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Synthesis of Aryl Ketones or Ketimines by Palladium-Catalyzed Arene C−H Addition to Nitriles

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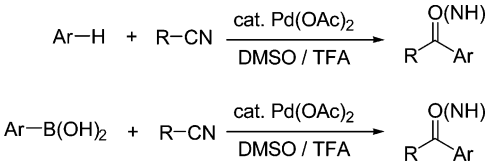
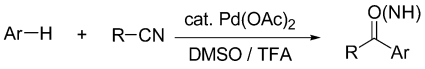


The unprecedented palladium-catalyzed C−H addition of arenes to nitriles provides moderate to excellent yields of aryl ketones or the corresponding hindered imines. The addition of a small amount of DMSO increases the yields dramatically. Both *intermolecular* and *intramolecular* reactions are successful, although the *intramolecular* reactions tend to be more sluggish. This novel chemistry is believed to involve palladium-catalyzed C−H activation of the arene by electrophilic aromatic substitution, followed by the unusual carbopalladation of a nitrile. Similar reactions have been successfully developed employing arylboronic acids and nitriles. A concise route to xanthones starting from cheap starting materials has been developed employing this synthetic protocol.

Introduction

Developing reliable methods for catalytic C−H functionalization has been a long-term goal in synthetic organic chemistry. For example, the catalytic addition of C−H bonds to unsaturated substrates has been one of the most attractive research subjects for synthetic chemists for years.[1] The late transition metals, such as Pd, have been shown to catalyze C−H addition to simple alkenes and alkynes and provide various valuable synthetic intermediates in an atom-economical manner.[2] To our knowledge, however, there are no examples of Pd-catalyzed C−H additions to polar multiple bonds, such as a nitrile.[3,4] In fact, the nitrile functionality remains untouched during most Pd-catalyzed organic reactions.[5] Indeed, the nitrile complexes, $PdCl_2(RCN)_2$ (R = Me, Ph), are widely used Pd catalysts and acetonitrile is a commonly employed solvent in organopalladium chemistry. Up to now, only a few examples of reactions involving the *intramolecular* carbopalladation of nitriles have been reported.[6,7] Recently, we communicated the first example of Pd-catalyzed simple C−H addition to nitriles, which provides a useful new synthesis of aromatic ketones or ketimines (eq 1).[8] Herein, we wish to provide a full account of the scope and



(1)

limitations of this chemistry. We have also developed a useful ketone synthesis by the reaction of arylboronic acids and nitriles

(1) For selective reviews, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(2) For selective examples, see: (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) Ritleng, V.; Sirlin, C.; Preffer, M. *Chem. Rev.* **2002**, *102*, 1731 and references therein.

(3) For a review covering metal-activated organonitriles, see: Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771.

(4) For recent rhodium-catalyzed nucleophilic additions to nitriles, see: (a) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339. (b) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855. (c) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229.

(5) (a) Tsuji, J. *Palladium Reagents and Catalysis: New Perspectives for the 21st Century*; John Wiley & Sons: New York, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

(6) (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) Yang, C. C.; Sun, P. J.; Fang, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2629. (h) Luo, F. H.; Chu, C. I.; Cheng, C. H. *Organometallics* **1998**, *17*, 1025. (i) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343.

(7) For a Pd(II)-assisted Ritter reaction, see: Hegedus, L. S.; Mulhern, T. A.; Asada, H. *J. Am. Chem. Soc.* **1986**, *108*, 6224.

(8) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302.

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TABLE 1. Optimization Studies (Eq 2)[a]

