ORGANIC LETTERS

2007
Vol. 9, No. 12
2373−2375

Palladium-Catalyzed Direct Arylation of Aryl(azaaryl)methanes with Aryl Halides Providing Triarylmethanes

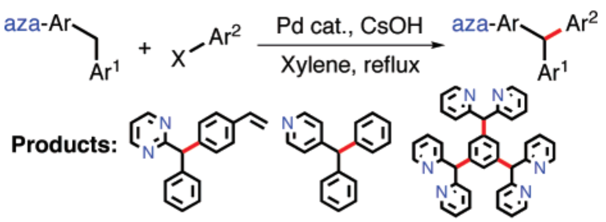
Takashi Niwa, Hideki Yorimitsu,* and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

yori@orgrxn.mbox.media.kyoto-u.ac.jp; oshima@orgrxn.mbox.media.kyoto-u.ac.jp

Received April 4, 2007

ABSTRACT



Direct arylation of aryl(azaaryl)methanes with aryl halides takes place at the benzylic position in the presence of a hydroxide base under palladium catalysis to yield triarylmethanes.

Transition-metal-catalyzed cross-coupling reactions are among the most important reactions in organic synthesis.[1] The conventional cross-coupling procedure requires preparation of organometallic reagents in advance of the reaction. Recent progress in this area has allowed for direct use of organic compounds bearing no metallic atoms as nucleophilic coupling partners. Among them, direct conversion of sp^2C-H bonds into sp^2C-sp^2C bonds of biaryls is widely investigated.[2−5] On the other hand, examples of direct arylation of sp^3C-H bonds are relatively less pronounced.[6−14] Here we report a new repertoire of direct arylation of sp^3C-H bonds, direct arylation of diarylmethanes providing triarylmethanes.

---

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (c) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Springer: Berlin, 2002. (d) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

(2) (a) Dyker, G., Ed. *Handbook of C−H Transformations*; Wiley−VCH: Weinheim, Germany, 2005. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101. (d) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241. (e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200−205. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238.

(3) Direct *ortho*-arylation of phenols: (a) Satoh, T.; Inoh, J.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239−2246. (b) Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5167−5170 and refs cited therein.

(4) Direct arylation of electron-rich arenes: Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748−11749 and refs cited therein. Also note that a large part of ref 2 describes this type of transformation.

(5) Direct arylation of electron-deficient arenes: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496−16497. (b) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8755. (c) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Baidossi, M.; Ponde, D. E.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1809−1812. (d) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020−18021.

(6) 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.

(7) Chelation-assisted direct arylations of sp^3C-H bonds via Pd(IV) intermediates: (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.

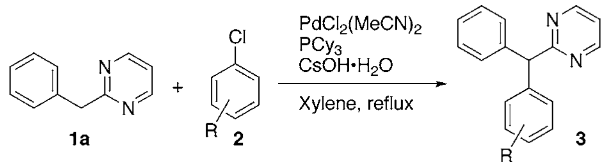
(8) Chelation-assisted oxidative alkylation of sp^3C-H bonds with alkylboron reagents: Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634−12635.

(9) Palladium-catalyzed cross-coupling reactions of 2,4,6-tri(*tert*-butyl)-bromobenzene with arylboronic acids resulting in sp^3C-H bond arylation: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

10.1021/ol0708119 CCC: $37.00

We focused on aryl(azaaryl)methanes as substrates to achieve our project. On the basis of the structural similarity between imines and azaarenes as well as the fact that direct α-arylation of carbonyl compounds proceeds efficiently,[6] it would be feasible that aryl(azaaryl)methanes undergo direct arylation at the benzylic position. This was indeed the case, and treatment of chlorobenzene (**2a**) with 2-benzylpyrimidine (**1a**) in the presence of cesium hydroxide[15] under $PdCl_2$/tricyclohexylphosphine (PCy_3) catalysis[16] in refluxing xylene provided 2-(diphenylmethyl)pyrimidine (**3a**) in high yield (Table 1, entry 1). A plausible reaction mechanism includes oxidative addition, deprotonation of **1a** with cesium hydroxide, transmetalation of phenyl(2-pyrimidyl)methylcesium with an arylpalladium chloride (or hydroxide) intermediate, and reductive elimination.

