

Synthesis of Aryl Ketones by the Pd-Catalyzed C–H Activation of Arenes and Intermolecular Carbopalladation of Nitriles

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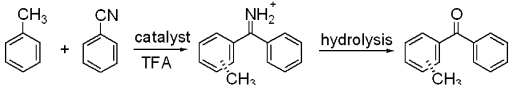
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The functionalization of relatively unreactive C–H bonds is an area of considerable current interest,¹ especially the catalytic addition of C–H bonds to unsaturated substrates.^{1b} While Pd has been shown to catalyze C–H addition to simple alkenes and alkynes,² to our knowledge, there are no examples of Pd-catalyzed C–H additions to polar multiple bonds, such as a nitrile.³ During most Pd-catalyzed organic reactions, the nitrile functionality remains untouched during the reaction.⁴ In fact, PdCl₂(RCN)₂ (R = Me, Ph) are widely used Pd catalysts, and acetonitrile is a commonly employed solvent in organopalladium chemistry. To date, only a few examples of reactions involving the intramolecular carbopalladation of nitriles have been reported.^{5,6} Herein, we report novel inter- and intramolecular examples of the Pd-catalyzed reaction of simple arenes and nitriles, which provides a useful new synthesis of aromatic ketones.

The reaction of toluene and PhCN was initially investigated under Fujiwara's C–H activation conditions in which a highly cationic Pd(II) species is generated in TFA.^{2c–e} A 10% yield of the corresponding diaryl ketone was obtained (Table 1, entry 1). Adding either THF or nitrobenzene had little effect on the reaction (entries 2 and 3). However, the addition of DMSO afforded a large increase in the yield (entries 4–6). A 76% yield of the desired product can be obtained when only 2 equiv of DMSO are employed (entry 5). It is noteworthy that the reaction can even be improved dramatically by adding only a catalytic amount of DMSO (compare entries 1 and 6). One possible explanation for the effect of DMSO involves the facile coordination between DMSO and Pd, which may either stabilize any Pd(II) reaction intermediate⁷ or facilitate the reoxidation of Pd(0) to Pd(II) (presumably by air) should the Pd(II) ever be reduced to Pd(0).⁸ Without the Pd(OAc)₂ catalyst, the reaction fails to give any ketone product at all (entry 7). Other Lewis acids, such as AlCl₃ and SnCl₄ (entries 8 and 9), as well as catalytic amounts of Pd/C and Pd(PPh₃)₄, are ineffective as catalysts.⁹ These results indicate that the reaction is most likely not a Lewis-acid-catalyzed Houben–Hoesch reaction¹⁰ and the Pd catalyst must be playing some unique role in this chemistry.

Using the optimized reaction conditions, a number of arenes and nitriles have been successfully employed in this ketone synthesis (Table 2). The reactions of benzonitrile and anisole or 1,3,5-trimethoxybenzene afford the corresponding ketone products in good yields (entries 2 and 3). The arene 4-*tert*-butylphenol gives the ortho acylation product cleanly in good yield (entry 4). Interestingly, biaryl ketimines, instead of ketones, are obtained as the only products after the workup when mesitylene and several different arenitriles were employed (entries 5–7). The steric hindrance around the imine group apparently hinders the hydrolysis process.¹¹ The relatively electron-poor *p*-BrC₆H₄CN reacts faster and leads to a higher yield of ketone than the more electron-rich *p*-MeOC₆H₄CN (entries 6 and 7). It is important to note that simple alkanenitriles, such as acetonitrile, also work well in this chemistry (entry 8). It is also noteworthy that intramolecular variations of

Table 1. Optimization Studies^a



entry	catalyst	additive ^b	% yield ^c
1	10% Pd(OAc) ₂		10
2	10% Pd(OAc) ₂	10 equiv of THF	20 (16)
3	10% Pd(OAc) ₂	10 equiv of nitrobenzene	15
4	10% Pd(OAc) ₂	10 equiv of DMSO	45
5	10% Pd(OAc) ₂	2 equiv of DMSO	76 (68)
6	10% Pd(OAc) ₂	0.4 equiv of DMSO	55
7		2 equiv of DMSO	0
8	20% AlCl ₃	2 equiv of DMSO	0
9	20% SnCl ₄	2 equiv of DMSO	0