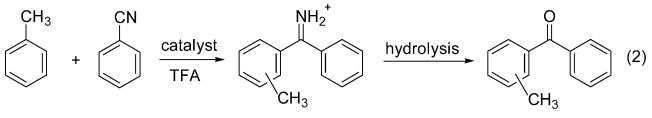
entry	catalyst	additive[b]	% yield[c]
1	10% $Pd(OAc)_2$	−	10[d]
2[e]	10% $Pd(OAc)_2$	−	0
3	10% $Pd(OAc)_2$	10 equiv of THF	20 (16)
4	10% $Pd(OAc)_2$	10 equiv of $PhNO_2$	15
5	10% $Pd(OAc)_2$	10 equiv of DMSO	45
6	10% $Pd(OAc)_2$	5 equiv of DMSO	56
7	**10% $Pd(OAc)_2$**	**2 equiv of DMSO**	**76 (68)[d]**
8	10% $Pd(OAc)_2$	1 equiv of DMSO	66
9	10% $Pd(OAc)_2$	0.4 equiv of DMSO	55
10[f]	5% $Pd(OAc)_2$	2 equiv of DMSO	61
11[g]	10% $Pd(OAc)_2$	2 equiv of DMSO	0
12	10% $PdCl_2(PPh_3)_2$	10 equiv of DMSO	trace
13	10% $Pd(PPh_3)_4$	10 equiv of DMSO	0
14	10% Pd/C	10 equiv of DMSO	0
15	10% $PtCl_2$ + 20% AgO_2CCF_3	2 equiv of DMSO	0
16	10% $RhCl_3$ + 30% AgO_2CCF_3	2 equiv of DMSO	0
17	20% $Hg(O_2CCF_3)_2$	2 equiv of DMSO	0
18	20% $AlCl_3$	2 equiv of DMSO	0
19	20% $SnCl_4$	2 equiv of DMSO	0
20	20% $TiCl_4$	2 equiv of DMSO	0
21	20% $Mg(OAc)_2$	2 equiv of DMSO	0
22	20% $Zn(OAc)_2$	2 equiv of DMSO	0
23	−	2 equiv of DMSO	0

[a] Unless otherwise indicated, all reactions were run by employing 2.0 mmol of toluene and 1.0 mmol of benzonitrile in the presence of the catalyst indicated in 2.5 mL of TFA at 90 °C for 24 h, followed by hydrolysis. [b] The equivalents of additives are based on benzonitrile. [c] GC yields; yields of products obtained by column chromatography are reported in parentheses. [d] Ortho, meta, and para isomers were obtained in a ratio of 51:16:33. [e] The reaction was run at room temperature. [f] The reaction was run for 48 h. [g] The reaction was run employing AcOH as the solvent, instead of TFA.

under similar reaction conditions. This chemistry has also provided a concise route to xanthones starting from cheap starting materials.

Results and Discussion

(a) Optimization of the Reaction Conditions. Recently, Fujiwara reported highly efficient Pd-catalyzed C−H additions to various alkynes and alkenes in TFA.[9] The highly cationic Pd(II) species, generated in TFA, is believed to be the key to the efficiency of this chemistry. We envisioned that such a highly cationic arylpalladium species, when generated in situ by the electrophilic palladation of arenes, should strongly coordinate with a nitrile and perhaps facilitate the "abnormal" carbopalladation of a nitrile. To this end, we initially studied the Pd-catalyzed reaction of toluene and benzonitrile in TFA (eq 2).



(2)

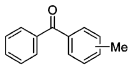
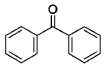
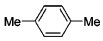
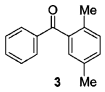
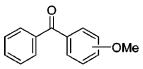
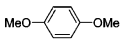
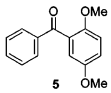
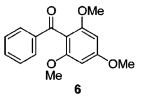
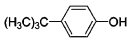
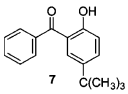
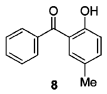
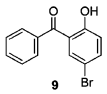
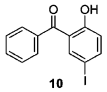
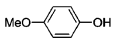
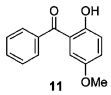
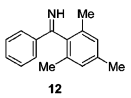
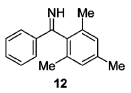
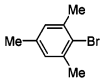
To our delight, a 10% yield of the desired products (o/m/p = 51:16:33) was obtained by employing 2 mmol of toluene, 1 mmol of benzonitrile, and 0.1 mmol of $Pd(OAc)_2$ in 2.5 mL of TFA at 90 °C for 24 h (entry 1, Table 1). No reaction occurs at room temperature (entry 2). Adding either THF or nitrobenzene, with the hope of stabilizing the possible Pd(II) intermediate while maintaining the highly cationic palladium intermediate, had little effect on the reaction (entries 3 and 4). However, the addition of DMSO afforded a large increase in the yield (entries 5−10). A 76% yield of the desired product can be obtained when 2 equiv of DMSO per nitrile is employed (entry 7). More or less, DMSO gave lower yields. It is noteworthy that the reaction can even be improved dramatically by adding only a catalytic amount of DMSO (compare entries 1 and 9). A slightly lower yield is obtained when only 5% $Pd(OAc)_2$ is employed (compare entries 7 and 10). The use of TFA as solvent is apparently crucial for the success of this chemistry because none of the desired product was obtained when acetic acid was employed as the solvent (entry 11). Other Pd catalysts, such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and Pd/C, are ineffective in this chemistry (entries 12−14). The Pd(II) catalyst is uniquely effective because other late transition metal salts or common Lewis acids all failed to give any of the desired product (entries 15−22). No reaction occurs in the absence of the catalyst (entry 23). Thus, the optimal procedure described in entry 7 of Table 1 has been employed to study the scope of this chemistry.

