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Selective *N*-Chelation-Directed C−H Activation Reactions Catalyzed by Pd(II) Nanoparticles Supported on Multiwalled Carbon Nanotubes

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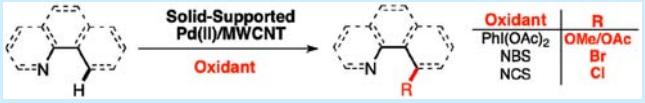
S *Supporting Information*

ABSTRACT: *N*-Chelation-directed C−H activation reactions that utilize the Pd(II)/Pd(IV) catalytic cycle have been previously reported. To date, these reactions employ only homogeneous palladium catalysts. The first use of a solid-supported Pd(II) catalyst [Pd(II) nanoparticles on multiwalled carbon nanotubes, Pd(II)/MWCNT] to carry out *N*-chelation-directed C−H to C−O, C−Cl, and C−Br transformations is reported. The results presented demonstrate that the solid-supported Pd(II)/MWCNT catalyst can effectively catalyze C−H activation reactions using the Pd(II)/Pd(IV) catalytic cycle.



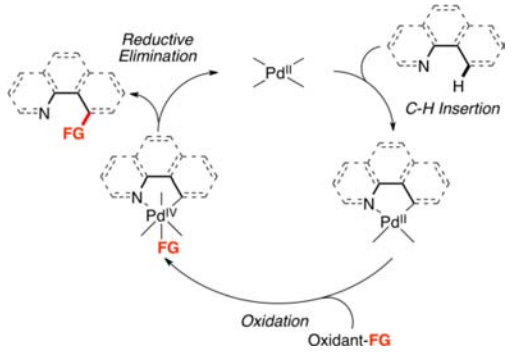
C−H activation chemistry has emerged as a new and important area of organic chemistry methodology development. The selective, direct functionalization of a specific C−H bond is the most atom-economical route to build complexity into small molecules. One method to achieve selectivity in C−H activation chemistry is to use palladium catalysis combined with an intramolecular directing group, such as a pyridinyl or other basic nitrogen functional group. Examples of selective C−H to C−O,[1] C−Halogen,[1a,2] C−C,[3] C−N,[4] C−F,[5] and C−CF_3[6] transformations using *N*-chelation-directed palladium catalysis have been reported in the literature. Unlike traditional cross-coupling chemistry, these C−H activation reactions utilize a novel Pd(II)/Pd(IV) catalytic cycle (Scheme 1).[7]

While there are extensive examples of *N*-chelation-directed C−H activation reactions using homogeneous Pd(II) sources, to our knowledge, there are no examples of this reaction that utilize a solid-supported Pd(II) catalyst. 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.[8]

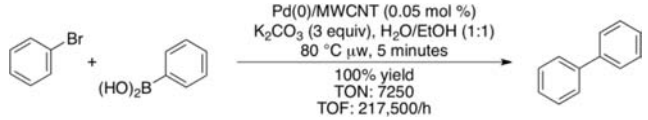
It has been previously reported that solid-supported Pd(0) on carbon nanotubes can be used as a highly efficient catalyst in the Suzuki cross-coupling reaction (Scheme 2).[9] Coupling reactions using these solid-supported nanoparticle catalysts display remarkable catalytic activity with a high turnover number (TON) and turnover frequency (TOF). The reactions generally are complete within 10 min, can be run at lower temperature (~80 °C) using either conventional or microwave heating, and can be run in either batch or flow format. In this previous work, we were able to control the Pd(0)/Pd(II) ratio based on the method of preparation and the type of carbon nanotube used as the solid support.[9]

Here we wished to test the hypothesis that a solid-supported nanoparticle catalyst containing predominantly Pd(II) can be

Scheme 1. Pd(II)/Pd(IV) Catalytic Cycle for *N*-Chelation-Directed C−H Activation Reactions



Scheme 2. Suzuki Reaction Catalyzed by Solid-Supported Pd(II) on Multiwalled Carbon Nanotubes (Pd(II)/MWCNT)



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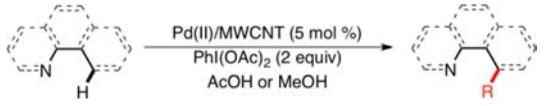
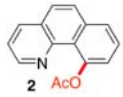
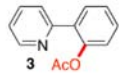
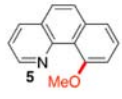
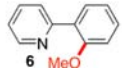
used to catalyze oxidative *N*-chelation-directed C−H activation reactions that undergo the Pd(II)/Pd(IV) catalytic cycle. As the catalyst, we have prepared nanoparticles containing predominantly Pd(II) supported on multiwalled carbon nanotubes (Pd(II)/MWCNT) by a modification of our previous procedure (see Supporting Information). We have evaluated the ability of this catalyst to carry out oxidative C−H to C−OMe/OAc, C−Cl, and C−Br functionalizations.

