J|A|C|S
COMMUNICATIONS

Selective Pd-Catalyzed Oxidative Coupling of Anilides with Olefins through C−H Bond Activation at Room Temperature

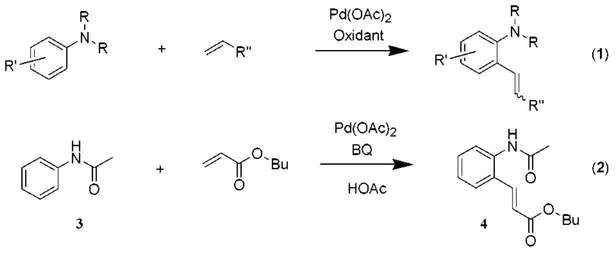
Maarten D. K. Boele,[†] Gino P. F. van Strijdonck,[†] André H. M. de Vries,[‡] Paul C. J. Kamer,[†]
Johannes G. de Vries,*[,‡] and Piet W. N. M. van Leeuwen*[,†]

Institute of Molecular Chemistry, Faculty of Science, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands, and DSM Research, P.O. Box 18, 6160 MD Geleen, The Netherlands

Received December 6, 2001; Revised Manuscript Received January 9, 2002

The arylation of olefins (Heck reaction) is a key reaction for constructing new C−C bonds.[1] Being a very mild method and showing compatibility with most functional groups, it is very attractive for the industrial production of fine chemicals.[2] Still, a major drawback accompanying this procedure is the restriction of possible substrates to mainly organic halides,[3] thereby creating a significant amount of salt waste. Therefore, a need exists for alternative Heck-type coupling reactions that would reduce this waste formation. C−H activation reactions, one of the most challenging fields in modern chemistry,[4] could provide such a methodology.

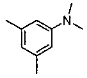
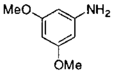
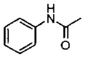
Murai has shown that the reductive coupling of arenes bearing an ortho-directing group with olefins proceeds smoothly using Ru-catalysts, producing alkylarenes.[5] Examples of the oxidative coupling in which the double bond is preserved are much less abundant. Fujiwara[4c,6] and later others[7] have exemplified the Pd-catalyzed oxidative coupling of arenes and olefins. In these cases, the required presence of peroxides in combination with strong acids and/or elevated temperatures is still a large drawback. Recently, Milstein and co-workers reported the use of Ru catalysts and O_2 as oxidant, producing only water as a side product.[8] This procedure shows moderate selectivity in some cases and requires high temperatures. Here we report a mild method for functionalizing aniline derivatives with olefins (eq 1) that uses $Pd(OAc)_2$ as a catalyst together with cheap oxidants and solvents at room temperature.



We first employed rapid screening experiments using a parallel synthesis apparatus and tested several potential catalyst precursors with different substrates.[9] From these experiments, a single lead emerged that prompted us to further research.

The results are summarized in Table 1. Aniline derivatives **1** and **2** are not reactive under the conditions tested (entries 1 and 2). In contrast, the reaction of acetanilide (**3**) with *n*-butyl acrylate proceeds smoothly and selectively at 80 °C using 2 mol % $Pd(OAc)_2$ and benzoquinone (BQ) as oxidant to yield the common Heck product (*E*)-3-(2-(acetylamino)phenyl)propenoic acid butyl ester (**4**, eq 2) exclusively, albeit in moderate yield. No formation of 3- or 4-substituted product is observed in any of the reactions performed, showing the importance of the ortho-directing effect of the amide group. Furthermore, we did not detect any trace of products resulting from N−H bond activation.

Table 1. Coupling of Aniline Derivatives with *n*-Butyl Acrylate Using $Pd(OAc)_2$[a]

Entry	Substrate		Temp (°C)	Solvent	Additives	Yield (%)
1		**1**	80	HOAc	none	0
2		**2**	80	HOAc	none	0
3		**3**	80	HOAc	none	35
4		**3**	20	HOAc	none	54
5		**3**	20	HOAc / Toluene[b]	TsOH[c]	72
6		**3**	20	HOAc / NMP[b]	TsOH[c]	23
7		**3**	20	HOAc / Toluene[b]	H_2O (5 % v/v)	49
8		**3**	20	CF_3COOH	none	61
9		**3**	20	HOAc / Toluene[b]	NaCl[c]	0
10[d]		**3**	20	HOAc / Toluene[b]	TsOH[c]	29

