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Palladium-Catalyzed Direct Ethynylation of C(sp^3)−H Bonds in Aliphatic Carboxylic Acid Derivatives

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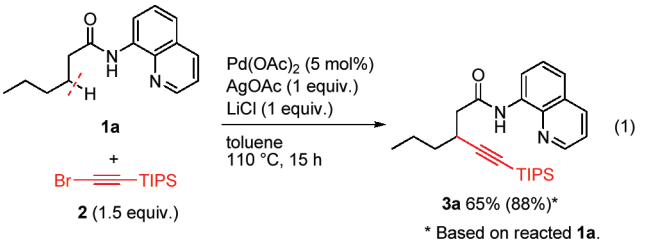
Supporting Information

ABSTRACT: The first catalytic alkynylation of unactivated C(sp^3)−H bonds has been accomplished. The method allows for the straightforward introduction of an ethynyl group into aliphatic acid derivatives under palladium catalysis. This new reaction can be applied to the rapid elaboration of complex aliphatic acids, for example, via azide/alkyne cycloaddition.

Alkynes are powerful building blocks in chemical synthesis because of the diverse range of reactivity of carbon−carbon triple bonds toward addition, cycloaddition, and metathesis reactions, among others.[1] Installation of the alkyne functionality conventionally requires functionalized starting materials such as halides or unsaturated bonds. If C−H bonds[2] could be alkynylated directly, it would provide methods with tremendous potential value. Nevertheless, this type of C−H bond alkynylation has been accomplished only within the realm of aromatic[3] and heteroaromatic substrates,[4] and unactivated C(sp^3)−H bonds have been inapplicable.[5] Herein we report a palladium-catalyzed alkynylation of unactivated C(sp^3)−H bonds in aliphatic carboxylic acid derivatives. In view of the prevalence of aliphatic acids in nature, the reaction allows for the direct introduction of an alkyne moiety into naturally occurring substances as a handle for further structural modification, for example, via azide−alkyne cycloaddition.[1b]

We recently reported the palladium-catalyzed direct alkynylation of C(aryl)−H bonds in acylated anilides using bromoalkynes.[3c] Our initial attempts to extend this catalytic system to aliphatic substrates were unsuccessful (**A** in Figure 1). We reasoned that the lack of reactivity may be due to an inappropriate directing group. Although less explored than the reaction involving C(sp^2)−H bonds, catalytic carbon−carbon bond formation via the activation of *unactivated C(sp^3)−H* bonds has recently been achieved by the research groups of Daugulis,[6] Yu,[7] and Sanford[8] as well as by us[9] through the use of suitable directing groups, which facilitate the difficult cyclometalation process.[10] It was envisaged that the putative metallacycles formed by the activation of C(sp^3)−H bonds can serve as viable catalytic intermediates for the alkynylation reactions. After an examination of several directing groups (**B**−**F** in Figure 1), 8-aminoquinoline[6] proved to be an optimal directing group to promote the desired alkynylation reaction. Thus, the reaction of aliphatic amide **1a** with bromoalkyne **2**[11] in the presence of $Pd(OAc)_2$ (5 mol %), AgOAc (1 equiv), and LiCl (1 equiv) at 110 °C for 15 h afforded the corresponding alkynylated product **3a** in 65% isolated yield (eq 1):[12]



Replacement of the 8-aminoquinoline moiety in **1a** with a 1-aminonaphthyl group (**G** in Figure 1) or N-methylation of the amide group (**H**) completely prevented the alkynylation, indicating that both the quinoline and the NH group are essential for the reaction.

