

Palladium-Catalyzed Direct *ortho*-Alkynylation of Aromatic Carboxylic Acid Derivatives

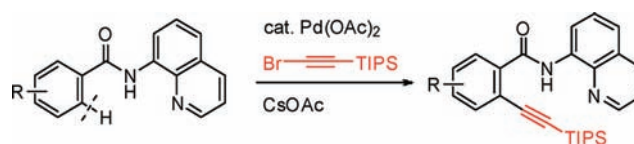
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Received November 19, 2011

ABSTRACT



The palladium-catalyzed direct alkynylation of C–H bonds in aromatic carboxylic acid derivatives is described. The use of 8-aminoquinoline as a directing group facilitates the alkynylation of an electronically diverse range of C(sp²)–H bonds.

Alkynes are ubiquitous targets in many aspects of organic chemistry, for example, as synthetic intermediates¹ or unique linear structural motifs.² The development of effective methods for the incorporation of this functional group is an important area of research. Although the Sonogashira–Hagihara reaction³ is the traditional method of choice, the direct alkynylation of C–H bonds has

recently emerged as a straightforward alternative, especially for the construction of C(sp²)–C(sp) bonds.^{4,5} To date, the direct alkynylation of a wide range of heteroarenes, such as azoles and thiophenes, have been reported.⁶ In contrast, the direct alkynylation of benzene derivatives

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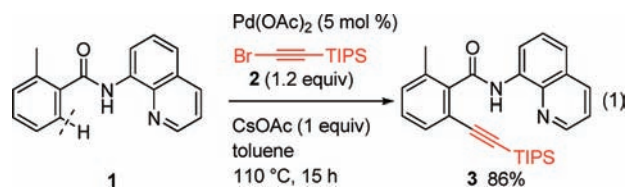
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remains relatively unexplored.⁷ We reported the first transition-metal-catalyzed direct alkylation of acetanilides using a TIPS-substituted bromoalkyne, but substrates bearing an electron-withdrawing group were inapplicable.^{7c} Subsequently, the direct alkylation of special classes of arene, such as the extremely electron-rich 1,3,5-trimethoxybenzene^{7d} and the extremely electron-deficient pentafluorobenzene,^{6m,7e} have been reported. Thus, a method that is applicable to an electronically diverse range of arenes is desired. Herein, we report the palladium-catalyzed direct *ortho*-alkynylation of aromatic carboxylic acid derivatives, wherein an array of functional groups are tolerated.

Recently, we found that the use of an 8-aminoquinoline-based directing group,⁸ originally developed by Daugulis in a direct arylation reaction,^{8a} is effective for the palladium-catalyzed direct alkylation of unreactive C(sp³)–H bonds.⁹ As an outgrowth of these studies, we postulated that this directing group may facilitate C(sp²)–C(sp) bond formation using an expanded array of arene substrates. Preliminary investigations revealed that 2-methyl-*N*-(8-quinolinyl)benzamide (**1**) and TIPS-protected bromoalkyne **2** (1.2 equiv), in the presence of Pd(OAc)₂ (5 mol %) and CsOAc (1 equiv) at 110 °C, afforded the corresponding *ortho*-alkynylated product **3** in 86% yield (eq 1).^{8b,10} A notable difference between this method and our previous direct alkylation of C(sp³)–H bonds⁹ is that no silver additives are required.



The effect of the directing group has been briefly assessed (Scheme 1). The procedure was not applicable to benzoic acid (**4**), methyl benzoate (**5**), benzamide (**6**), or *N*-phenylbenzamide (**7**) under the prescribed conditions. In contrast, bidentate directing groups, including 2-pyridinylmethylamine (**8**)¹¹ and 8-aminoquinoline (**1**), effectively promoted the reaction. Further investigations revealed that the 8-aminoquinoline director exhibits a

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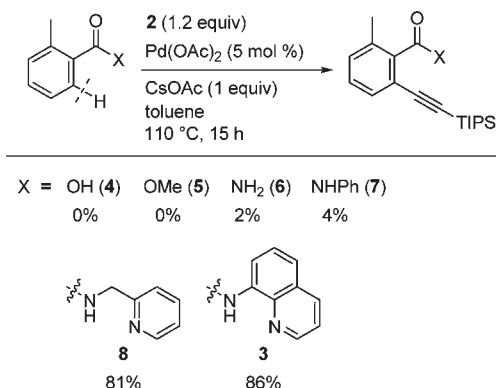
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(12) For example, the ethynylation of *N*-(2-pyridinylmethyl)-1-naphthamide afforded the corresponding ethynylated product in 30% yield, with a 22% recovery of the starting material, under the optimized conditions, while **15** was obtained in 88% yield (see Scheme 2).

