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Pd-catalyzed aerobic oxidative coupling of anilides with olefins through regioselective C–H bond activation

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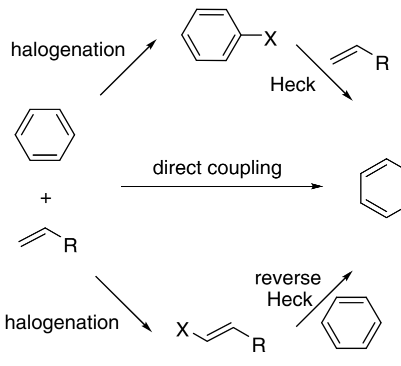
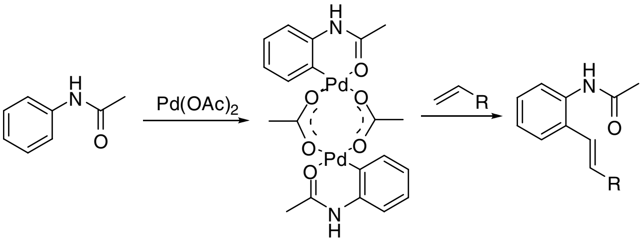
Abstract—Pd-catalyzed aerobic oxidative coupling of anilides with olefins was achieved through selective C–H bond activation. Compared to the previous studies, not only did we successfully use molecular oxygen to replace the chemical oxidant, but we also obtained improved yields for a number of substrates. The reaction tended to give high yields for electron-rich anilides and electron-deficient olefins, with a best yield up to 91%.

Pd-catalyzed selective activation of C–H bonds can lead to useful organic reactions to assemble value-added molecules through C–C bond formation.[1] This synthetic strategy is attractive for the chemical and pharmaceutical industries, not only because it may greatly simplify and shorten the synthetic sequence for various types of organic compounds, but also because it may allow the utilization of cheap and environmentally benign reactants (e.g., hydrocarbons instead of organic halides).[2] Currently, catalytic C–H bond activation has become an area of rapid growth where many interesting challenges still remain to be overcome.[3] One such example is the direct, oxidative coupling of olefins with aromatic hydrocarbons (Scheme 1). Compared to the standard Heck reaction[4] and the more recent 'reverse' Heck reaction,[5] direct olefin arylation reaction is obviously advantageous in terms of starting material price and byproduct (i.e., halogenated salt) disposal.



Scheme 1.

Evidently a certain oxidant is required to achieve the above direct coupling between an olefin and an arene. Pd(II) could be one of the choices. For instance, in early 1981 Horino and Inoue reported that the reaction of acetanilides with $Pd(OAc)_2$ gave an *ortho*-palladated complex, which could further react with an olefin to produce the corresponding 2-[(acetylamino)phenyl] olefin (Scheme 2).[6] An obvious disadvantage of this reaction was that a stoichiometric amount of expensive Pd was required to complete the transformation. To overcome this limitation, de Vries and van Leeuwen reported in 2002 the interesting finding that combination of a catalytic amount (2 mol %) of Pd and a stoichiometric amount of a chemical oxidant (i.e., benzoquinone) could also be used to achieve the same olefin arylation reaction as shown in Scheme 2.[7]



Scheme 2.

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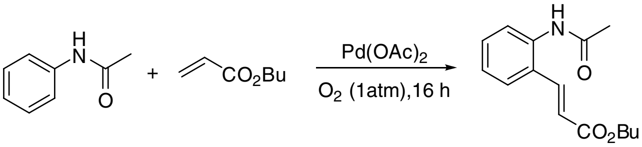
In the present study we report a further, significant improvement for the above C–H activation reaction, where the chemical oxidant has been successfully changed to molecular oxygen. We consider this improvement to be important not only from the viewpoint of economical efficiency (O_2 is available at virtually no cost), but also from the perspective of environmental friendliness (aerobic oxidation produces water instead of any other environmentally hazardous byproduct). As for the subject of oxidative olefin–arene coupling via C–H bond activation, Milstein and co-workers once reported the use of Ru catalysts and O_2 as oxidant.[8] However, fairly high temperatures (e.g., 180 °C) and high pressures (e.g., 2 atm O_2 and 6.1 atm CO) were required in this Ru system. Here, we accomplish a Pd-catalyzed, O_2-mediated regioselective olefin–anilide coupling catalytically under much milder conditions (namely, only at 60 °C and under 1 atm O_2).