We initially chose substrates that have been previously reported to undergo the C−H functionalization reactions, so that we could compare the results of our solid-supported Pd(II)/MWCNT catalyst to that of the known homogeneous Pd(II) system ($Pd(OAc)_2$). We first explored the C−H to C−O transformation, which utilizes $PhI(OAc)_2$ as the oxidant (Table 1). Treatment of 8-methylquinoline with Pd(II)/MWCNT and $PhI(OAc)_2$ in acetic acid at 120 °C for 10 min (Table 1, entry 1) afforded the desired 8-(acetoxymethyl)-quinoline (**1**) in 90% yield, comparable to the previously reported yield of 88% with the homogeneous catalyst.[1a] However, treatment of benzo[*h*]quinoline (entry 2) and 2-phenylpyridine (entry 3) failed to give any of the desired acylation products **2** and **3**, respectively, even at extended reaction times and higher temperatures. Only starting material was recovered in these reactions.

Table 1. C−H to C−O Functionalizations Catalyzed by Pd(II)/MWCNT



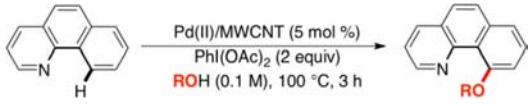
entry[a]	product	solid-supported Pd(II)/MWCNT temp	time	yield	yield and time with $Pd(OAc)_2$[b]
1		120 °C	0.2 h	90%	88%, 22 h
2		120 °C	1 h	0%	86%, 12 h
3		120 °C	1 h	0%	52%, 12 h
4		100 °C	0.2 h	99%	77%, 18 h
5		100 °C	0.2 h	90%	95%, 22 h
6		100 °C	5 h	25%	–[c]

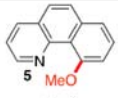
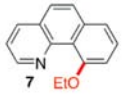
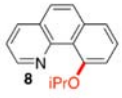
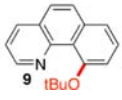
[a]Solvent for entries 1−3: AcOH; entries 4−6: MeOH. [b]Previously reported results with homogeneous $Pd(OAc)_2$; see ref 1a. [c]Yield with homogeneous Pd catalyst has not been reported.

Having confirmed that solid-supported Pd(II)/MWCNT can catalyze a reaction that undergoes the Pd(II)/Pd(IV) catalytic cycle and encouraged by the initial success of the acylation reaction with 8-methylquinoline, we elected to evaluate whether other oxygen containing functional groups could be installed using our catalyst. We repeated the reaction of 8-methylquinoline with Pd(II)/MWCNT and $PhI(OAc)_2$, except this time using methanol as a solvent (Table 1, entry 4). We obtained a near-quantitative yield (99%) of the desired 8-(methoxymethyl)quinoline (**4**) in 10 min at 100 °C, which is a significant improvement over the reported yield of 77% with the homogeneous catalyst system. Application of these conditions to benzo[*h*]quinoline (entry 5) afforded a 90% yield of **5**, again comparable to the reported yield with the homogeneous catalyst (95%). However, treatment of 2-phenylpyridine with Pd(II)/MWCNT/$PhI(OAc)_2$/MeOH (entry 3) did result in formation of the product **6** after an extended reaction time, albeit in much lower yield (25%).