(b) Reaction of Various Nitriles and Arenes. Using the optimized reaction conditions, a number of arenes and nitriles have been successfully employed in this ketone synthesis (Table 2). The reaction of benzonitrile and benzene afforded a much lower yield of the desired product (compare entries 1 and 2), possibly because of the fact that benzene is less electron rich than toluene and benzene is rather volatile at the reaction temperature. The reactions of benzonitrile and relative electron-rich *p*-xylene (entry 3), anisole (entry 4), 1,4-dimethoxybenzene (entry 5), and 1,3,5-trimethoxybenzene (entry 6) have all afforded the corresponding ketones in good yields. It is noteworthy that the ortho and para isomers **4a** and **4b** were obtained in a ratio of 52:48 when anisole was employed (entry 4). The arenes 4-*tert*-butylphenol and 4-methylphenol cleanly gave the acylation products ortho to the hydroxyl group in good yields (entries 7 and 8). The arene 4-bromophenol also afforded the acylation product ortho to the hydroxyl group, although in a much lower yield (entry 9). None of the desired product was obtained when 4-iodophenol was employed, possibly because this substrate is unstable in TFA under the reaction conditions or because oxidative addition of the C−I bond to the Pd intermediate disrupts our desired chemistry (entry 10). The arene 4-methoxyphenol also failed to give any of the desired product, possibly because of oligomerization (entry 11). Mesitylene is more reactive, affording good yields at only 65 or 75 °C (entries 12 and 13). Interestingly, biaryl ketimines, instead of ketones, are obtained as the only products in these reactions. Other sterically hindered arenes, such as bromomesitylene and 1,2,4,5-tetramethylbenzene have also afforded the corresponding ketimines as products (entries 14 and 15). The steric hindrance around the imine group apparently hinders the hydrolysis process.[10] The relatively electron-poor *p*-BrC_6H_4CN reacts faster and leads to a higher yield of ketimine than the more electron-rich *p*-$MeOC_6H_4CN$ (compare entries 16 and 17). Various halogen-containing benzonitriles are excellent substrates for this chemistry, providing the corresponding ketimines in good to excellent yields (entries 17−22). For example, the reaction of 1,3,5-trimethoxybenzene and 2-fluorobenzonitrile afforded the corresponding ketimine in 89% yield (entry 21), compared with

(9) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633 and references therein.

(10) The sterically hindered biaryl ketimines cannot be hydrolyzed even after heating at 100 °C for 24 h in aqueous HCl or K_2CO_3 solutions.

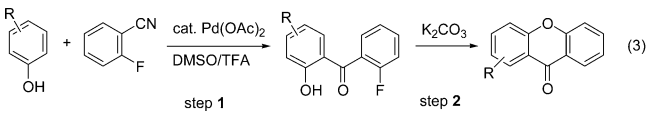
TABLE 2. Pd-Catalyzed Reaction of Nitriles and Arenes (Eq 1)[a]

