond forming reactions.

C–H activation/C–C bond forming reactions that undergo the Pd(II)/Pd(IV) catalytic cycle. Here we report our initial study on these C–H arylation reactions directed by chelating groups.

To begin our work, we explored the reaction of known substrates for chelation-directed C–H activation/C–C bond forming reactions with the symmetrical $[Ph_2I]BF_4$ arylation reagent under previously reported conditions. As the catalyst, we used solid-supported Pd(II)/MWCNT nanoparticles that we have previously reported.[6] The results for these reactions are shown in Table 1, along with the results using homogenous Pd(II) catalyst ($Pd(OAc)_2$).[2a] Treatment of 2-phenyl-3-methylpyridine (**1**) with Pd(II)/MWCNT (5 mol%) and $[Ph_2I]BF_4$ (1.2 eq.) in acetic acid at 100 °C for 3 hours (Table 1, entry 1) afforded the desired 2-([1,1′-biphenyl]-2-yl)-3-methylpyridine (**1a**) in 90% yield, comparable to the yield of 88% with the homogeneous catalyst. Treatment of 1-(3-(pyridin-2-yl)phenyl)ethanone (**2**) with Pd(II)/MWCNT and $[Ph_2I]BF_4$ at 100 °C for 24 hours (Table 1, entry 2) afforded the desired 1-(2-(pyridin-2-yl)-[1,1′-biphenyl]-4-yl)ethanone (**2a**) in 80% yield, again comparable to the yield of 80% with the homogeneous catalyst. Notably, only the single isomeric product **2a** was formed in this reaction, suggesting that the regioselectivity of the C–H activation step is dictated by steric factors rather than by dual chelation effects of the pyridinyl nitrogen and the ketone to the Pd(II) metal center. Treatment of 1-acetyl-indoline (**3**) with Pd(II)/MWCNT and $[Ph_2I]BF_4$ at 100 °C for 12 hours (Table 1, entry 3) afforded the desired 1-acetyl-7-phenyl-indoline (**3a**) in only 27% yield, far lower than the previously reported yield of 49% with the homogeneous catalyst. Similarly, treatment of 1-phenylpyrrolidin-2-one (**4**) with Pd(II)/MWCNT and $[Ph_2I]BF_4$ at 100 °C for 24 hours (Table 1, entry 4) afforded the desired 1-([1,1′-biphenyl]-2-yl)pyrrolidin-2-one (**4a**) in only 32% yield, lower than the previously reported yield of 75% with the homogeneous catalyst. Together, entries 3 and 4 demonstrate that while the Pd(II)/MWCNT catalyst can produce product in these reactions, substrates with amide-type chelation groups are not as effective substrates with the solid-supported catalyst as they are with homogeneous Pd(II). This could be because the lone pair of electrons on the amide oxygen are less basic, making Pd(II) chelation the rate limiting step. We concluded our exploration of scaffolds with the treatment of benzo[*h*]quinoline (**5**) with Pd(II)/MWCNT and $[Ph_2I]BF_4$ at 100 °C for 12 hours (Table 1, entry 5), which to our surprise afforded the desired 10-phenylbenzo[*h*]quinoline (**5a**) in 19% yield. Benzo[*h*]quinoline (**5**) is sterically quite large as a substrate for this arylation reaction and chelation-directed C–H activation/C–C bond forming reactions with $[Ph_2I]BF_4$ have not been previously reported on this compound. We therefore expected not to form any of the product **5a** in this reaction.

Table 1 Exploration of substrates

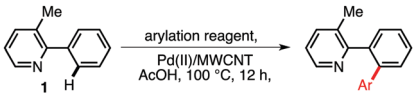


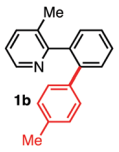
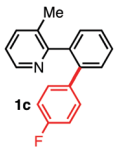
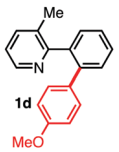
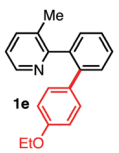
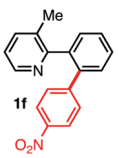
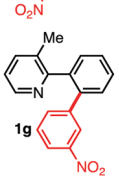
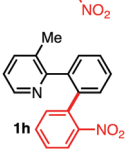
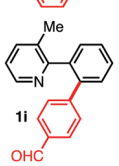
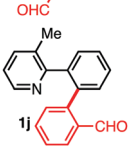
Entry	Substrate	Product	Pd(II)/MWCNT	$Pd(OAc)_2$
1			90%, 3 h	88%, 3 h
2			80%, 24 h	80%, 24 h
3			27%, 12 h	49%, 12 h[a]
4			32%, 24 h	75%, 24 h[a]
5			19%, 12 h	—[b]

[a] Previously reported results with homogeneous $Pd(OAc)_2$; see ref. 2*a*. [b] Yield with homogeneous Pd catalyst has not been reported.