^a All reactions were run by employing 2.0 mmol of toluene, 1.0 mmol of benzonitrile, 0.10 mmol of Pd(OAc)₂ in 2.5 mL of TFA at 90 °C for 24 h, followed by hydrolysis. ^b The equivalents of additive are based on benzonitrile. ^c GC yields; yields of products obtained by column chromatography are reported in parentheses.

this reaction have been successful, although they tend to be sluggish, and so far we have only been able to generate seven-membered ring ketones in decent yields (entries 9 and 10). None of the above reactions provide any of the desired products without the Pd catalyst.

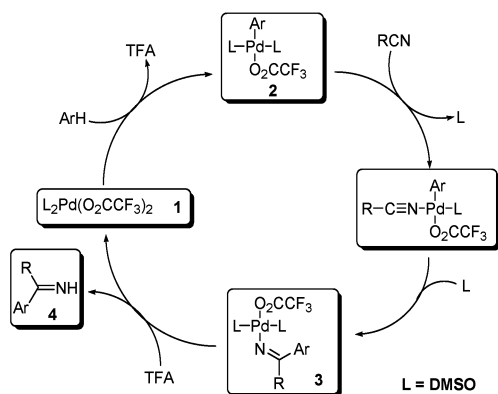
We tentatively propose the following reaction mechanism for this unique process (Scheme 1): (1) electrophilic metalation of the arene by the Pd(II) catalyst **1**, which generates arylpalladium species **2**;^{2c–e} (2) coordination of the nitrile to the Pd; (3) carbopalladation of the nitrile to form the imine–Pd(II) complex **3**; (4) protonation of **3** by TFA, which affords the ketimine product **4** and regenerates the Pd(II) catalyst. The preference for ortho and para isomers over the meta isomer in the products from toluene or anisole is consistent with electrophilic palladation of the arene² (entries 1 and 2, Table 2). Nucleophilic attack of the arylpalladium intermediate on the nitrile is consistent with the faster reaction and higher yield obtained when using the more electron-deficient *p*-BrC₆H₄CN over the more electron-rich *p*-MeOC₆H₄CN (entries 6 and 7, Table 2).

This mechanism suggests that the arylpalladium species **2**, if generated by some other means, should also react with nitriles under similar reaction conditions. Indeed, we have found that arylboronic acids react under our standard reaction conditions with PhCN to provide the corresponding ketimine or ketone products in good yields (Scheme 2). Presumably, these reactions proceed by (1) transmetalation between the arylboronic acid and Pd(II) generating arylpalladium **2**,¹² and (2) carbopalladation of the PhCN by **2** to form the nitrile addition products (see Scheme 1). It is worth noting that *p*-tolylboronic acid gives primarily the para isomer, which seems to rule out protonation of the arylboronic acid to produce toluene, which then undergoes coupling in the usual fashion, because toluene under these same reaction conditions using 5 equiv of PhCN is observed to give a 50:12:38 *o/m/p* ratio in a 62% yield. However, the minor amounts of ortho and meta isomers may be

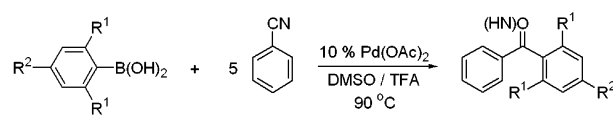
Table 2. The Pd-Catalyzed Reaction of Nitriles and Arenes^a

entry	arene	R	temp (°C)	product(s)	% yield ^b
1			90		68 ^c
2			100		70 ^d
3			100		66
4			90		71
5			75		80
6 ^e			90		61
7			90		90
8		Me	80		62
9 ^f			95		60
10 ^f			100		55

