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Org. Lett., **2008**, 10 (20), 4689-4691• DOI: 10.1021/ol802070d • Publication Date (Web): 23 September 2008

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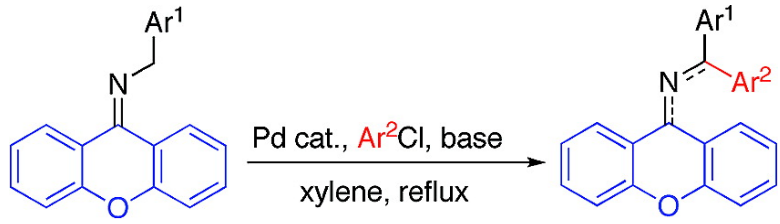

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ORGANIC LETTERS

2008
Vol. 10, No. 20
4689−4691

Palladium-Catalyzed Benzylic Arylation of *N*-Benzylxanthone Imine

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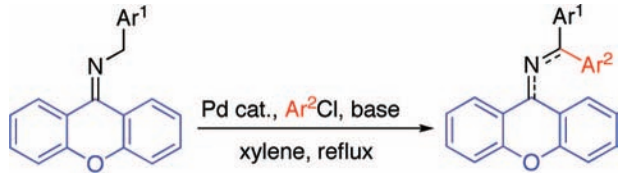
Received September 4, 2008

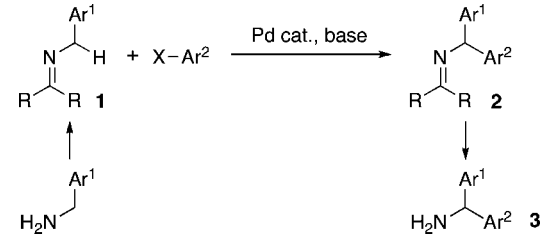
ABSTRACT



The direct benzylic arylation of *N*-benzylxanthone imine with aryl chloride proceeds under palladium catalysis, yielding the corresponding coupling product. The product is readily transformed to benzhydrylamine. Taking into consideration that the imine is readily available from benzylic amine, the overall transformation represents a formal cross-coupling reaction of aryl halide with α-aminobenzyl metal.

Transition-metal-catalyzed direct arylation at sp^3-hybridized carbons having acidic hydrogens has been emerging as one of the recent remarkable advances in cross-coupling reaction.[1−5] In light of the importance of this transformation, further progress should be made. We thus envisioned a new application of the direct arylation, specifically, intermolecular benzylic arylation of *N*-benzyl imines (Scheme 1). Imine **1**, readily prepared from benzylamine and ketone, has benzylic hydrogens of high acidity.[6] Palladium-catalyzed arylation of **1** with aryl halide would afford **2**. Hydrolysis of **2** should finally yield **3**. The overall transformation represents a formal cross-coupling reaction of aryl halide with an α-aminobenzyl metal.

Scheme 1. Concept of Benzylic Arylation of Benzylamine



Treatment of *N*-benzylxanthone imine (**1a**) with chlorobenzene in the presence of cesium hydroxide and a palladium catalyst afforded the corresponding coupling product **2a** and its isomer **2a′** in a ratio of 7:3 (Scheme 2).

(1) α-Arylation of carbonyls: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383. (c) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (d) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465–475. (e) Satoh, T.; Inoh, J.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239–2246. γ-Arylations of α,β-unsaturated carbonyl compounds: (f) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206. (g) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582.

(2) Intermolecular arylation at the activated benzylic or allylic positions: (a) Inoh, J.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676. (b) Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.; Pivsa-Art, S.; Satoh, T.; Nomura, M. *Chem. Eur. J.* **2000**, *6*, 3426–3433. (c) Dyker, G.; Heiermann, J.; Miura, M. *Adv. Synth. Catal.* **2003**, *345*, 1127–1132. (d) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373–2375. (e) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641–1643. (f) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267.

(3) Intramolecular arylative cyclization at the benzylic positions: (a) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462–3465. (b) Ren, H.; Li, Z.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 416–433. (c) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289–2292. (d) Hu, Q.-S. *Synlett* **2007**, 1331–1345. (e) Catellani, M.; Motti, E.; Ghelli, S. *Chem. Commun.* **2000**, 2003–2004. (f) Salcedo, A.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 3600–3603.

(4) Arylation of *N*-*tert*-butylhydrazones as an acyl anion equivalent: Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 14800–14801.