We next wished to explore the scope of aryl rings that could be transferred in the C–H activation/C–C bond forming reaction using the solid-supported Pd(II)/MWCNT catalyst. In order to selectively transfer a specific aryl ring, we used unsymmetrical arylating reagents [Mes-I-Ar], consisting of a mesitylene group (which cannot be transferred due to its large steric bulk) and a substituted aryl group (which is transferred selectively to the substrate). For this scope study, we utilized 2-phenyl-3-methylpyridine (**1**) as the substrate. Aryl rings with both electronically neutral (4-Me, **1b**) and electronically withdrawing groups (4-F, **1c**; 4-NO_2, **1f**; and 4-CHO, **1i**) in the *para* position were effectively transferred in the reaction (Table 2, entries 1, 2, and 5) with yields of 87% (**1b**), 79% (**1c**), 61% (**1f**), and 77% (**1i**), respectively. However, the electronically rich 4-methoxy-phenyl group (Table 2, entry 3) did not react very well, affording a yield of only 33% of **1d**. This is in contrast to the reported yield of 81% for **1d** using a homogenous Pd(II) catalyst.[2a] Increasing the reaction time did not improve the yield. This effect was not seen with the 4-ethoxy-phenyl group (Table 2, entry 4), which afforded a yield of 79% of **1e**. We also explored the steric

Table 2 Scope of arylation reagents with 2-phenyl-3-methylpyridine

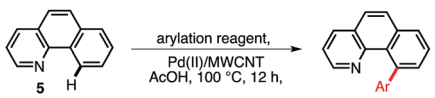


Entry	Arylation reagent	Product	Yield (%)
1	[Mes-I-*p*-Me-Ph]BF_4		87
2	[Mes-I-*p*-F-Ph]BF_4		79
3	[Mes-I-*p*-OMe-Ph]BF_4		33
4	[Mes-I-*p*-OEt-Ph]BF_4		79
5	[Mes-I-*p*-NO_2-Ph]BF_4		61
6	[Mes-I-*m*-NO_2-Ph]BF_4		69
7	[Mes-I-*o*-NO_2-Ph]BF_4		58
8	[Mes-I-*p*-CHO-Ph]BF_4		77
9	[Mes-I-*o*-CHO-Ph]BF_4		18

tolerance of the reaction for transfer of aryl groups with substitutions at the *para*, *meta*, or *ortho* positions. With the strongly electron withdrawing nitro-phenyl group, *para*- (**1f**), *meta*- (**1g**), and *ortho*-substituted (**1h**) phenyl rings were all effectively transferred (Table 2, entries 5–7), with even the sterically hindered *ortho*-NO_2-phenyl group affording a 58% yield. However, the weakly electron withdrawing *ortho*–CHO-phenyl group was not effectively transferred and gave a poor yield of 18%, compared to the 77% yield with the *para*-CHO-phenyl group (Table 2, entry 8 *vs.* 9). The difference in the reactivities of *ortho*-nitro (Table 2, entry 7) and *ortho*-CHO (Table 2, entry 9) could be explained by the difference in electronic nature of the substituents. The strong electron withdrawing effect of the nitro group makes the [Mes-I-*o*-NO_2-Ph] reagent highly reactive towards oxidative addition to the Pd(II)-substrate complex to afford the Pd(IV) reaction intermediate (Scheme 1). Though it is in the *ortho* position and will cause some steric hindrance, the strong electronics might be dictating the overall course of the reaction, which explains the higher yield. The *ortho*-CHO, being sterically bulky and only weakly electron withdrawing, is less reactive for the oxidative addition and therefore affords a lower yield.

We also investigated whether the rigid and bulky benzo[*h*]-quinoline substrate **5** could undergo C–H activation/C–C bond forming reactions using the solid-supported Pd(II)/MWCNT catalyst and unsymmetrical [Mes-I-Ar] arylating reagents. Though the yield of the 10-phenylbenzo[*h*]quinoline (**5a**) is low (19%; Table 3, entry 1), this is an attractive transformation due to its simplicity and use of lower cost palladium catalyst. Synthesis of products such as **5a–c** (Table 3) have been reported, but typically requires more expensive catalysts such as rhodium, ruthenium, or iridium.[7] Treatment of benzo[*h*]quinoline (**5**) with Pd(II)/MWCNT and [Mes-I-*p*-Me-Ph]BF_4 at 100 °C for 12 hours resulted in arylation with the electronically neutral *p*-Me-Ph group to afford the desired 10-(*p*-tolyl)benzo[*h*]quinoline (**5b**) in 15% yield (Table 3, entry 2), similar to the results using the symmetrical [Ph_2I]BF_4 arylation reagent to afford 10-phenyl-benzo[*h*]quinoline (**5a**) (Table 3, entry 1). Similar treatment with [Mes-I-*p*-F-Ph]BF_4 resulted in arylation with the electronically withdrawing *p*-F-Ph group to afford the desired 10-(4-florophenyl)-benzo[*h*]quinoline (**5c**) in 35% yield (Table 3, entry 3). The increase in yield for this reaction could be due to the electron withdrawing nature of 4-F-phenyl group, making the [Mes-I-*p*-F-Ph]