Table 1. Pd-Catalyzed Arylation of 2-Benzylpyrimidine[a]



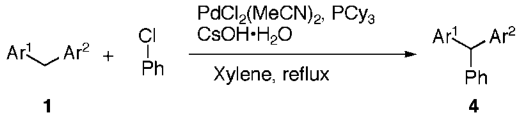
entry	R	**2**	time/h	**3**	yield/%
1	H	**2a**	3	**3a**	86
2	(1-naphthyl)	**2b**	2	**3b**	96
3	2-Me	**2c**	2	**3c**	94
4	4-OMe	**2d**	8	**3d**	86
5	4-NMe_2	**2e**	18	**3e**	63[b]
6	4-$CH{=}CH_2$	**2f**	5	**3f**	62
7	4-$CO_2{}^tBu$	**2g**	24	**3g**	29[c]

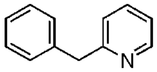
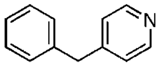
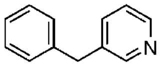
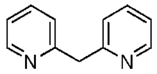
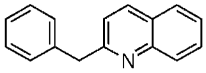
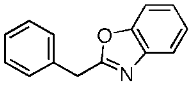
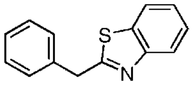
[a] A mixture of **1a** (0.50 mmol), **2** (0.60 mmol), $PdCl_2(MeCN)_2$ (0.025 mmol), PCy_3 (0.075 mmol), and $CsOH{\cdot}H_2O$ (1.0 mmol) was boiled in xylene (1.0 mL). [b] $CsOH{\cdot}H_2O$ (1.5 mmol) was used. [c] Di(*tert*-butyl)(2-phenylphenyl)phosphine was used. 30% of **1a** was recovered. *t*-Butyl benzoate (4%) and **2g** (6%) were detected. The yields are based on ^1H NMR.

A variety of aryl chlorides underwent the arylation reaction. Aryl chloride **2c** having a methyl group at the 2 position participated in the reaction similarly (entry 3). Electron-rich 4-chloroanisole (**2d**) reacted with the aid of PCy_3 to yield the corresponding triarylmethane in excellent yield (entry 4). The reaction of 4-chloro-*N*,*N*-dimethylaniline (**2e**) required prolonged reaction time and an excess of the base to proceed to completion (entry 5). The reaction of 4-chlorostyrene (**2f**) provided the desired product **3f** (entry 6), although **2f** can alternatively undergo self-contained Mizoroki–Heck reactions which lead to oligo(4-phenylenevinylene).[17] Unfortunately, attempted reactions of electron-deficient **2g** resulted in incomplete conversion. The highest yield was obtained when di(*tert*-butyl)(2-phenylphenyl)phosphine was used as a ligand (entry 7). The reaction of **2g** would proceed via [4-(*tert*-butoxycarbonyl)phenyl][phenyl(pyrimidyl)methyl]palladium, which would suffer from slow reductive elimination because of the electron-withdrawing nature of the carbonyl group. In addition, cleavage of the ester bond was observed.

Other aryl(azaaryl)methanes were subjected to the arylation reaction (Table 2). The reaction of 2- or 4-benzylpyridine proceeded smoothly (entries 1 and 2). It is worth noting that we could obtain tetraarylmethane, triphenyl(4-pyridyl)-

Table 2. Pd-Catalyzed Phenylation of Aryl(azaaryl)methanes[a]



entry	**1**	time	**4**	yield /%
1	 **1b**	18 h	**4a**	87
2	 **1c**	14 h	**4b**	92[b]
3	 **1d**	6 h	**4c**	<1
4	 **1e**	6 h	**4d**	91
5	 **1f**	3 h	**4e**	91[c]
6	 **1g**	19 h	**4f**	71[c]
7	 **1h**	17 h	**4g**	82[c]

[a] A mixture of **1** (0.50 mmol), chlorobenzene (0.60 mmol), $PdCl_2(MeCN)_2$ (0.025 mmol), PCy_3 (0.075 mmol), and $CsOH{\cdot}H_2O$ (1.0 mmol) was boiled in xylene (1.0 mL). [b] Triphenyl(4-pyridyl)methane (8%) was obtained. [c] Iodobenzene and KOH were used instead of chlorobenzene and $CsOH{\cdot}H_2O$, respectively.

---

(10) Direct arylations of α,*β*-unsaturated carbonyl compounds at the *γ*-position and of 4-alkylnitrobenzenes were reported. In the latter report, an example of direct arylation of 4-methylpyrimidine yielding 4-(diarylmethyl)pyrimidine was reported: (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206. (b) Inoh, J.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676.

(11) Ruthenium-catalyzed arylation: Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221.

(12) Copper-catalyzed oxidative functionalization: Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969.

(13) Pd-catalyzed arylation of cyclopentadienes: (a) Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.; Pivsa-Art, S.; Satoh, T.; Nomura, M. *Chem.–Eur. J.* **2000**, *6*, 3426–3433. (b) Dyker, G.; Heiermann, J.; Miura, M. *Adv. Synth. Catal.* **2003**, *345*, 1127–1132.