entry	arene	R	temp (°C)	product(s)	% yield[b]
1			90	 **1a-c**	68[c]
2			90	 **2**	48
3			90	 **3**	73
4			100	 **4a,b**	70[d]
5			100	 **5**	75
6			100	 **6**	66
7			90	 **7**	71
8			95	 **8**	55
9			95	 **9**	33
10			95	 **10**	0
11			95	 **11**	0
12			65	 **12**	72
13			75	 **12**	80
14			90	**13**	66
15			75	**14**	80
16[e]			90	**15**	61
17			90	**16**	90
18			90	**17**	88
19			90	**18**	72
20			90	**19**	78
21			95	**20**	89
22			95	**21**	82
23		Me	80	**22**	62
24			90	**23**	0
25[f]			95	**24**	16
26[f]			100	**25**	55
27[f]			95	**26**	0
28[f]			95	**27**	0
29[f]			95	**28**	0
30[f]			95	**29**	0
31[f]			95	**30**	35
32[f]			95	**31**	60

[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 (see the Experimental Section for details). [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.

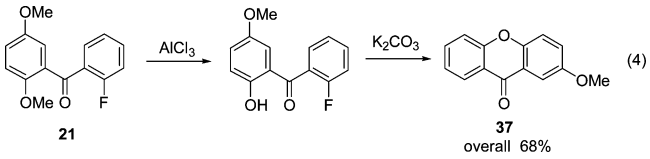
a 66% yield of the ketone product obtained when 1,3,5-trimethoxybenzene and benzonitrile were employed (entry 6). A ketone was obtained when 1,4-dimethoxybenzene was employed with this latter nitrile (entry 22). It is important to note that acetonitrile also worked well in this chemistry (entry 23). Unfortunately, an indole failed to give any of the desired product (entry 24), possibly because the substrate is not stable under our reaction conditions. Interestingly, *intramolecular* variations of this reaction are more difficult than the *intermolecular* reactions. For example, only a 16% yield of the xanthone product **24** was obtained when *σ*-phenoxybenzonitrile was employed (entry 25). Fortunately, a seven-membered ring product **25** was formed more readily, although a higher temperature was required (entry 26). Simple phenyl-containing alkanenitriles failed to generate the expected *intramolecular* cyclization products (entries 27−29). However, introducing two methyl groups on the carbon adjacent to the nitrile facilitated cyclization to the corresponding six- and seven-membered ring products **30** and **31** in moderate yields (entries 31 and 32), possibly because of the gem-disubstituent effect.[11] Noteworthy is the fact that the formation of five- and six-membered ring ketones is more difficult than formation of a seven-membered ring ketone (compare entries 30, 31, and 32). This unusual trend suggests that this reaction is most likely not a Lewis-acid-catalyzed Houben−Hoesch reaction[12] (see the Reaction Mechanism section). *In fact, none of the above reactions in Table 2 provide any of the desired products without the Pd catalyst.*

(c) Two-Step Approach to Xanthones. Xanthones are abundant in numerous natural products and possess many important biological activities.[13] As an application of our chemistry, a simple approach to xanthones has been developed, which involves ketone formation using simple phenols and 2-fluorobenzonitrile as starting materials, followed by *intramolecular* cyclization under mild conditions (eq 3).



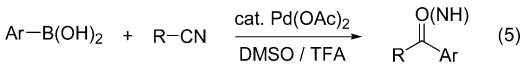
(3)

Various xanthones have been obtained from cheap, readily available starting materials in moderate yields (Table 3, entries 1−4). It is noteworthy that a chloride-containing xanthone was obtained (entry 4) because this substrate should be subject to facile functionalization via various Pd-catalyzed reactions.[14] 4-Phenylphenol failed to give the ketone product, possibly because of solubility problems with this phenol in TFA (entry 5). 4-Methoxyphenol also failed to give the desired ketone product (entry 6). However, xanthone **37** can be obtained in 68% overall yield via selective demethylation of the ketone **21** obtained previously by our ketone synthesis (see entry 22 in Table 2), followed by cyclization by K_2CO_3 (eq 4).



(4)

(d) Reaction of Nitriles and Arylboronic Acids. The success of the Pd-catalyzed reaction of arenes and nitriles suggests that a similar reaction should occur with nitriles if an arylpalladium species is generated by transmetalation.[18] Indeed, we have found that arylboronic acids react under our standard reaction conditions with nitriles to provide the corresponding ketimine or ketone products (eq 5, Table 4).