We next sought to determine whether alcohols other than methanol could be installed in substrates using the solid-supported catalyst. Treatment of benzo[*h*]quinoline with Pd(II)/MWCNT and $PhI(OAc)_2$ in alcohol solvents (Table 2) demonstrated that methoxy (from methanol, entry 1, product **5**) and ethoxy (from ethanol, entry 2, product **7**) functional groups can be installed in moderate to high yields with our catalyst. However, as the size of the alcohol increased, incorporation of the functional group into the product decreased (with isopropyl, entry 3, product **8**) and eventually failed (in the *tert*-butyl case, entry 4, product **9**). Previously reported data for the homogeneous catalyst system show only a moderate decrease in yield as the size of the alcohol increases.[1a]

Table 2. C−H to C−O−Alkyl Functionalizations Catalyzed by Pd(II)/MWCNT



entry	ROH	product	yield Pd(II)/MWCNT	yield $Pd(OAc)_2$
1	MeOH		90%	95%
2	EtOH		73%	80%
3	*i*PrOH		33%	72%
4	*t*BuOH		0%	–[a]

[a]Yield with homogeneous Pd catalyst has not been reported.

Having demonstrated that solid-supported Pd(II)/MWCNT can catalyze the C−H to C−O functionalization reaction, we next turned our attention to halogenation reactions (Table 3). Treatment of benzo[*h*]quinoline with Pd(II)/MWCNT and *N*-chlorosuccinimide (NCS) in acetonitrile at 100 °C for 5 h (Table 3, entry 1) afforded the desired 10-chlorobenzo[*h*]-quinoline (**10**) in 92% yield, comparable to the previously reported yield of 95% with the homogeneous catalyst. It should be noted that the reaction with the Pd(II)/MWCNT is much faster than with homogeneous $Pd(OAc)_2$ (5 h vs 3 days).

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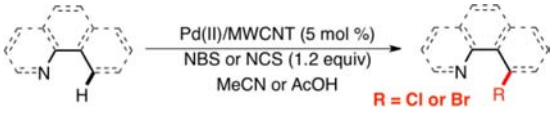
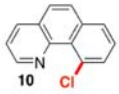
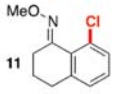
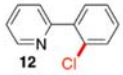
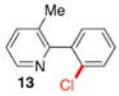
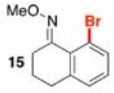
Table 3. C−H to C−Cl/C−Br Functionalizations Catalyzed by Pd(II)/MWCNT



entry[a,b]	product	solid-supported Pd(II)/MWCNT temp	time	yield	yield and time with $Pd(OAc)_2$
1		100 °C	5 h	92%	95%, 3 days
2		120 °C	1.5 h	61%	88%, 12 h
3		100 °C	6 h	55%[c]	–[e]
4		120 °C	0.2 h	50%[c]	65%, 12 h
5		100 °C	1.5 h	89%[d]	93%, 1.5 days
6		120 °C	5 h	30%	62%, 12 h
7		100 °C	6 h	40%[d]	63%, 12 h
8		120 °C	5 h	51%[c]	56%, 12 h

[a]Oxidants for entries 1−4: NCS; entries 5−8: NBS. [b]Solvents for entries 1, 3, 5, and 7: MeCN; entries 2, 4, 6, and 8: AcOH. [c]10 mol % Pd(II)/MWCNT was used. [d]1.5 equiv of NBS was used. [e]A directly analogous yield for the homogeneous catalyst has not been reported.

Chlorination of (*E*)-3,4-dihydronaphthalen-1-(2*H*)-one *O*-methyl oxime (entry 2), 2-phenylpyridine (entry 3), and 3-methyl-2-phenylpyridine (entry 4) in either acetic acid (entries 2 and 4) or acetonitrile (entry 3) all afforded the desired chlorinated products **11**−**13** in moderate yields in reaction times from 10 min to 6 h. While the yields for these transformations are lower than those for the comparable reaction with the homogeneous catalyst, the reaction times are much shorter, pointing to faster reaction kinetics (*vide infra*). The 2-phenylpyridine substrates (entries 3 and 4) required additional catalyst loading to reach this level of conversion and product isolation. For all of these substrates, further increasing the number of equivalents of NCS led to the formation of other products.