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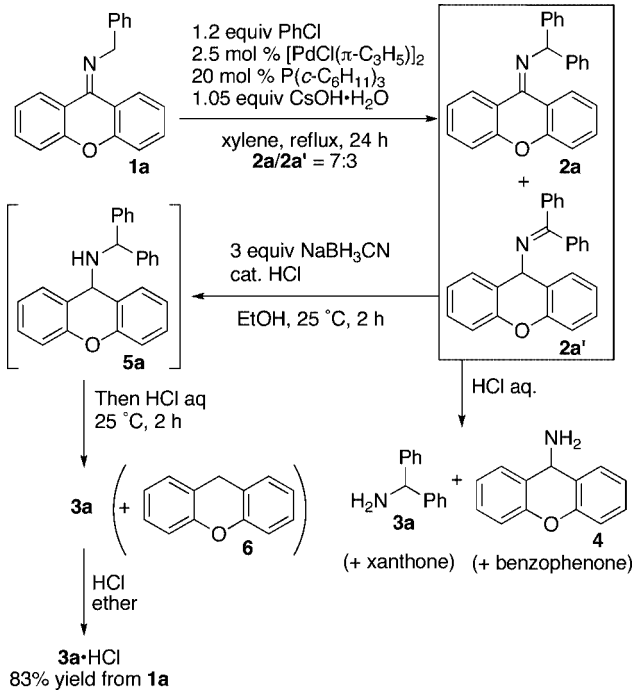
Scheme 2. Phenylation of *N*-Benzylxanthone Imine

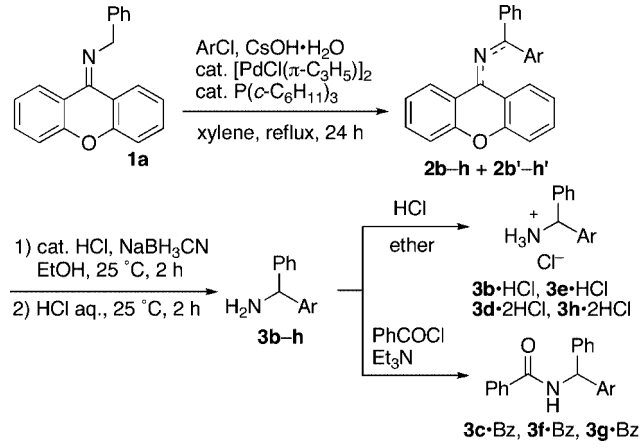


Facile deprotonation of initially formed **2a** at the benzylic position took place in situ, which led to the formation of a mixture of **2a** and **2a′**. Hydrolysis of the mixture of **2a** and **2a′** afforded a mixture of desired **3a** and undesired amine **4**. Hence, the mixture of imines **2a** and **2a′** was reduced with sodium cyanoborohydride to afford **5a**, which was then hydrolyzed under acidic conditions to provide benzhydrylamine (**3a**) and **6**.[7] Oxygen-bridged xanthone is a suitable precursor of *N*-benzyl imine **1** because the exclusive formation of highly delocalized and thus stable 9-xanthenyl cation allowed the regioselective hydrolysis of **5a**, producing **3a**. After acid/base extraction in a separatory funnel, the product **3a** was isolated as its hydrochloride salt **3a**•HCl in 83% overall yield. Notably, each step was high yielding, and no chromatographic purification was needed during the process.

Bromobenzene reacted with **1a** as smoothly as chlorobenzene to yield **3a**•HCl in 80% yield. On the other hand, the use of iodobenzene resulted in the formation of a complex mixture. When other trialkylphosphines, such as PMe_3, P(*c*-$C_5H_9)_3$, P(*n*-Bu)$_3$, and P(*t*-Bu)$_3$, were used instead of P(*c*-$C_6H_{11})_3$, the reaction was sluggish (30−50% combined yields of **2a** and **2a′**) and a mixture of unidentified byproducts was obtained. Use of triarylphosphines in the arylation of **1a** with bromobenzene also led to low combined yields of **2a** and **2a′** (30−50%), along with byproducts and recovered **1a** (10−30%). The 1:4 molar ratio of Pd/P(*c*-$C_6H_{11})_3$ led to the highest catalytic activity. The combined yield of **2a** and **2a′** was less than 20% when a Pd/P(*c*-$C_6H_{11})_3$ ratio was 1:3. As the precursor of the catalyst, other palladium complexes, such as Pd(acac)$_2$, $PdCl_2(PhCN)_2$, and Pd(OAc)$_2$, showed comparable yet slightly lower catalytic activity. A temperature as high as 140 °C was essential: a similar reaction in refluxing toluene failed to afford **2a** and **2a′**. The choice of base is quite important, and the use of KOH, *t*-BuOK, and Cs_2CO_3 gave only traces of **2a** and **2a′**.