(5)

Good to excellent yields have been obtained when electron-rich arylboronic acids react with benzonitrile (entries 1−4). Small amounts of ortho and meta isomers were also obtained when *p*-tolylboronic acid was employed (footnote c in entry 2). Keep in mind that a 50:12:38 o/m/p ratio of ketone products was obtained in 62% yield when toluene was allowed to react with 5 equiv of PhCN under these same reaction conditions. The minor amounts of o and m isomers may be arising by an alternate protonolysis process, which generates toluene, which subsequently undergoes direct reaction with benzonitrile. Thus, this arylboronic acid approach to aromatic ketones solves some of the regiochemical problems observed when simple arenes are employed. Similarly, an 8:92 o/p ratio of ketones was obtained when *p*-methoxyphenylboronic acid was employed (footnote d in entry 3), whereas a 52:48 ratio was observed when anisole was employed directly in this process. The reaction of mesitylboronic acid and *p*-bromobenzonitrile afforded the ketimine product in a good yield (entry 5), as opposed to the Suzuki coupling product one would normally expect if this reaction was run in the presence of a base. A 38% yield of the desired ketone product was obtained when electron-poor *p*-nitrophenylboronic acid was employed (entry 6). Unfortunately, none of the desired product was obtained when 2-thienylboronic acid was used, possibly because of the instability of this boronic acid in TFA (entry 7).

Reaction Mechanism. A plausible mechanism for this ketone synthesis is illustrated in Scheme 1. It involves the following key steps: (1) electrophilic metalation of the arene by the Pd(II) catalyst **A**,[15] which generates arylpalladium species **B**;[9,16] (2) coordination of the nitrile to the Pd; (3) carbopalladation of the nitrile to form the imine−Pd(II) complex **C**;[17] (4) protonation of **C** by TFA, which affords the ketimine product **D** and

(11) For a review, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(12) 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.

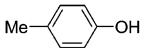
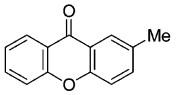
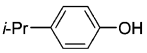
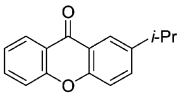
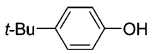
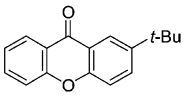
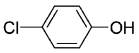
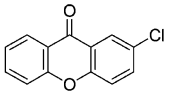
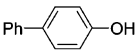
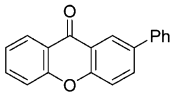
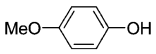
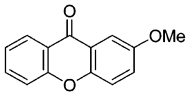
(13) For selective examples, see: (a) Schwaebe, M. K.; Moran, T. J.; Whitten, J. P. *Tetrahedron Lett.* **2005**, *46*, 827. (b) Mulholland, D. A.; Koorbanally, C.; Crouch, N. R.; Sandor, P. *J. Nat. Prod.* **2004**, 67, 1726. (c) Kenji, M.; Yukihiro, A.; Hong, Y.; Kenji, O.; Tetsuro, I.; Toshiyuki, T.; Emi, K.; Munekazu, I.; Yoshinori, N. *Bioorg. Med. Chem.* **2004**, *12*, 5799. (d) Pedro, M.; Cerqueira, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. *Bioorg. Med. Chem.* **2002**, *10*, 3725 and references therein.

(14) For a review of the Pd-catalyzed functionalization of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **2002**, *41*, 4176.

(15) The complex $(DMSO)_2Pd(O_2CCF_3)_2$ has been well characterized; see: Bancroft, D. P.; Cotton, F. A.; Verbruggen, M. *Acta Crystallogr. Sect. C* **1989**, *45*, 1289.

(16) For the formation of arylpalladium complexes by electrophilic palladation of arenes in TFA, see also: (a) Lu, W.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, *586*, 290. (b) Fuchita, Y.; Hiraki, K.; Kamogawa, Y.; Suenaga, M.; Toggoh, K.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1081. (c) Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, *109*, 8109. (d) Clark, F. R. S.; Norman, R. O. C.; Thommas, C. B.; Willson, J. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1289.