A variety of aliphatic carboxylic acid derivatives were successfully alkynylated using an 8-aminoquinoline directing group (Table 1). Substrates bearing the sterically demanding isopropyl (**1b**) or cyclohexyl (**1c**) groups were accommodated. This alkynylation was also tolerant of a wide range of functional groups, including ethers (**1d**, **1f**, and **1l**), esters (**1g**), halides (**1h**, **1i**, **1m**, and **1o**), and a nitro group (**1n**). C(sp^3)−H bonds adjacent to heteroatoms (**1d**) and those at the benzylic position (**1k**−**o**) underwent the alkynylation similarly without reoptimization of the catalytic system. Interestingly, the electronic nature of benzylic substrates had a minimal impact on the yield, which is in sharp contrast to our previously reported palladium-catalyzed C(aryl)−H bond alkynylation.[3c] The current limitation for this

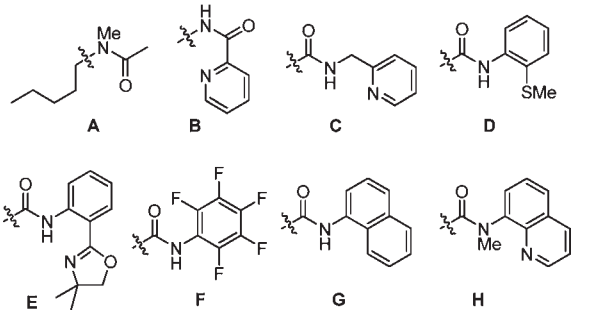


Figure 1. Ineffective Directing Groups.

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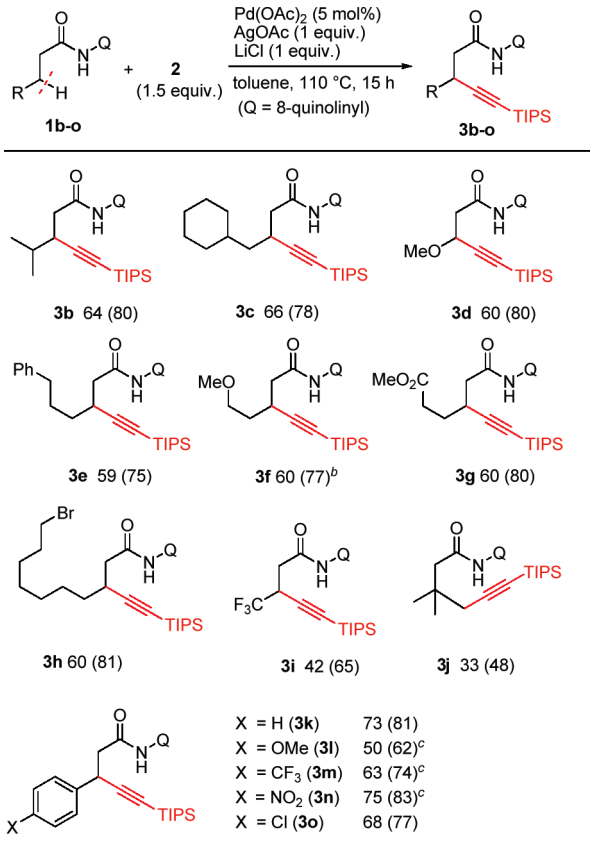
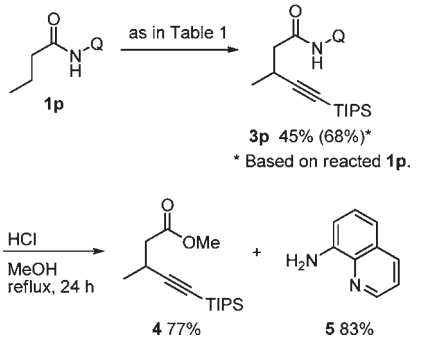
Table 1. Pd-Catalyzed Direct Alkynylation of Aliphatic C−H Bonds with Bromoalkyne 2[a]



[a] Reaction conditions: amide (0.5 mmol), **2** (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), AgOAc (0.5 mmol), and LiCl (0.5 mmol) in toluene (1 mL) at 110 °C for 15 h. The numbers refer to isolated yields based on the amides, and those in parentheses refer to yields based on the reacted amides. [b] The reaction was run for 24 h. [c] $Pd(OAc)_2$ (0.05 mmol) was used.