A variety of aryl chlorides participated in the reaction (Table 1). Both electron-rich (entries 1−3) and electron-deficient (entry 6) aryl chlorides reacted smoothly to yield the corresponding benzhydrylamine derivatives in good yields. 2-Chlorotoluene underwent the reaction similarly, irrespective of the steric hindrance of the 2-methyl group (entry 4). The reaction of 4-chlorostyrene provided the desired product **3f**•Bz in moderate yield (entry 5), although the aryl chloride can alternatively undergo self-contained Mizoroki−Heck reaction, forming oligo(4-phenylenevi-

Table 1. Arylation of **1a** and Isolation of Benzhydrylamine Derivatives[a]



entry	Ar-Cl	product	overall yield (%)
1	4-MeC_6H_4Cl	**3b**•HCl	73
2	4-MeOC_6H_4Cl	**3c**•Bz[b]	75
3	4-$Me_2NC_6H_4$Cl	**3d**•2HCl	82
4	2-MeC_6H_4Cl	**3e**•HCl	73
5[c]	4-CH_2=CHC_6H_4Cl	**3f**•Bz[b]	47
6	4-Me_2NC(=O)C_6H_4Cl	**3g**•Bz[b]	71
7	2-chloropyridine	**3h**•2HCl	80

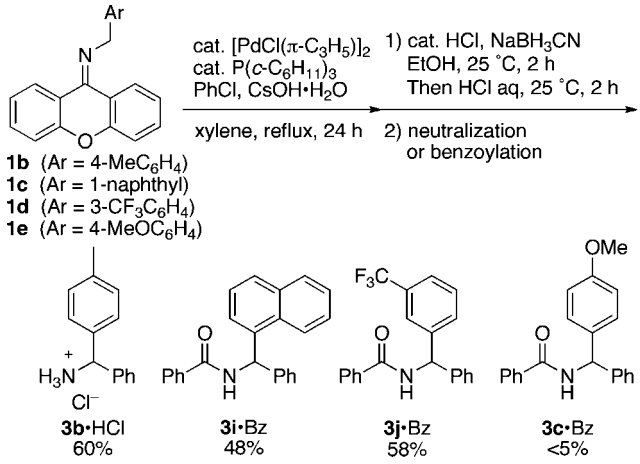
[a] The reaction conditions are the same as shown in Scheme 2. [b] Instead of treatment with HCl, **3c**, **3f**, and **3g** were benzoylated for chromatographic isolation. [c] Formic acid was used instead of hydrochloric acid for the removal of the xanthenyl group.

(5) Other C(sp^3)-H arylation involving cleavage of less acidic hydrogens: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657–3659. (c) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391–3394. (d) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (e) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. (f) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (g) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221. (h) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571. (i) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759–1762.

(6) The pK_a value of the benzylic protons of Ph_2C=NCH_2Ph was reported to be 24.3 in dimethyl sulfoxide at 25 °C. See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

nylene).[8] Installation of heteroarene at the benzylic position was satisfactory (entry 7). Not only *N*-benzyl imine **1a** but also other *N*-arylmethyl imines **1b**−**d** were arylated (Scheme 3). However, **1e** having an electron-donating group suffered

Scheme 3. Scope of *N*-(Arylmethyl)xanthone Imines



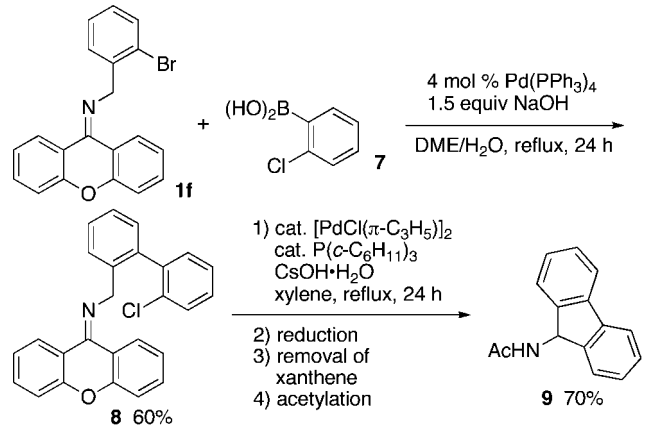
from very low conversion, probably due to the slower deprotonation.

The Suzuki−Miyaura cross-coupling reaction of **1f** with arylboronic acid **7** afforded biaryl **8** in high yield (Scheme 4). The intramolecular benzylic arylation of **8** created fluorenylamine skeleton, eventually leading to the formation

(7) Xanthene (**6**) was formed through the reduction of xanthenyl cation with the remaining sodium cyanoborohydride in the same pot. No xanthenyl alcohol, which could be generated by the nucleophilic attack of hydroxide to the cation, was observed.

(8) Heitz, W.; Brugging, W.; Freund, L.; Gailberger, M.; Greiner, A.; Jung, H.; Kampschulte, U.; Niessner, N.; Osan, F.; Schmidt, H. W.; Wicker, M. *Makromol. Chem.* **1988**, *189*, 119–127.

Scheme 4. Synthesis of Fluorenylamine



of **9**. The transformation from **1f** and **7** to **9** thus offers a new route to 9-fluorenylamine derivatives.

By converting benzylamine to *N*-benzylxanthone imine, metalation at the benzylic position becomes facile. The present method provides a new concept for transition-metal-catalyzed functionalization of aminated carbons.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research and GCOE Research from MEXT and JSPS. T.N. acknowledges JSPS for financial support.

Supporting Information Available: Experimental procedure and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802070D