Scheme 1. Effect of the Directing Groups^a

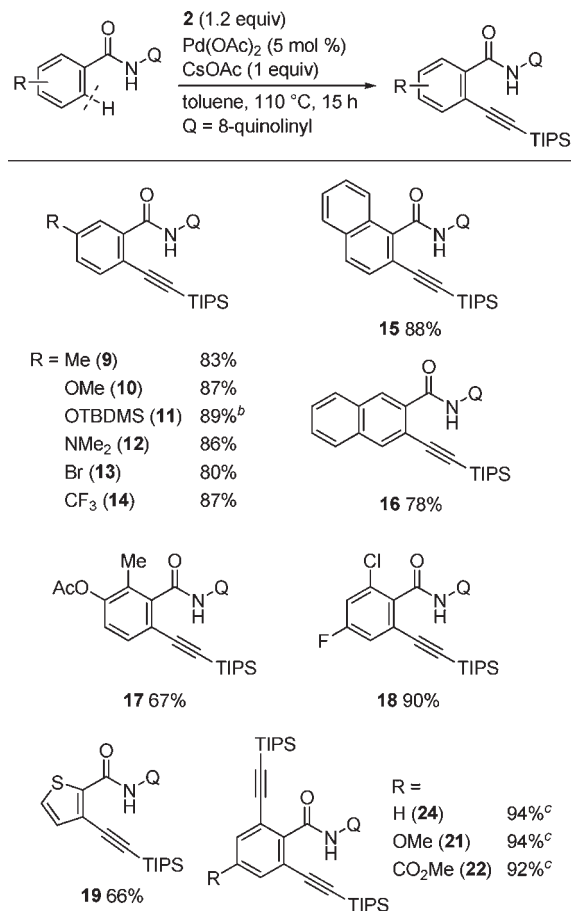


^a Reaction conditions: benzoic acid derivatives (0.3 mmol), **2** (0.36 mmol), Pd(OAc)₂ (0.015 mmol), CsOAc (0.3 mmol), toluene (0.6 mL), 110 °C, 15 h.

broader substrate scope,¹² and we therefore decided to employ this directing group for further exploration.

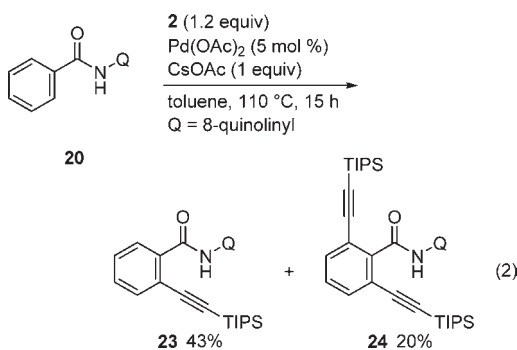
A variety of benzoic acid derivatives could be alkylation using an 8-aminoquinoline directing group (Scheme 2).

Scheme 2. Scope of the Reaction^a

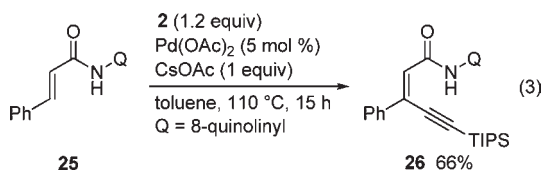


^a Reaction conditions: benzamide (0.3 mmol), **2** (0.36 mmol), Pd(OAc)₂ (0.015 mmol), CsOAc (0.3 mmol), toluene (0.6 mL), 110 °C, 15 h. ^b Run for 24 h. ^c **2** (0.72 mmol) and CsOAc (0.6 mmol) were employed.

Both electron-rich (**9–12**, **17**, **21**) and electron-deficient (**13**, **14**, **18**, **22**) benzoic acids smoothly underwent direct alkynylation to furnish the corresponding cross-coupling products in high yield. Labile functional groups, such as silyl ethers (**11**), bromides (**13**), chlorides (**18**), and esters (**17** and **22**), also remained intact under these conditions. When *meta*-substituted benzamides were used, the alkynylation proceeded selectively at the less hindered position (**9–14**). A naphthalene ring system can be successfully applied to this protocol, leading to the regioselective formation of the alkynylated products (**15** and **16**). Moreover, heteroarenes, such as thiophene (**19**), can serve as suitable substrates as well.^{6p} The palladium-catalyzed reaction of *N*-(8-quinolinyl)benzamide **20** with **2**, under optimized conditions, afforded a mixture of mono- (**23**) and dialkynylated product (**24**), in 43% and 20% yield, respectively (eq 2). Although the selective formation of **23** was unsuccessful, the selective synthesis of **24** was made possible by employing 2.4 equiv of **2**. 1,3-Dialkynylated benzene derivatives are important building blocks for the synthesis of rigid macrocyclic molecules and serve as intriguing targets in both material and supramolecular chemistry.¹³ Dialkynylated arenes can be similarly prepared from *para*-substituted benzamides (**21** and **22**) under the outlined modified conditions.