Turning to the C−H to C−Br functionalizations, treatment of benzo[*h*]quinoline with Pd(II)/MWCNT and *N*-bromosuccinimide (NBS) in acetonitrile at 100 °C for 1.5 h (Table 3, entry 5) afforded the desired 10-bromobenzo[*h*]quinoline (**14**) in 89% yield, comparable to the previously reported yield of 93% with the homogeneous catalyst. Again, it should be noted that the reaction with the Pd(II)/MWCNT is much faster than that with homogeneous $Pd(OAc)_2$ (1.5 h vs 1.5 days). Bromination of (*E*)-3,4-dihydronaphthalen-1-(2*H*)-one *O*-methyl oxime (entry 6), 2-phenylpyridine (entry 7), and 3-methyl-2-phenylpyridine (entry 8) in either acetic acid (entries 6 and 8) or acetonitrile (entry 7) all afforded the desired brominated products **15**−**17** in moderate yields in reaction times of 5−6 h. Again, the yields are lower than the comparable reaction with homogeneous catalyst but the reaction times are much shorter, pointing to faster reaction kinetics (*vide infra*). Both the benzo[*h*]quinoline and 2-phenylpyridine substrates (entries 5 and 7) required additional NBS (1.5 equiv vs 1.2 equiv) to reach this level of conversion and product isolation. Increasing the amount of NBS beyond 1.5 equiv led to the formation of other products. For the 3-methyl-2-phenylpyridine (entry 8), additional catalyst loading was required to reach this level of conversion and product isolation.

To characterize the solid-supported Pd(II)/MWCNT catalyst, we measured the composition of the palladium both before and after C−H activation reaction by XPS (see Figure S1 in Supporting Information). Prior to use in the C−H activation reactions, the solid-supported catalyst was found to be a mixture of Pd(II) (76.54%) and Pd(0) (23.46%), with Pd(II) being the predominant component. After the C−H to C−OMe functionalization of benzo[*h*]quinoline (Table 1, entry 5), XPS showed that the solid-supported catalyst contained only Pd(II), showing that all of the Pd(0) in the catalyst prior to the reaction is converted to Pd(II) and supporting the mechanism that these reactions use Pd(II) as the starting oxidation state.

For all of the C−H activation reactions, we observed that the reactions catalyzed by Pd(II)/MWCNT seemed to be faster than those with the homogeneous $Pd(OAc)_2$. To quantify this observation, we calculated turnover frequencies (TOFs) for one example reaction of each functionalization (see Table S1 in Supporting Information) with both the solid-supported Pd(II)/MWCNT and homogeneous palladium catalysts. For the C−H to C−OAc and C−OMe functionalization reactions, the turnover frequencies for the solid-supported Pd(II)/MWCNT catalyst were ∼27-fold higher than that for the homogeneous catalyst. For the C−H to C−Cl and C−Br reactions, the turnover frequencies for the solid-supported Pd(II)/MWCNT catalyst were ∼4-fold higher. This represents a significant improvement over previously reported results, particularly with regard to the C−H to C−OMe functionalization reactions.

To demonstrate the ability of the Pd(II)/MWCNT catalyst to be recycled, we ran the C−H to C−OMe functionalization on 8-methylquinoline (Table 1, entry 4), recovered the catalyst by centrifugation, and iteratively repeated the reaction with the same batch of catalyst. We were able to recycle the catalyst a remarkable 16 times with minimal reduction in yield and no catalyst deactivation (see Table S2 in Supporting Information). We terminated the experiment after 16 recycles and have yet to determine the limits of the recyclability of the catalyst. These data demonstrate that there must be good retention or highly efficient leaching/redeposition of Pd in these reactions. Otherwise, leaching would result in loss of catalytic activity after multiple recycles.

To determine whether the palladium metal from the solid-supported Pd(II)/MWCNT catalyst leached into the C−H activation reactions and contaminated the products, we removed the catalyst by filtration over Celite from a C−H to C−OMe functionalization reaction on benzo[*h*]quinoline (Table 1, entry 5) and measured the palladium content in

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solution by ICP-MS. The palladium content of the reaction mixture was found to be <250 ppb, demonstrating that very little metal leached into the 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 *N*-chelation-directed 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 benzo[*h*]quinoline (Table 1, entry 5). After 10 min 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 <250 ppb of residual Pd that remains in solution is not adequate to catalyze the C−H activation reaction.

In conclusion, we have demonstrated that solid-supported Pd(II)/MWCNT can catalyze *N*-chelation-directed C−H to C−OAc, C−OMe, C−Cl, and C−Br activation reactions. For all of the C−H activation reactions examined, the solid-supported catalyst demonstrated consistently higher turnover frequencies than the reported homogeneous 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 in the products. We are currently working to optimize the reactions reported here as well as apply this catalyst to other *N*-chelation-directed C−H activation reactions.

■ ASSOCIATED CONTENT

Supporting Information

Figure S1, Tables S1 and S2, experimental procedures, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
A patent application is being filed for this work.

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