We began the study by focusing on the reaction between acetanilide and *n*-butylacrylate under 1 atm of O_2. It was found that at room temperature the oxidative coupling did not take place with 2 mol % of $Pd(OAc)_2$ (Table 1, entry 1). However, when the temperature was raised to 80 °C we were pleased to find that the desired reaction occurred, albeit with a low yield (49%, entry 2). This observation demonstrated that the idea of using O_2 as the oxidant was valid for the direct arylation of olefin. The mechanism of this reaction was presumably composed of three steps: (1) insertion of Pd(II) to the C–H bond at the *ortho* position in the acetanilide to form an *ortho*-palladated complex; (2) cross-coupling between the *ortho*-palladated complex and *n*-butylacrylate to produce the desired product and Pd(0); and (3) re-oxidation of Pd(0) to Pd(II) to repeat the catalytic cycle. Because the first two steps were demonstrated to be fine in the original study by Horino and Inoue,[6] we hypothesized that the recycling of Pd(II) from the reduced Pd(0) should constitute the limiting factor for the catalytic turnovers.

Table 1. Pd-catalyzed aerobic oxidative coupling of acetanilide with *n*-butyl acrylate[a]



Entry	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (mol %)	TsOH (mmol)	*T* (°C)	Yield (%)
1	2	0	1.5	25	0
2	2	0	1.5	80	49
3[b]	2	0	1.5	80	44
4[c]	2	0	1.5	80	51
5	2	5	1.5	80	81
6	2	5	1.5	60	84
7	2	5	1.5	25	0
8	2	10	1.5	60	80
9	2	2	1.5	60	87
10	1	5	1.5	60	53
11	1	1	1.5	60	52
12	3	5	1.5	60	90
13	3	3	1.5	60	90
14	3	3	1.0	60	92
15	3	3	0.5	60	69
16[d]	3	3	1.0	60	76
17[e]	3	3	1.0	60	89

[a] Reaction conditions: acetanilide (3 mmol), *n*-butyl acrylate (3 mmol), HOAc (5 mL), toluene (2.5 mL) O_2 (1 atm), 16 h, GC yield.

[b] 20 mol % NEt_3 was added.

[c] 20 mol % of pyridine was added.

[d] Only 6 mL of HOAc as solvent.

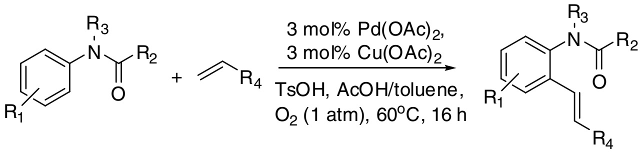
[e] HOAc (3 mL), toluene (3 mL).

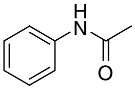
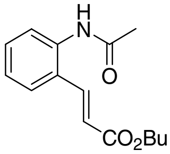
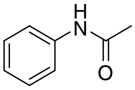
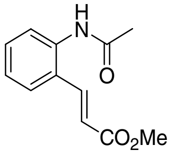
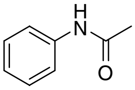
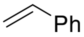
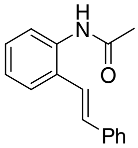
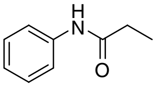
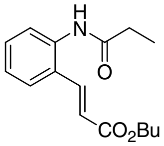
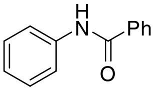
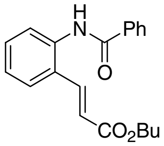
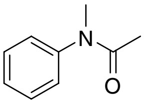
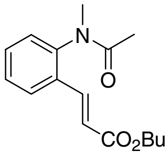
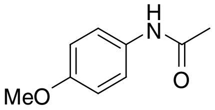
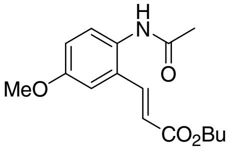
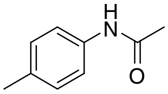
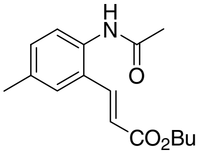
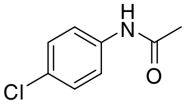
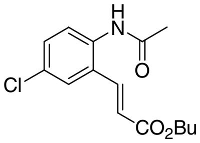
On the basis of various recent reports about Pd-catalyzed aerobic oxidative transformations including alcohol oxidation,[9] amine oxidation,[10] and oxidative C–C[11] and C–N couplings,[12] we found that two approaches were often used to accelerate the re-oxidation of Pd(0). The first approach was the use of a ligand including pyridine and Et_3N to facilitate the direct oxidation of Pd(0) to Pd(II) by O_2. The second was the addition of a co-catalyst such as Cu(II) salts that could mediate the redox between Pd(0) and O_2. It was found that the addition of Et_3N or pyridine did not improve the yield (entries 3 and 4). On the other hand, the addition of a catalytic amount of $Cu(OAc)_2$ (5 mol %) was found to increase the yield dramatically to about 80% (entry 5).