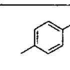
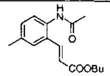
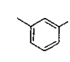
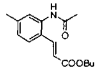
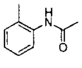
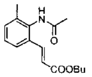
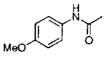
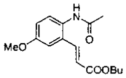
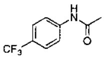
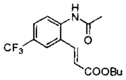
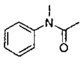
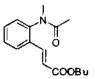
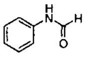
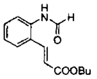
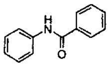
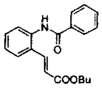
[a] Substrate (3.0 mmol), *n*-butyl acrylate (3.3 mmol), $Pd(OAc)_2$ (0.06 mmol), BQ (3.0 mmol). Yields are isolated yields. See the Supporting Information for details. [b] 1:2 ratio (v/v). NMP = *N*-methyl pyrrolidinone. [c] 1.5 mmol. [d] Performed with H_2O_2 as the oxidant.

Remarkably, lowering the reaction temperature to 20 °C results in higher yields (Table 1, entries 3 and 4). Acetic acid proves to be the solvent of choice, and using mixtures (up to 1:1 v/v) of HOAc with CH_2Cl_2 or THF does not affect the yields to a large extent. No C−H activation of aromatic solvents such as toluene is observed under these conditions. Coordinating solvents such as NMP hamper the catalytic reaction (entry 6). The presence of a substoichiometric amount (0.5−1.0 equiv) of *p*-toluenesulfonic acid (TsOH) has a large beneficial effect, resulting in a 72% isolated yield when acetanilide is employed as the substrate (Table 1, entry 5). Larger amounts of TsOH do not improve the yields, but instead promote a side reaction of the alkene, probably an acid-catalyzed polymerization. Fujiwara and co-workers showed that the acidity of the solvent can have a large influence on the reaction rate in their Pd(II)-catalyzed hydroarylation of alkenes, CF_3COOH being much more effective than HOAc. These observations can be explained in terms of increasing electrophilicity of the Pd(II) center by replacement of AcO^- by CF_3COO^-, resulting in faster metalation of the aromatic C−H bond.[6b] In our case, employing CF_3COOH

[†] University of Amsterdam.
[‡] DSM Research; Department of Life Sciences-Chemistry & Catalysis.

10.1021/ja0176907 CCC: $22.00

Table 2. Coupling of Substituted Anilide Derivatives with *n*-Butyl Acrylate Using $Pd(OAc)_2$ in Acetic Acid[a]

Entry	Substrate		Product		Yield (%)
1		**5**		**13**	85
2		**6**		**14**	91
3		**7**		**15**	38[b]
4		**8**		**16**	62
5		**9**		**17**	(29)
6		**10**		**18**	0
7		**11**		**19**	(26)
8		**12**		**20**	55

[a] Reactions performed as in Table 1, entry 5. Yields in parentheses were determined by GC.[9] [b] Determined by ^1H NMR.

as the solvent (without TsOH added) results in similar catalyst performance as HOAc/TsOH (entry 8, Table 1).

Other metal complexes, e.g. $Ru_3(CO)_{12}$, $[RuCl_2(p\text{-cymene})]_2$, $PtCl_2$, and $Ni(OAc)_2$, show no activity under these conditions. Pd sources such as $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and Pd on charcoal result in low (<10%) conversions. Addition of inorganic acids (HCl, H_2SO_4) has a large detrimental effect on the catalytic performance. Apparently, halides block the catalytic cycle by coordinating to the Pd(II) center, thereby decreasing its electrophilicity (entry 9). Furthermore, the presence of halide anions can favor protonolysis of Pd−alkyl bonds over β-H elimination.[10] No addition products are observed in our reactions, regardless of the conditions employed. Other alkenes, like styrene, can be applied, although less mild conditions are required in these cases.[11]

Use of other oxidants, e.g. hydrogen peroxide (see entry 10 of Table 1) or $Cu^{II}(OAc)_2$, give conversions that are significantly lower compared to benzoquinone. The role of the BQ can be 2-fold. It serves as the oxidant, resulting in the formation of Pd(II) and hydroquinone. This reaction is known to be accelerated by acid.[12] In addition, BQ can act as a ligand, stabilizing the different Pd species present during the catalytic cycle.[6c,13] In our case, addition of more than 1 equiv of BQ does not improve the yield significantly.