(14) Pd-catalyzed intramolecular arylative cyclization: (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.

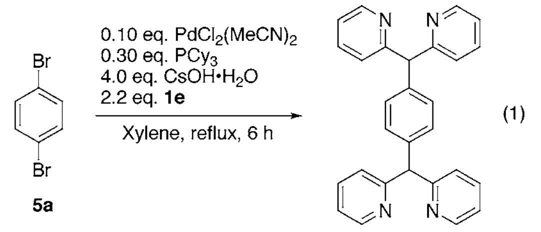
(15) The effect of base is summarized in the Supporting Information.

(16) The result of the ligand screening is tabulated in the Supporting Information.

(17) 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.

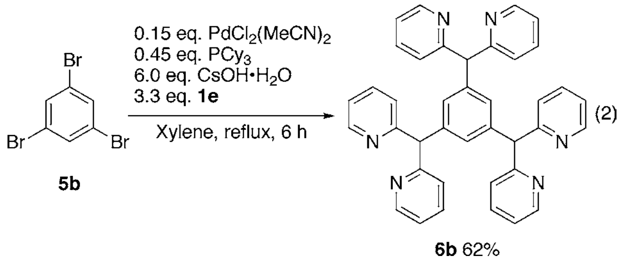
methane, in 8% yield, in the reaction of **1c**. Further optimization of the reaction conditions will allow us to prepare tetraarylmethane through a cross-coupling methodology.[18] Unfortunately, 3-benzylpyridine (**1d**) resisted the reaction (entry 3). Di(2-pyridyl)methane (**1e**) and 2-benzylquinoline (**1f**) readily reacted to proceed to completion within 6 h (entries 4 and 5). The reactions of 2-benzylbenzoxazole and -benzothiazole were successful by using KOH[19] as a base, albeit with prolonged reaction times (entries 6 and 7). The reactions of 2-picoline and of diphenylmethane resulted in no conversion. The acidity of the protons to be substituted by an aryl group is probably a decisive factor for the success of the reaction. The pK_a values of the acidic protons of **1b**, **1c**, **1d**, diphenylmethane, and water in DMSO were reported to be 28.2, 26.7, 30.15, 32.2, and 32, respectively.[20] A hydroxide ion would fail to deprotonate **1d** and diphenylmethane under the reaction conditions. An attempted reaction of 4-benzylbenzonitrile resulted in hydrolysis of the nitrile group to yield 4-benzylbenzoic acid (83%).

The present method is concise and reliable enough to offer a straightforward route to highly azaarylated structures in one pot. The reactions of 1,4-dibromobenzene (**5a**) and 1,3,5-tribromobenzene (**5b**) with **1e** afforded new multicoordinating molecular structures **6a** and **6b** (eqs 1 and 2). They are potentially useful in constructing supramolecular architecture not only as they are[21] but also as their anionic forms upon deprotonation of the methyne protons.[22]



5a

6a 70%



5b

6b 62%

Azaarenes can find many applications in various fields of chemical science. We have found a new method to synthesize triarylmethanes[23] having at least one azaaryl group through the palladium-catalyzed direct benzylic arylation of aryl(azaaryl)methanes.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research and COE Research from MEXT and JSPS.

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

OL0708119

---

[18] The Friedel–Crafts arylation reaction of triarylmethanols or their analogues with aniline is the most popular method. (a) Zimmermann, T. J.; Müller, T. J. J. *Synthesis* **2002**, 1157–1162. (b) Su, D.; Menger, F. M. *Tetrahedron Lett.* **1997**, *38*, 1485–1488. (c) Grimm, M.; Kirste, B.; Kurreck, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1097–1098.

[19] In the case that $CsOH{\cdot}H_2O$ was used, we obtained moderate yields of **4f** and **4g** with contamination by byproducts. The byproducts were likely formed by ring opening of the oxazole and thiazole units.

[20] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

[21] Use of di(2-pyridyl)methane: Steel, P. J.; Sumby, C. J. *Dalton* **2003**, 4505–4515 and refs cited therein.

[22] Gornitzka, H.; Catherine, H.; Bertrand, G.; Pfeiffer, M.; Stalke, D. *Organometallics* **2000**, *19*, 112–114 and refs cited therein.

[23] Triarylmethanes are typically prepared by (1) addition of aryl Grignard reagents to carbonyls yielding triarylmethanols and subsequent reduction of the hydroxy group under acidic conditions or (2) Friedel–Crafts arylaton of diarylmethanols. Muthyala, R.; Katritzky, A. R.; Lan, X. *Dyes Pigm.* **1994**, *25*, 303–324 and refs cited therein.