Table 3 Scope of arylation reagents with benzo[*h*]quinoline



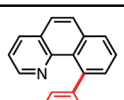
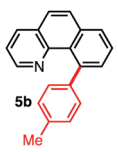
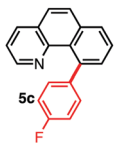
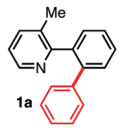
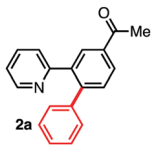
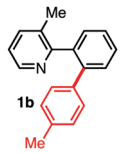
Entry	Arylating agent	Product	Yield (%)
1	[Ph_2I]BF_4		19
2	[Mes-I-*p*-Me-Ph]BF_4		15
3	[Mes-I-*p*-F-Ph]BF_4		35

Table 4 Turnover frequencies for C–H activation/C–C bond forming reactions

Entry	Product	Turnover frequency (h^{-1}) Pd(II)/MWCNT	Pd(OAc)$_2$	Fold increase
1	 1a	16.48	5.74	2.9
2	 2a	1.62	0.64	2.5
3	 1b	3.63	1.41	2.6

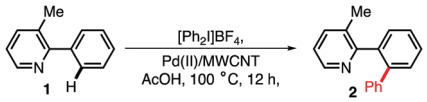
reagent more reactive towards oxidative addition to the Pd(II)-substrate complex to afford the Pd(IV) reaction intermediate (Scheme 1). Attempts to carry out the C–H activation/C–C bond forming reaction on benzo[*h*]quinoline with electronically donating [Mes-I-Ar] arylating reagents failed to demonstrate any conversion to the desired products.

We observed in our previous work that C–H activation reactions catalyzed by the solid-supported Pd(II)/MWCNT catalyst have faster reaction kinetics and higher turnover frequencies (TOFs) compared to the homogeneous catalyst. To quantify this observation for the C–H activation/C–C bond forming reactions, we calculated turnover frequencies for several substrates (Table 4) with both the solid-supported Pd(II)/MWCNT and homogeneous palladium catalysts. Turnover frequencies were calculated as the moles of product per moles of Pd(II) per hour. For these C–H activation/C–C bond forming reactions, turnover frequencies with the solid-supported catalyst were 2.5- to 2.9-fold higher than for the homogeneous catalyst. This increase in the turnover frequencies, while modest, is an advantage of using the Pd(II)/MWCNT catalyst for these types of C–H activation or direct arylation type reactions.

To demonstrate the ability of the Pd(II)/MWCNT catalyst to be recycled, we ran the C–H activation/C–C bond forming reaction on 2-phenyl-3-methylpyridine (**1**), recovered the catalyst by centrifugation, and iteratively repeated the reaction with the same batch of catalyst. We were able to recycle the catalyst 3 times with minimal reduction in yield and no catalyst deactivation (Table 5, details in the ESI†). In the fourth recycle reaction, the percent conversion dropped below 10% demonstrating that the catalyst was deactivated.

To determine whether the palladium metal from the solid supported Pd(II)/MWCNT catalyst leached into the C–H activation/C–C bond forming reactions and contaminated the products, we removed the catalyst by filtration over Celite from the arylation reaction of 2-phenyl-3-methylpyridine (**1**) and measured the palladium content in solution by ICP-MS. The palladium content of the reaction mixture was found to be 38.4 ppm, demonstrating that very little (5.6%) of the Pd metal on the solid supported surface leached into the

Table 5 Recycling of the Pd(II)/MWCNT catalyst



Run	% Conversion[a]
Initial reaction	100
Recycle 1	100
Recycle 2	100
Recycle 3	94
Recycle 4	7

[a] % Conversion measured by GC-MS.

reaction medium. Combined with the ease of removing the catalyst from the reaction mixtures, this low level of palladium in the reaction mixture is an improvement on the existing homogeneous catalyst for this type of C–H activation reactions.

To demonstrate that the trace palladium in the reaction mixture is not the source of catalytic activity, a hot filtration experiment was performed with 2-phenyl-3-methylpyridine (**1**). After 12 h at 100 °C, the Pd(II)/MWCNT catalyst was removed by hot filtration over Celite. Fresh substrate and oxidant were added to the filtrate, which was reheated to 100 °C. No further conversion to product or catalytic activity was observed in the filtrate in the absence of Pd(II)/MWCNT, showing that the $<$40 ppm of residual Pd that remains in solution is not adequate to catalyze the C–H activation/C–C bond forming reaction.

In conclusion, we have demonstrated that solid-supported Pd(II)/MWCNT can catalyze C–H activation/C–C bond forming reactions of heteroatom-chelating substrate with both symmetrical ([Ph_2I]BF_4) and unsymmetrical ([Mes-I-Ar]) arylating reagents. The catalyst can be recovered and recycled up to three times in these reactions and turnover frequencies are up to 2.9-fold higher with the solid-supported catalyst. The solid-supported Pd(II)/MWCNT also offers the advantages of ease of removal by filtration and low levels of residual palladium metal contamination ($<$40 ppm) in the products.

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Notes and references

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