Substituents on the aromatic moiety of the acetanilide substrate influence the efficiency of the coupling reaction significantly (see Table 2). As anticipated, ortho substitution hampers the reaction. It has been reported that the palladation of ortho-substituted acetanilides does not take place at all[14] or at elevated temperatures only.[15] In the case of 3-methylacetanilide (**6**) the reaction efficiency is enhanced to give a 91% yield of **14**. Interestingly, the reaction of *N*-methylacetanilide (**10**) gave no conversion at all. Formanilide and benzanilide (entries 7 and 8) can be applied, although the yields in these cases are low to moderate. Minor amounts (<1%) of disubstitution are observed in only a few cases, indicating disfavored electronic and steric properties of the product to a second substitution.

The reaction also exhibits a large electronic dependence. Competition experiments of a series of 4-substituted acetanilides show that electron-rich arenes react significantly faster ($k_{obs}(\mathbf{5}) > k_{obs}(\mathbf{8}) \approx k_{obs}(\mathbf{3}) \gg k_{obs}(\mathbf{9})$), although no linear Hammett plots could be obtained. The reaction exhibits a kinetic isotope effect ($k_H/k_D = 3$), indicating slow C−H bond activation. Ryabov et al. have shown that the stoichiometric reaction of $[(C_6H_4NHC(O)CH_3)Pd^{II}(OAc^-)]_2$ complexes with styrenes can be acid catalyzed, and that protonation is likely to occur at the bridging acetate ligands.[16] This protonation is followed by alkene coordination and the rate-limiting insertion of alkene into the palladium−carbon bond. We tested the dimeric ortho-palladated anilide complexes in the reaction with *n*-butyl acrylate and found that the reaction rate is at least an order of magnitude higher using the preformed complexes compared with the in situ generated catalysts. These results support a reaction pathway via slow electrophilic attack of cationic $[PdOAc]^+$ species on the π-system of the arenes.[6c]

In summary, a very selective and mild oxidative coupling reaction between aniline derivatives and acrylates is reported that occurs through ortho C−H bond activation. The reaction is catalyzed by electrophilic Pd complexes and occurs even at room temperature with use of a cheap oxidant in yields up to 91%. Current research is focused on extending the scope and gaining more detailed information on the exact mechanism of the reaction.

Acknowledgment. This research was sponsored by the Netherlands Ministry of Economic Affairs, Grant EETK9710.

Supporting Information Available: Experimental details, spectroscopic and analytical data of products, and kinetic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (b) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379−2411. (c) Herrmann, W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, Germany, 1996; Vol. 2, pp 712−732.
(2) De Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086−1092.
(3) Alternatives exist; see for example: Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; De Vries, J. G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 662−664.
(4) For recent reviews on C−H activation see for example: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (b) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1699−1712. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639. (d) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: New York, 1999; pp 47−79.
(5) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (b) Ie, Y.; Chatani, C.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475−1488 and references therein.
(6) (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166−7169. (b) Fujiwara, Y.; Jia, C. *Pure Appl. Chem.* **2001**, *73*, 319−324. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097−2100. (d) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119−1122.
(7) (a) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699−2702. (b) Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, 55−56. (c) Matsumoto, T.; Yoshida H. *Chem. Lett.* **2000**, 1064−1065.
(8) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337−338.
(9) For experimental details see the Supporting Information.
(10) (a) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724−3728. (b) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775−780.
(11) The yield for *p*-chlorostyrene with 5 mol % $Pd(OAc)_2$ at 40 °C is 58%.
(12) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790−1793.
(13) (a) Bäckvall, J.-E. *Pure Appl. Chem.* **1992**, *64*, 429−437 and references therein. (b) Roffia, P.; Conti, F.; Gregorio, G.; Pregaglia, G. F.; Ugo, R. *J. Organomet. Chem.* **1973**, *391*, 391−394 and references therein.
(14) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416−4422.
(15) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759−5760.
(16) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Organomet. Chem.* **1991**, *406*, 309−321.

JA0176907