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Palladium-Catalyzed Direct Alkynylation of C−H Bonds in Benzenes

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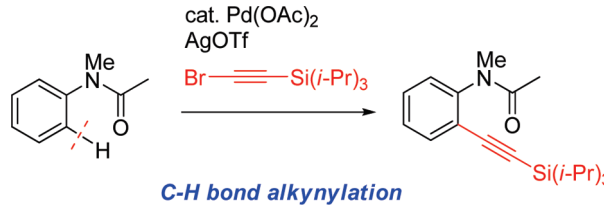
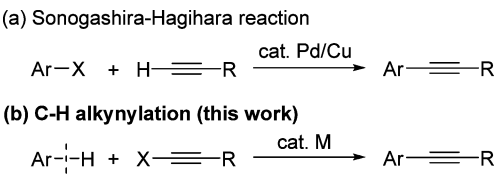
ABSTRACT



Palladium-catalyzed *ortho*-alkynylation of aromatic C−H bonds in anilides is described. Preliminary mechanistic studies reveal that electrophilic palladation is involved. Synthetic elaborations of alkynylated products are also demonstrated.

Alkynylarenes constitute an important class of substructures due to their utility as synthetic intermediates and as versatile structural motifs in supramolecular and materials chemistry. The most frequently utilized method for the preparation of alkynylarenes is the Sonogashira−Hagihara reaction, in which C(aryl)−C(sp) bonds are constructed by the palladium/copper-catalyzed cross-coupling of aryl halides and terminal alkynes (Scheme 1a).[1] On the other hand, catalytic aromatic C−H bond functionalization using a readily available alkynyl source (Scheme 1b) should offer a complementary and powerful approach, especially in the case of the synthesis of densely functionalized alkynylarenes. Nevertheless, to the best of our knowledge, only a handful of reports[2] have mentioned such an approach despite the recent explosive advancement in C−H bond functionalization reactions.[3]

Scheme 1. Alkynylation of Benzene Derivatives



Yamaguchi reported a pioneering example of direct alkynylation using $GaCl_3$ as a catalyst, although the substrates were limited to lithium phenoxides and anilides.[2a,b] Transition-metal catalysis also is a promising approach, but it has

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(1) Selected reviews: (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874. (d) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (e) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954.

(2) (a) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528. (b) Amemiya, R.; Fujii, A.; Yamaguchi, M. *Tetrahedron Lett.* **2004**, *45*, 4333. (c) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (d) Gu, Y.; Wang, X.-m. *Tetrahedron Lett.* **2009**, *50*, 763.

(3) Selected recent reviews: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (d) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (h) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, 24. (i) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (j) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (k) *Topics in Organometallic Chemistry*; Chatani, N., Ed.; Springer-Verlag: Berlin, 2007; Vol. 24.

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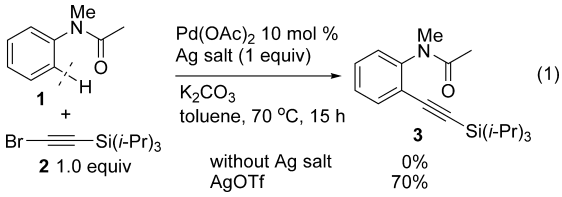
been successful only with a limited class of electron-rich heterocycles (i.e., indolizines[2c] and indoles[2d]). Herein, we report the palladium-catalyzed direct alkynylation of benzene derivatives with the aid of chelation assistance. Preliminary mechanistic studies indicated that alkynylation would proceed through a pathway that is distinctly different from that reported for heterocycles.