TABLE 3. Synthesis of Xanthones (Eq 3)

entry	phenol	product	% yield of step **1**[a,c]	% yield of step **2**[b,c]
1		 **32**	52	95
2		 **33**	55	98
3		 **34**	61	96
4		 **35**	42	98
5		 **36**	0	-
6		 **37**	0	-

[a] Unless indicated otherwise, all reactions were run by employing 2.5 mmol of phenol, 1.0 mmol of 2-fluorobenzonitrile, 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, and the products were purified by column chromatography. [b] The reactions were run by employing 0.25 mmol of ketone and 0.50 mmol of K_2CO_3 in acetone at 50 °C for 2 h. [c] Isolated yields.

regenerates the Pd(II) catalyst. On the other hand, the arylpalladium species **B** can undergo further electrophilic metalation with another molecule of arene and subsequent reductive elimination can produce the biaryl side product sometimes observed in our reactions.

Alternatively, a Pd(II)-catalyzed Houben−Hoesch-like[12] mechanism is also possible as shown in Scheme 2. The key steps here would be: (1) coordination of the nitrile to Pd(II); (2) nucleophilic attack of the arene on the activated nitrile to generate a cationic intermediate; (3) deprotonation to generate imine−Pd(II) complex **C**; and (4) protonation of **C** by TFA, which affords the ketimine product **D** and regenerates the Pd(II) catalyst.

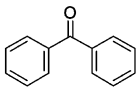
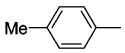
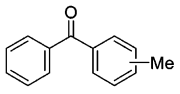
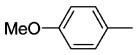
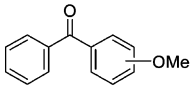
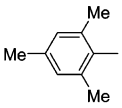
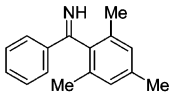
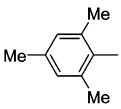
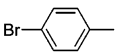
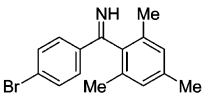
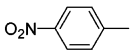
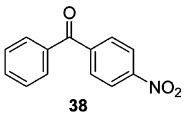
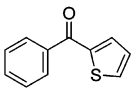
We strongly favor the mechanism in Scheme 1 over the latter mechanism because of the following observations.

(A) The key mechanistic steps proposed in Scheme 1 all have precedent. The electrophilic palladation of arenes under similar conditions is well documented in the literature.[9,16] Our observation of the preference for o- and p-isomers over the m-isomer in the products from toluene or anisole is consistent with electrophilic palladation of the arene[9] (entries 1 and 4, Table 2). Facile carbopalladation of the nitrile should arise from the highly cationic arylpalladium complex **B** generated under our reaction conditions.[17] The carbopalladation step might involve nucleophilic attack of the arylpalladium intermediate **B** on the nitrile, which is consistent with the observation that faster reactions and higher yields are obtained when using the more electron-deficient *p*-BrC_6H_4CN over the more electron-rich *p*-$MeOC_6H_4CN$ (entries 16 and 17, Table 2).

(B) The Pd(II) catalyst plays a unique role in the success of this chemistry. The combination of a very small amount of Pd(II) and TFA should not be enough to induce the Houben−Hoesch reaction given the fact that the pK_a of $RCN{\cdot}H^+$ is around −10 and a stronger acidic media should be necessary to induce a Houben−Hoesch reaction.[12b] Many other strong Lewis acids, including $AlCl_3$ and $SnCl_4$, do not catalyze this transformation as indicated in Table 1. These results strongly suggest that the Houben−Hoesch mechanism in Scheme 2 is not operable in our reaction.

(17) For a recent example involving the insertion of a nitrile into a Pd−C bond, see: Vicente, J.; Abad, J. A.; Lopez-Saez, M.; Jones, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6001.

TABLE 4. Pd-Catalyzed Reaction of Nitriles and Arylboronic Acids (Eq 5)[a]

entry	Ar	R	temp (°C)	product(s)	% yield[b]
1			90	 **2**	71
2			90	 **1a-c**	78[c]
3			100	 **4a,b**	75[d]
4			90	 **12**	83
5			90	 **16**	72
6			90	 **38**	38
7			90	 **39**	0

[a] Unless indicated otherwise, all reactions were run by employing 1.0 mmol of arylboronic acid, 5.0 mmol of nitrile, 0.10 mmol of $Pd(OAc)_2$, and 0.10 mL of DMSO in 2.5 mL of TFA at 90 °C 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 9:3:88. [d] Ortho and para isomers were obtained in a ratio of 8:92.