To further increase the yield, we next studied the byproducts in the reaction. It was soon realized that *n*-butyl acrylate could easily polymerize at high temperatures. To diminish this side reaction, we tried to lower the reaction temperature. It was found that at 60 °C the yield was slightly higher (84%, entry 6) whereas at room temperature no reaction could take place (entry 7). Subsequent studies at 60 °C showed that a higher loading of Cu would reduce the yield, probably because Cu could compete with Pd for the amide nitrogen binding (entries 8 and 9). Meanwhile, a lower loading of Pd would also reduce the yield (entries 10 and 11) for an obvious reasons. Eventually the optimal loadings of $Cu(OAc)_2$ and $Pd(OAc)_2$ were both found to be 3 mol % (entries 12 and 13), under which conditions the yield reached 90%. We also found that TsOH had some important influence on the reaction (entries 13–15) allowing for a loading of 1.0 mmol. The reason for the beneficial effect of TsOH was that TsO^- could increase the electrophilicity of Pd(II) center by replacing AcO^- and therefore, cause a faster activation of the C–H bond. Furthermore, it was found that the optimal solvent system was AcOH/toluene (2:1) where the yield reached 92% (entry 14). In comparison, the yield in pure AcOH was only 76% (entry 16) and the yield in AcOH/toluene (1:1) was 89% (entry 17). Noteworthily de Vries and van Leeuwen reported an optimal yield of 72% in their Pd/benzoquinone procedure,[7] as compared to 92% in our case. Thus we not only successfully used molecular oxygen to replace benzoquinone as oxidant, but also achieved a higher yield in the reaction.

Having successfully optimized the conditions,[13] we next examined the scope of this newly developed reaction for the aerobic oxidative coupling of various anilines and olefins. Here we determined the isolated yields instead of the GC yields in order to ensure the practical effi-

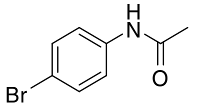
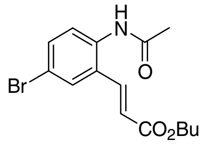
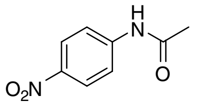
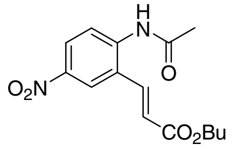
Table 2. Aerobic oxidative coupling of anilides with olefins[a]



Entry	Anilide	Olefin	Product	Yield (%)	Ref. yield[c] (%)
1				82	(72)
2				57	—
3				26	—
4				71[b]	—
5				79	(55)
6				0	—
7				89	(62)
8				91	(85)
9				11[b]	—

(*continued on next page*)

Table 2 (*continued*)

Entry	Anilide	Olefin	Product	Yield (%)	Ref. yield[c] (%)
10				14	—
11				0	—

[a] Anilide (3 mmol), olefin (3 mmol), Pd(OAc)$_2$ (3 mol %), Cu(OAc)$_2$ (3 mol %), TsOH (1 mmol), HOAc (5 mL), toluene (2.5 mL), O_2 (1 atm), 60 °C, 16 h. Isolated yields.

[b] Yield determined by ^{1}H NMR.

[c] Yields reported in Ref. 7.

ciency of our procedure (Table 2). It was found that besides *n*-butyl acrylate, methyl acrylate and styrene could also be applied to the reaction (entries 1–3). Nonetheless, the yield for styrene was relatively low (26%). A similar observation was reported by de Vries and van Leeuwen with their Pd/benzoquinone procedure,[7] where the coupling yield for 4-chlorostyrene was only 58%. Thus, it appeared that the Pd-catalyzed oxidative olefin arylation was more suitable for electron-deficient alkenes.