^a Unless indicated otherwise, all reactions were run by employing 2.0 mmol of arene, 1.0 mmol of nitrile, 0.10 mmol of Pd(OAc)₂, and 0.10 mL of DMSO in 2.5 mL of TFA for 24 h. The reactions were then worked up under acidic or basic conditions. ^b Isolated yields. ^c Ortho, meta, and para isomers were obtained in a ratio of 51:16:33. ^d Ortho and para isomers were obtained in a ratio of 52:48. ^e The reaction was run for 48 h. ^f The reaction employed 0.20 mmol of nitrile, 0.03 mmol of Pd(OAc)₂, 0.20 mL of DMSO, and 5.0 mL of TFA for 36 h.

Scheme 1

arising by a protonolysis process. These results support our proposed mechanism for the reaction of arenes and nitriles, involving Pd-catalyzed C–H activation, followed by intermolecular carbopalladation of a nitrile. The more sluggish formation of five- and six-membered ring cyclic ketones over seven-membered ring ketones by intramolecular variations of this process may be due to the fact that it is impossible for the anticipated arylpalladium intermediate to form a stable cyclic intermediate in which the Pd is also coordinated with the pair of electrons on the nitrile nitrogen in these smaller ring systems.

Scheme 2

R ¹	R ²	% yield
H	H	71 (ketone)
Me	Me	83 (imine)
H	Me	78 (ketone, o/m/p = 9:3:88)

Transmetalation:

Unlike the Houben–Hoesch reaction,¹⁰ which requires electron-rich phenol or aryl ethers as substrates and dry gaseous HCl to get decent yields of ketones, our Pd-catalyzed approach is successful with less electron-rich arenes. Both inter- and intramolecular examples of this Pd-catalyzed process have been successful. This chemistry provides a mechanistically novel and synthetically useful transformation of nitriles to ketones or ketimines.

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Supporting Information Available: Reaction procedures, product characterization data, and ¹H and ¹³C NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.
- (2) (a) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. *M. J. Am. Chem. Soc.* **2002**, *124*, 1586. (c) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (d) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633 and references therein.
- (3) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771.
- (4) (a) Tsuji, J. *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; Wiley: New York, 1995. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.
- (5) (a) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238. (b) Pletnev, A. A.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 2133. (c) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276. (d) Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9428. (e) Tian, Q.; Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 339. (f) Yang, C. C.; Tai, H. M.; Sun, P. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2843. (g) Luo, F. H.; Chu, C. I.; Cheng, C. H. *Organometallics* **1998**, *17*, 1025. (h) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343.
- (6) For a Pd(II)-assisted Ritter reaction, see: Hegedus, L. S.; Mulhern, T. A.; Asada, H. *J. Am. Chem. Soc.* **1986**, *108*, 6224.
- (7) (a) Bancroft, D. P.; Cotton, F. A.; Verbruggen, M. *Acta Crystallogr., Sect. C* **1989**, *45*, 1289. (b) van Benthem, R. A. T. M.; Hiemstra, H.; van Leeuwen, P. W. N. M.; Geus, J. W.; Speckamp, W. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 457.
- (8) (a) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (b) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (c) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.
- (9) Other Lewis acids, such as TiCl₄ (20%), Mg(OAc)₂ (20%), Zn(OAc)₂ (20%), Hg(O₂CCF₃)₂ (20%), RhCl₃ (10%) plus Ag₂O₂CCF₃ (30%), PtCl₂ (10%) plus Ag₂O₂CCF₃ (20%), have been employed as catalysts, but none of them provided any of the desired ketone product.
- (10) For the Houben–Hoesch reaction, see: (a) Spoerri, P. E.; DuBois, A. S. *Org. React.* **1949**, *5*, 387. (b) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037.
- (11) The sterically hindered biaryl ketimines cannot be hydrolyzed even after heating at 100 °C for 24 h in either aqueous HCl or K₂CO₃ solutions.
- (12) For recent examples, see: (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768. (b) Oh, C.; Jung, H.; Kim, K.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805.

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