(C) If a Houben−Hoesch mechanism operates, one would expect the *intramolecular* reactions to be more facile than the *intermolecular* reactions because of easier access to the arene. However, the *intramolecular* variation of the reaction is much more sluggish than the *intermolecular* variation as described earlier. A unique trend for the *intramolecular* variation (seven- over six- and five-membered ring formations) is observed, which is inconsistent with a Houben−Hoesch mechanism. However, the more sluggish formation of five- and six-membered ring ketones over seven-membered ring ketones by *intramolecular* variations of our palladium process may be explained by the mechanism shown in Scheme 1 because it is more difficult 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.

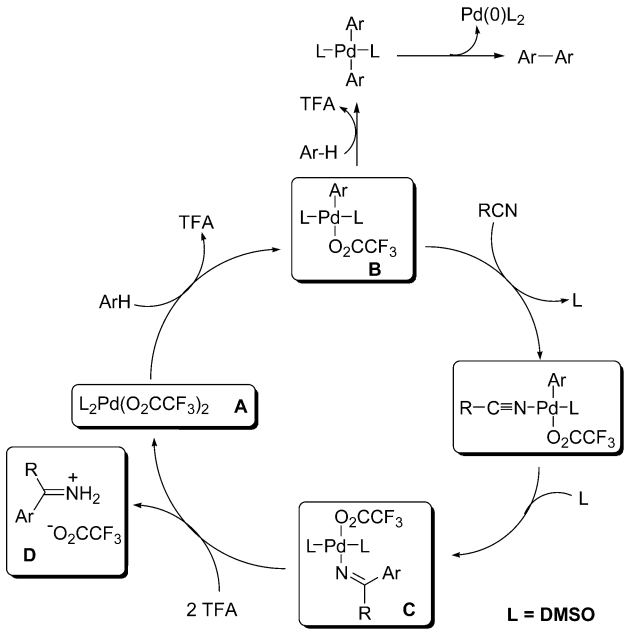
(D) If a Houben−Hoesch mechanism operates, one would expect a sterically hindered arene to encounter difficulties approaching the nitrile, thus leading to more sluggish reactions. However, this contradicts the fact that the sterically hindered mesitylene is apparently much more reactive than toluene in our Pd reactions.

(E) The mechanism in Scheme 1 suggests that the arylpalladium species **B**, if generated by some other means, should also react with nitriles under similar reaction conditions. The success of the reactions between arylboronic acids and nitriles under similar reaction conditions strongly supports this C−H activation mechanism. We believe that transmetalation between the arylboronic acid and the Pd(II) catalyst should generate such arylpalladium species under our reaction conditions (Scheme 3).[18]

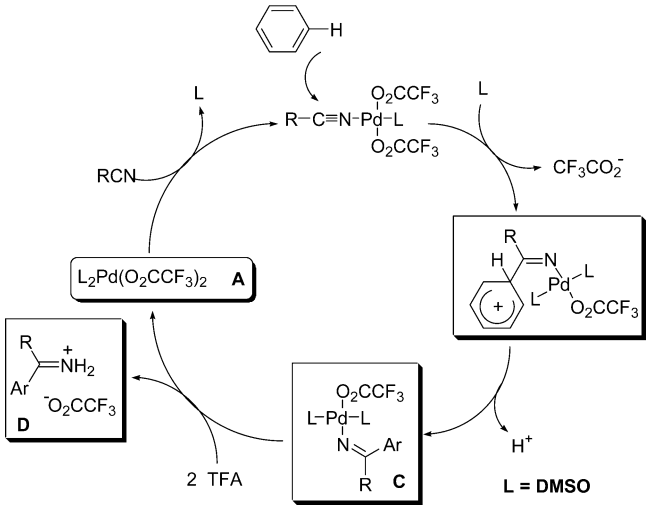
The presence of DMSO greatly increases the yield of the reaction. It is not clear what exactly the role of the DMSO is in

(18) For recent examples involving the transmetalation of arylboronic acids by Pd(II), 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. (c) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259.