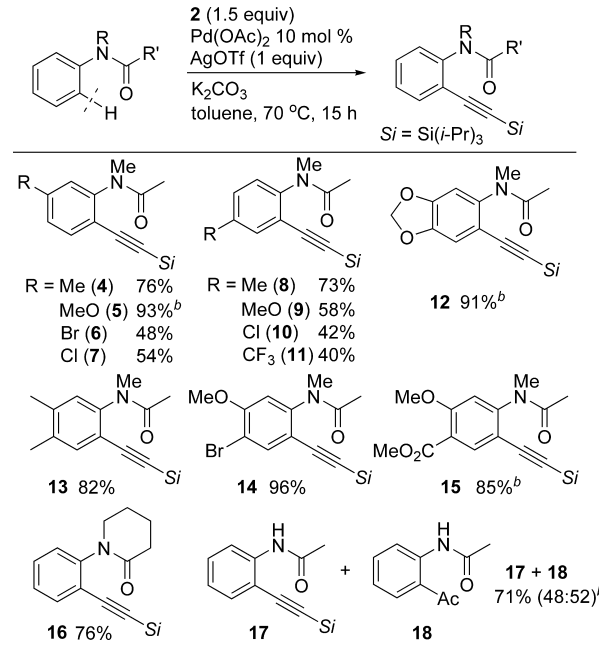
At the outset of our investigation, we observed that the catalytic conditions developed for heterocycles (10 mol % of $PdCl_2(PPh_3)_2$, KOAc)[2c,d] were inapplicable to the direct alkynylation of anilide **1** with bromoalkyne **2**. We reasoned that the electrophilicity of the postulated alkynylpalladium species,[2c] generated by oxidative addition of **2**, would be insufficient to react with anilide **1**, which is a considerably poorer π-nucleophile than either indolines or indoles. We postulated that the addition of silver salts would increase the electrophilicity of the palladium species by sequestering the bromide ligand, thus accelerating the palladation of **1**, as is frequently observed in other C−H bond functionalization reactions.[4] Indeed, the palladium-catalyzed reaction of anilide **1** with bromoalkyne **2** furnished the expected *ortho*-alkynylated product **3** in the presence of silver salts. After a series of optimization studies,[5] the yield was finally improved to 70% (eq 1). Further investigation revealed that the choice of the substituent on the alkynylating agent exerted a critical impact on the reaction outcome. Replacing the triisopropylsilyl group in **2** with a *tert*-butyldimethylsilyl group led to a significant reduction in yield (39%),[6] while bromoalkynes bearing other substituents, such as Ph, hexyl, and ester, did not form the corresponding products, due in part to their instability under these conditions. Although the scope regarding the bromoalkyne component proved to be limited, this does not deteriorate the utility of the reaction severely, since the triisopropylsilyl group at the alkyne terminus can readily be deprotected and elaborated (vide infra).



Under the catalytic conditions established above, we next explored the scope of anilides. Electron-rich substrates bearing alkyl or methoxy groups furnished the corresponding alkynylarenes in good yields (**4**, **5**, **8**, **9**, **12**, and **13** in Scheme 2) and formed no dialkynylated products.[7] On the other hand, diminished but still synthetically acceptable yields were obtained with anilides bearing electron-withdrawing groups (**6**, **7**, **10**, and **11**). These results agreed with the general reactivity trend observed in C−H functionalization reactions involving electrophilic palladation.[8] The negative effect of electron-withdrawing groups was offset when such substrates were accompanied by an electron-donating group (**14** and **15**). These examples highlight the synthetic advantage of the direct alkynylation method compared with the Sonogashira−Hagihara reaction, in which the preparation of complicated aryl halides is required. Regarding the directing groups, cyclic amides (**16**) and acetanilide with an unprotected N−H group also efficiently underwent alkynylation,[9] although under the catalytic conditions in the latter case, the primary product **17** was susceptible to hydrolytic cleavage of a C−Si bond to afford **18**.[10]

To probe the nature of the C−H bond cleavage, we next investigated the kinetic isotope effect of this direct alkynylation reaction (Scheme 3). Both intra- and intermolecular

Scheme 2. Pd-Catalyzed Direct Alkynylation of Aromatic C−H Bonds with Bromoalkyne **2**[a]



[a] Reaction conditions: anilide (0.5 mmol), bromoalkyne **2** (0.75 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOTf (0.5 mmol), and K_2CO_3 (0.50 mmol) in toluene (1.0 mL) at 70 °C, 15 h. Isolated yields based on anilides are shown. [b] Run at 50 °C.

(4) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926, and references therein.

(5) Notes: (a) Other palladium sources tested: $PdCl_2$ (trace), $Pd_2(dba)_3$•$CHCl_3$ (67%), $Pd(OCOCF_3)_2$ (58%), $Pd(OAc)_2$/2PPh_3 (53%) . (b) Other silver salts tested: $AgBF_4$ (57%), $AgSbF_6$ (13%), AgOAc (0%), Ag_2CO_3 (0%). (c) Other bases tested: KOAc (trace), K_3PO_4 (38%), Cs_2CO_3 (trace), Et_3N (39%). (d) The corresponding chloro- and iodoalkynes afforded **3** in 2% and 48% yield, respectively.

(6) Superior performance of Si(*i*-Pr)$_3$-protected alkynes was also reported in other catalysis: (a) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919. (b) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (c) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (d) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-i. *J. Am. Chem. Soc.* **2009**, *131*, 3176.

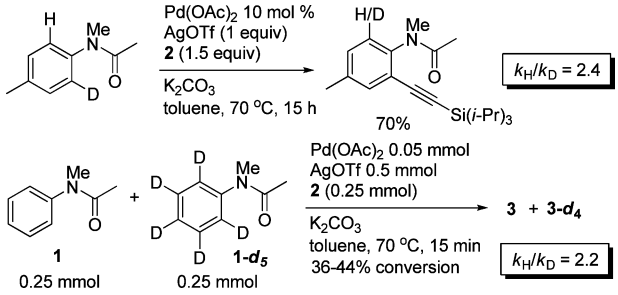
(7) Difunctionalization is often a problem in chelation-assisted direct functionalization of C−H. For example, see: Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(8) Selected examples: (a) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (b) Shi, Z.-J.; Li, B.-J.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (c) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.