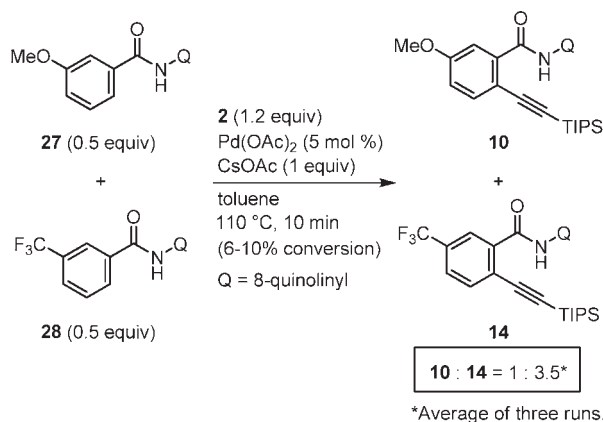


This palladium-catalyzed direct alkynylation is also applicable to vinylic C–H bonds (eq 3). The method allows the rapid assembly of conjugated enynes from readily available α,β -unsaturated acids.



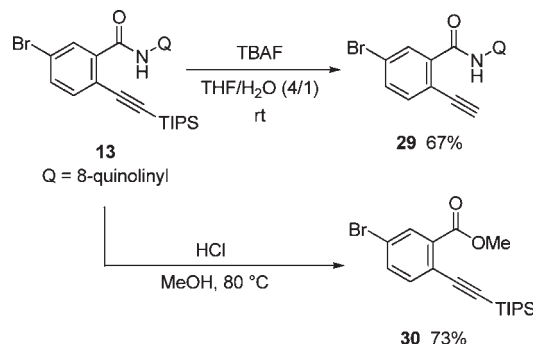
To gain a mechanistic insight, the electronic effects of the amide substrates on the overall rates of catalysis were examined. A competition experiment, using both electron-rich (**27**) and electron-deficient (**28**) amides, suggested that the alkynylation proceeds faster for the latter (Scheme 3). These results are in sharp contrast to the trends

Scheme 3. Competitive Experiment



observed in our previous palladium-catalyzed alkynylation reactions with acetanilides. In that instance, electron-donating groups accelerated the reaction.^{7c} Thus, the C–H bond cleavage process in this system has an opposite electronic demand to the S_EAr pathway.¹⁴ This suggests a different mechanism, such as concerted metalation/deprotonation,¹⁵ is likely to be in operation. It should also be noted that an intermolecular KIE of 2.1 was observed.¹⁶

Scheme 4. Transformations of Alkynylated Products



The alkynylated products are amenable to further elaboration into synthetically valuable compounds (Scheme 4). Although a TIPS-substitution at the alkyne moiety is essential for this catalysis,¹⁷ this protecting group is easily removed via treatment with TBAF, to afford the corresponding terminal alkynes, which can themselves be elaborated into an array of substituted alkynes. The 8-aminoquinoline directing group is also removable through simple acid hydrolysis, furnishing versatile benzoic

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(16) See Supporting Information for details.

(17) The alkynylation using phenylethynyl bromide and (triisopropylsilyl) acetylene instead of **2** was unsuccessful.

acid derivatives¹⁸ without deteriorating the TIPS-alkyne moiety.

In summary, we have developed a protocol for the palladium-catalyzed direct alkynylation of benzoic acid derivatives. The use of 8-aminoquinoline as a directing group promotes the *ortho*-alkynylation of a diverse array of electron-rich and -deficient C–H bonds, without the need for any silver salts. High functional group compatibility, as well as facile introduction and removal of the directing group, renders the present method a highly versatile procedure for the construction of C(sp²)–C(sp) linkages. Further developments for direct alkynylation and related reactions, using a range of directing groups, are in progress in our laboratory.

(18) Methyl ester **30** and its derivatives have the potential to serve in the synthesis of heterocycles. For example, see: (a) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (b) Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas “Molecular Activation Directed toward Straightforward Synthesis” from The Ministry of Education, Culture, Sports, Science and Technology, Japan. M.T. acknowledges the HISHO Program of Osaka University. Y.A. expresses his special thanks to JSPS for a Research Fellowship for Young Scientists and to the Global COE Program of Osaka University. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with the MS, HRMS, and elemental analyses.

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>.