As to the acyl groups, we examined acetyl, propionyl, and benzoyl (entries 1, 4, 5). The isolated yields were found to be 82%, 71%, and 79%, respectively. These results showed that both the aliphatic and aromatic acyl groups could be well tolerated in the reaction. It is worth noting that de Vries and van Leeuwen reported an isolated yield of 55% for their *N*-phenylbenzamide case,[7] which should be compared to 79% in our reaction.

Next we examined *N*-methyl-*N*-phenylacetamide (entry 6). This substrate was found to provide no desired product even after an elongated reaction time. Compared to *N*-phenylacetamide in entry 1, it was evident that the presence of an *N*-methyl group completely blocked the C–H activation. This observation indicated that the nitrogen atom (or the amidyl oxygen in a deprotonated amide, but not in an *N*-methylated amide) should be deeply involved in the Pd-mediated C–H process, presumably by coordinating to the metal in the same manner as originally proposed by Horino and Inoue.[6] Thus, the oxidative coupling reaction developed in this study was dependent on the amide directing group. The requirement for an amide directing group also promised a high regioselectivity in the C–H bond activation, as manifested by the fact that only one coupling product could be observed in the reactions.

Substituents on the aromatic ring of the acetanilide were also found to influence the efficiency of the coupling significantly. Electron rich substrates (i.e., 4-methoxyphenyl-acetamide and *p*-tolylacetamide) tended to give relatively higher yields (entries 7 and 8), whereas electron deficient substrates (i.e., 4-chloro-phenylacetamide and 4-bromophenyl-acetamide) displayed a much lower reactivity (entries 9 and 10). Interestingly, for the halogenated substrates we only observe the oxidative coupling products at the anilide *ortho* position, but not any Heck-type products at the halogenated positions. Furthermore, for the most electron deficient substrate (i.e., 4-nitrophenyl-acetamide) we could not isolate any desirable product (entry 11). It should be pointed out that some similar substituent effects were reported by de Vries and van Leeuwen.[7] In their work, 4-methoxyphenyl-acetamide gave a yield of 62%, as compared to 89% in our case. Although they only tested one electron-deficient substrate (i.e., 4-trifluoromethyl-phenyl-acetamide), they reported an NMR yield of 29% for this particular case.

To summarize, in the present study we reported Pd-catalyzed aerobic oxidative coupling of anilides with olefins via regioselective C–H bond activation.[14,15] Compared to the previous work by de Vries and van Leeuwen,[7] we not only successfully used molecular oxygen to replace the chemical oxidant, but also obtained improved yields for a number of substrates. The reaction tended to give higher yields for the electron-rich anilides and electron-deficient olefins. Our current research is focused on extending the aerobic method to other Pd-catalyzed selective C–H bond activation processes, where the oxidants are often reported to be expensive or dangerous materials such as PhI(OAc)$_2$, Ag$_2$O, and ^{t}BuOO^{t}Bz.

Acknowledgment

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13. *A typical experimental procedure for the aerobic oxidative coupling of anilides with olefins:* To a 25 mL one-neck flask equipped with a stir bar was added 3.0 mmol of anilide, 20.3 mg (0.09 mmol) of $Pd(OAc)_2$, 16.3 mg (0.09 mmol) of $Cu(OAc)_2$, 197 mg (1.0 mmol) of *p*-toluenesulfonic acid, and 5 mL of acetic acid. Next a solution of 3.0 mmol olefin in 2.5 mL of toluene was added to the mixture at room temperature. A balloon of oxygen was then attached to the reaction flask via a three way joint. The flask was evacuated and refilled with oxygen three times. The reaction was stirred for 16 h at 60 °C under oxygen. The resulting mixture was diluted in 20 mL of diethyl ether, and carefully neutralized with a 2.5 M NaOH solution. After extraction of the aqueous phase with an additional 20 mL of diethyl ether, the combined organic phases are washed with brine (20 mL), dried by $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography to yield the desired product.
14. There have been several recent reports about Pd-catalyzed aerobic couplings between olefins and aromatic compounds without any directing group. Although these studies are highly interesting, reactions through this approach may not be regioselective because all of the *o*-, *m*-, and *p*-substituted products were found to be produced. See: (a) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512–3515; (b) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477; (c) Sakaguchi, S.; Tani, M.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221–1226.
15. For very recent related studies on selective C–H activation of acetanilide, see: (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416–7417; (b) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067.