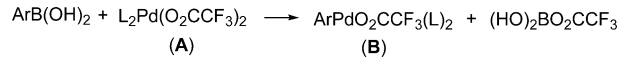
SCHEME 1. Proposed Mechanism



SCHEME 2. Proposed Mechanism



SCHEME 3. Transmetalation



the reaction.[19] DMSO is known to be a unique ligand in many useful Pd(II) transformations.[20] We propose that the DMSO-coordinated complex **A**[15] effectively undergoes electrophilic C−H activation of the arene to generate a DMSO-stabilized arylpalladium intermediate **B**.[21] The coordination of DMSO in **B** might stabilize this Pd(II) intermediate, increasing the lifetime of this reactive species and suppressing its further reaction with another molecule of arene. On the other hand, DMSO might also facilitate the reoxidation of Pd(0) to Pd(II) by air[22] should the Pd(II) ever be reduced to Pd(0) by the arenes.

Conclusions

The unprecedented palladium-catalyzed C−H addition of arenes to nitriles provides moderate to excellent yields of aryl ketones or the corresponding hindered ketimines. The addition of a small amount of DMSO increases the yields dramatically. Both *intermolecular* and *intramolecular* examples of this process are successful. This novel chemistry is believed to involve palladium-catalyzed C−H activation of the simple arene, followed by an unusual carbopalladation of the nitrile. Similar reactions have been successfully developed employing arylboronic acids and nitriles. A concise route to xanthones starting from cheap starting materials has been developed employing this synthetic protocol.

Experimental Section

Intermolecular Reaction of Nitriles and Arenes (Table 2, Entries 1−24). The arene (2.0 mmol), the nitrile (1.0 mmol), $Pd(OAc)_2$ (0.10 mmol), DMSO (0.10 mL), and TFA (2.5 mL) were placed in a 6 dram vial. The vial was sealed, and the contents were stirred and heated at the indicated temperature for 24 h. The ketone products were obtained using the following acid workup procedure, and the ketimine products were obtained by using the following basic workup procedure.

(a) Acidic workup. Water (15 mL) was added to the vial, and the resulting mixture was heated at 70 °C for 2 h. The mixture was then cooled and extracted with diethyl ether three times. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column.

(b) Basic Workup. The reaction mixture was cooled to room temperature, and then K_2CO_3 was added to the vial until no CO_2 bubbles were generated (*Caution! A large amount of CO_2 is generated because of the reaction of TFA and K_2CO_3*). The resulting mixture was extracted with diethyl ether three times. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column.

Intramolecular Reaction of Arylalkanenitriles (Table 2, Entries 25−32). The nitrile (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), DMSO (0.2 mL), and TFA (5.0 mL) were placed in a 6 dram vial. The vial was sealed, and the contents were stirred and heated at the indicated temperature for 24 h. The resulting mixture was then worked up according to the above acidic workup procedure.

General Procedure for the Intramolecular Cyclization Leading to Xanthones (Step 2 in Eq 3). The (2-fluorophenyl)(2-hydroxyphenyl)methanone (0.25 mmol), K_2CO_3 (0.50 mmol), and acetone (15 mL) were placed in a round-bottom flask. The flask was sealed, and the contents were stirred at 50 °C for 2 h. The suspension was then filtered through a pad of Celite and washed with 50 mL of ethyl ether. The filtrate was concentrated to afford the desired xanthones.

Reaction of Nitriles and Arylboronic Acids (Table 4). The nitrile (5.0 mmol), the arylboronic acid (1.0 mmol), $Pd(OAc)_2$ (0.10

(19) Our efforts to isolate the DMSO-coordinated palladium intermediates have been unsuccessful.

(20) For other examples of the importance of DMSO as a solvent or ligand in Pd-catalyzed processes, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (b) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357. (c) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (d) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (e) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (f) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

(21) DMSO-coordinated arylpalladium complexes have been characterized. See: Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323.

(22) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400 and references therein. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (c) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.

mmol), DMSO (0.10 mL), and TFA (2.5 mL) were placed in a 6 dram vial. The vial was sealed, and the contents were stirred and heated at 90 °C for 24 h. The resulting mixture was then worked up according to the above acidic or basic workup procedures.

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Supporting Information Available: Experimental details and product characterization data and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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