Scheme 1. Recovery of the Directing Group



method is that only secondary C−H bonds are alkynylated in synthetically useful yields, while primary and tertiary C−H bonds undergo alkynylation with a lower efficiency.[13] This preference for secondary C−H bonds is a notable feature of an 8-aminoquinoline directing group.[6] Importantly, when substrates bearing no hydrogen at the β-position (e.g., **1j**) were used, alkynylation proceeded regioselectively at the γ-position. This demonstrates one of the rare examples wherein catalytic C(sp^3)−H

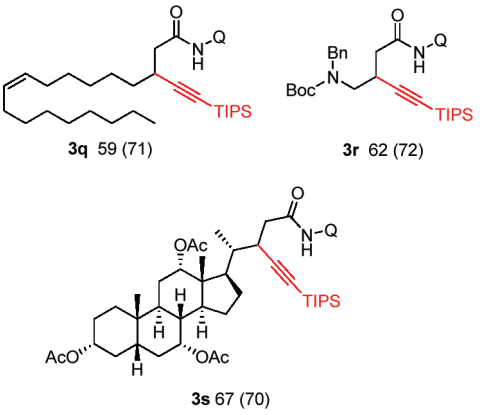
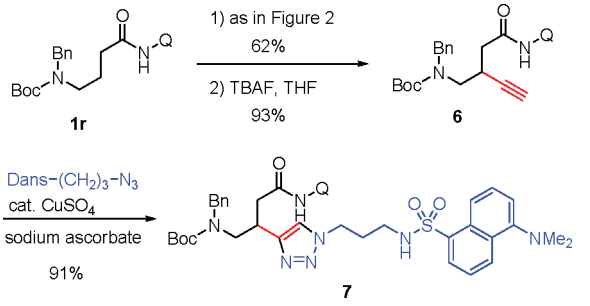


Figure 2. Pd-catalyzed direct alkynylation of bioactive carboxylic acid derivatives. Reaction conditions: amide (Q = 8-quinolinyl, 0.5 mmol), **2** (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), AgOAc (0.5 mmol), and LiCl (0.5 mmol) in toluene (1 mL) at 110 °C for 15 h. Numbers refer to isolated yields based on the amides, and those in parentheses refer to yields based on the reacted amides. In the case of the reaction of **1s** to give **3s**, 0.05 mmol of $Pd(OAc)_2$ was used, and the product was obtained as a 1.5:1 mixture of diastereomers.

Scheme 2. Installation of a Fluorophore via Sequential C−H Bond Alkynylation/Azide−Alkyne Cycloaddition



functionalization occurs at the γ-position of aliphatic carboxylic acid derivatives.[6d]

One of the eminent advantages of using an 8-aminoquinoline director is its readily attachable and detachable nature. This amide bond can be formed by applying the conventional condensation procedure to aliphatic acids.[14] After serving as a directing group, the amide can be transformed into a versatile ester functionality while the silylalkyne moiety remains intact (Scheme 1).

We also found that the palladium-catalyzed alkynylation reaction was applicable to some natural-product-derived substrates (Figure 2). An aliphatic C−H bond at the β-position of oleic acid could be alkynylated in a regioselective manner, even in the presence of normally more reactive allylic C−H bonds,[10] to produce **3q**. γ-Aminobutyric acid (GABA) derivative **1r** underwent the alkynylation, with which the *N*-Boc and *N*-benzyl protecting groups were compatible. Moreover, substrate **1s** containing a steroidal architecture was successfully utilized in this protocol. These results highlight the potential utility of this alkynylation in the postsynthetic elaboration of complex natural products. Thus, the obtained alkynylated products can serve as versatile synthetic intermediates. For example, fluorophore labeling of GABA derivative **1r** with a dansyl group was successfully accomplished via a C−H alkynylation/desilylation/copper-catalyzed azide−alkyne cycloaddition sequence (Scheme 2).[1b]