(9) *N*,*N*-Dimethylaminomethyl, 2-pyridyl, *N*,*N*-dimethylaminocarbonyl, and acetoxy groups did not serve as directing groups.

(10) Compound **17** was converted into **18** in the presence of TfOH. See the Supporting Information for details.

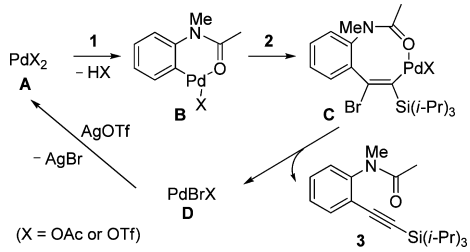
Scheme 3. Kinetic Isotope Effects



competitive experiments indicated that the cleavage of an ortho C−H bond was involved in a turnover-limiting step ($k_H/k_D > 2$). These results strikingly contrast with the fact that only a minor kinetic isotope effect ($k_H/k_D = 1.15$) was observed for the C−H alkynylation of heterocycles.[2c]

As is the case for heterocycles,[2c] we initially envisioned that the reaction proceeds through an electrophilic substitution by an alkynylpalladium species, which is generated by the oxidative addition of **2** to the in situ generated Pd(0) species. However, on the basis of the observed primary kinetic isotope effect, we propose that the direct alkynylation proceeds via the mechanism depicted in Scheme 4. Electro-

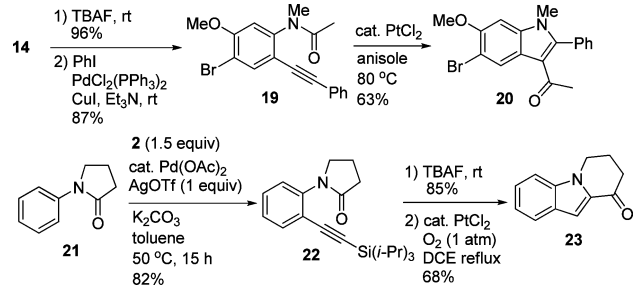
Scheme 4. Plausible Mechanism



philic *ortho*-metalation of anilide **1** by $Pd(OAc)_2$ initially forms palladacycle **B**, which subsequently adds across bromoalkyne **2** to afford vinylpalladium intermediate **C**.[11] β-Bromo elimination from **C**[12] finally provides alkynylation product **3** and bromopalladium salt **D**.[13] An exchange of the bromide ligand in **D** for a less coordinating OTf anion generates the PdX_2 (X = OAc or OTf), which is capable of undergoing electrophilic metalation of **1**. It is important to note that a significant primary kinetic isotope effect was observed in other C−H bond functionalization reactions that are proposed to proceed via the intermediates similar to **B**.[8b,14] In addition, the stoichiometric reaction of an acetanilide-derived palladacycle similar to **B** with **2** afforded **17** in 65% yield (see the Supporting Information for details). This observation further supports the intermediacy of palladacycle **B**.

The synthetic utility of the alkynylated products is worth mentioning (Scheme 5). The triisopropylsilyl groups in the

Scheme 5. Synthetic Applications



products obtained by our method can be removed under mild conditions to liberate terminal alkynes, which are amenable to further structural modification, i.e., by the Sonogashira−Hagihara reaction (**14** → **19** in Scheme 5). In addition, *ortho*-alkynylated anilides serve as valuable precursors for indole-based heterocycles (**19** → **20**,[15a] **22** → **23**[15b]).

In conclusion, we have developed a new method that allows the alkynylation of *ortho* C−H bonds of anilides. The reaction complements the conventional Sonogashira−Hagihara reaction in that C−H bonds in complex arene substrates can be directly alkynylated using readily available bromoalkyne **2**. Efforts are underway to develop an additional method for C−H bond alkynylation and other less explored functionalizations.

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Supporting Information Available: Detailed experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) A related stoichiometric reaction: Dupont, J.; Pfeffer, M.; Daran, J.-C.; Gouteron, J. *J. Chem. Soc., Dalton Trans.* **1988**, 2421. (b) The reaction of palladacycle, similar to **B**, with alkyl halides: Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759.

(12) A related stoichiometric reaction: Zanini, M. L.; Meneghetti, M. R.; Ebeling, G.; Livotto, P. R.; Rominger, F.; Dupont, J. *Polyhedron* **2003**, *22*, 1665.

(13) A Pd^{II}/Pd^{IV} cycle via oxidative addition of **2** onto **B** might be possible.

(14) (a) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (b) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. See also: (c) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

(15) (a) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (b) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346.