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In conclusion, we have developed a palladium-catalyzed alkynylation reaction of aliphatic C−H bonds in carboxylic acids simply by attaching an 8-aminoquinoline directing group to the acid. Functional group tolerance and applicability to natural-product-based substrates have been demonstrated. In view of the widespread utility of the copper-catalyzed azide/alkyne cycloaddition in modifying natural and non-natural products, the present protocol offers a new method for preparing complex alkyne components in a more straightforward manner. Further studies to explore catalytic methods for the functionalization of $C(sp^3)$−H bonds are now in progress.

■ ASSOCIATED CONTENT

Supporting Information. 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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■ REFERENCES

(1) (a) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005. For a themed issue on click chemistry, see:(b) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231 and articles cited therein. For a review of alkyne metathesis, see:(c) Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, *349*, 93. For a review of cycloisomerization using alkynes, see:(d) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371.

(2) For selected reviews of catalytic C−H bond-functionalization reactions, see: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2010**, *111*, 1293. (g) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (h) Hirano, K.; Miura, M. *Synlett* **2011**, 294.

(3) (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) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (d) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (e) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (f) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. For reviews, see:(g) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (h) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495.

(4) (a) Kalinin, V. K.; Pashchenko, D. N.; She, F. M. *Mendeleev Commun.* **1992**, *2*, 60. (b) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. b. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513. (c) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (d) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Vakul'skaya, T. I.; Kazheva, O. g. N.; Aleksandrov, G. G.; Dyachenko, O. A.; Mikhaleva, A. b. I. *Tetrahedron* **2008**, *64*, 5541. (e) Gu, Y.; Wang, X.-m. *Tetrahedron Lett.* **2009**, *50*, 763. (f) Rodriguez, A.; Fennessy, R. V.; Moran, W. J. *Tetrahedron Lett.* **2009**, *50*, 3942. (g) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (h) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (i) Besselièvre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (j) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (k) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (l) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (m) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Commun.* **2010**, *46*, 4184. (n) Berciano, B. P.; Lebrequier, S.; Besselièvre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038. (o) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (p) Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102. (q) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474. Also see refs 3f−3h.

(5) Alkynylation of *activated* $C(sp^3)$−H bonds is known. For selected examples involving $C(sp^3)$−H bonds α to heteroatoms, see: (a) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *J. Chem. Res., Synop.* **1993**, 434. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (c) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. For benzylic and allylic C−H bonds, see:(d) Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1446. For $C(sp^3)$−H bonds α to carbonyls, see:(e) González, D. F.; Brand, J. P.; Waser, J. *Chem.—Eur. J.* **2010**, *16*, 9457.

(6) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. For elegant applications of the method to complex-molecule synthesis, see: (d) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (e) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (f) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414. (g) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192.

(7) (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) 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. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (d) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (e) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (f) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (g) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (h) Wasa, M.; Yu, J.-Q. *Tetrahedron* **2010**, *66*, 4811.

(8) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541.

(9) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070.

(10) For catalytic $C(sp^3)$−H bond functionalization reactions without chelation assistance and those other than C−C bond formation, see the following leading reviews: (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (b) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191.

(11) (a) Bromoalkyne **2** can be readily prepared from commercially available triisopropylacetylene in one step. See: Jiang, M. X.-W.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970.(b) The exceptional effectiveness of TIPS-protected alkynes has often been observed in other catalytic reactions. See refs 3c, 4h, 4o, and 4p and references therein. (c) Bromoethynylbenzene and 1-bromooct-1-yne did not afford the corresponding alkynylated products.

(12) See the Supporting Information for details of optimization studies.

(13) The yield for the amide of propanoic acid was 7%; the yield for the amide of 3-methylbutanoic acid was ∼17%, and a γ-alkynylated product was also formed.

(14) See the Supporting Information for the preparation of the starting amides.