Published in final edited form as:

Angew Chem Int Ed Engl. 2017 February 06; 56(7): 1873–1876. doi:10.1002/anie.201610426.

Ligand-Enabled Alkynylation of C(sp³)–H Bonds with Pd(II) Catalysts**

Haiyan Fu, Dr.⁺, Peng-Xiang Shen⁺, Jian He, Fanglin Zhang, Dr., Suhua Li, Dr., Peng Wang, Tao Liu, and Jin-Quan Yu, Prof. Dr.

Department of Chemistry, The Scripps Research Institute (TSRI), 10550 North Torrey Pines Road, La Jolla, CA 92037(USA)

Abstract

The palladium(II)-catalyzed β - and γ -alkynylation of C(sp³)–H bonds of amides enabled by pyridine-based ligands has been developed. This alkynylation reaction is compatible with substrates containing α -tertiary or α -quaternary carbon centers. The β -methylene C(sp³)–H bonds in various carbocyclic rings are also successfully alkynylated.

Graphical abstract

Keywords

amino acids; alkynylation; C; H activation; palladium; pyridine

Alkynes are important synthetic moieties in material sciences and organic synthesis, as they can be utilized as a pivotal handle for further transformations.^[1] Besides the Pd(0)-catalyzed Sonogashira reaction,^[2] transition-metal-catalyzed direct C–H alkynylation reactions provide a complementary method to install C–C triple bonds into complex molecules. Over the past several years, alkynylation of C(sp²)–H bonds has been achieved using a number of transition metal catalysts.^[3–7] In sharp contrast, the alkynylation of inert C(sp³)–H bonds remains underdeveloped and only few examples are presented.^[8–10] Chatani reported Pd(II)-catalyzed alkynylation of methylene C(sp³)–H bonds using a bidentate auxiliary (eq 1).^[8a]

**We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01 GM084019) for financial support. H. Fu is a visiting scholar from Sichuan University sponsored by Young Teacher Abroad Training Program of Sichuan University.

Correspondence to: Jin-Quan Yu.

⁺These authors contributed equally to this work.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201xxxxx>.

Our group also developed a distinct approach to alkynylating β -methyl $C(sp^3)$ -H bonds using Pd(0)/phosphine or Pd(0)/*N*-heterocyclic carbene (NHC) catalysts (eq 2).^[8b] Despite the success in Pd-catalyzed alkynylation of amide substrates containing α -hydrogen atoms, amides derived from aliphatic acids bearing α -quaternary carbon centers gave poor reactivity.^[8] Co- and Ni-catalyzed β -alkynylation have also been developed using a bidentate auxiliary, albeit limited to amide substrates containing quaternary carbon centers.^[9] To broaden the substrate scope in $C(sp^3)$ -H alkynylation, it is highly desirable to develop new ligands that can promote alkynylation reactions under mild conditions. Herein, we report the first example of ligand-enabled $C(sp^3)$ -H alkynylation via Pd(II)/Pd(IV) catalysis (eq 3). This reaction protocol is compatible with a wide range of carboxylic acid derivatives, including α -amino acid substrates as well as α -quaternary and cyclic amide substrates.

Encouraged by our recent finding that pyridine- and quinoline-based ligands facilitate $C(sp^3)$ -H arylation via a Pd(II)/Pd(IV) catalytic cycle,^[11,12] we envisioned that a modified ligand scaffold might also promote $C(sp^3)$ -H alkynylation through the same redox chemistry. The preliminary test was carried out by reacting **1a** with 2.0 equivalent of TIPS-ethynyl bromide in the presence of 10 mol% of Pd(OAc)₂, 1.0 equiv of AgOAc, 12 mol% of pyridine **L1** in toluene at 110 °C for 20 h. To our delight, 38% of desired alkynylated product **3aa** was obtained, accompanying with 5% of cyclized product **4aa**. The control experiment revealed that both the pyridine ligand and AgOAc were required (see Supporting Information). To further explore the ligand effect, a series of pyridine-based ligands were screened. Noticeably, 2-picoline increased the yield of **3aa** from 38% to 58%. Ligands (**L3**, **L5**, **L8**, and **L9**) containing a methyl group at the 2-position and alkyl groups at other positions further increased the yield to 66%. In contrast, the ligands without alkyl substituents at the 2-position (**L4** and **L6**) decreased the yield to 34% and 40%, respectively. Based on these results, cycloalkane-fused pyridines were then exploited to improve the reaction efficiency. Gratifyingly, 2,3,4,5-di-cyclohexane-fused pyridine **L14** gave 85% yield of desired product **3aa**, with no detectable side-product **4aa**. Quinoline and isoquinoline-based ligands did not increase the yield of **3aa**.

With the established conditions in hand, we then explored the scope of alkynyl bromides using **L14** as ligand. TIPS-protected ethynyl bromide afforded the desired alkynylated product in 81% isolated yield, and the reaction could be scaled up to a 5.0 mmol scale without a decrease in yield. TBS- and TBDPS-protected ethynyl bromide gave the corresponding product in 76% and 72% yields, respectively. The less steric demanding tripropyl- and TES-protected ethynyl bromides could also be used as coupling partners, albeit resulting in lower yields. Alkynylation with trityl ethynyl bromide gave the final product **3af** in 52% yield. Using TIPS-protected ethynyl bromide as the coupling partner, we then tested alkynylation of other types of amino acid-derived amides. In the alkynylation of α -quaternary substrates (**1b** and **1c**), the corresponding products were prone to cyclization, providing **4ba** and **4ca** respectively, possibly due to repulsion from the α -substituents (eqs 4 and 5). The protocol can also be applied to remote γ - $C(sp^3)$ -H alkynylation. For example, the alkynylation of valine-derived *N*-arylamide **1d** with TIPS-protected ethynyl bromide in *t*-AmylOH afforded γ -alkynylated product **3da** in 46% yield when using **L16** as ligand and

Ag₂CO₃ as oxidant (eq 6). Isoleucine derivative **1e** could also provide the γ -alkynylated product in 22% yield.

Under the slightly modified reaction conditions (see SI), we systematically tested the scope of the aliphatic acid substrates using **L3** as the optimal ligand. For the amides containing α -hydrogen atoms (**5a–h**), the alkynylated products (**6a–h**) were obtained in good yields. When both β -methyl and β -methylene C(sp³)–H bonds are present in substrates (**5a**, **5c**, **5e**, **5f**, and **5h**), the β -methyl C(sp³)–H bonds were selectively alkynylated over the methylene C(sp³)–H bonds. Encouragingly, the β -methylene C(sp³)–H bonds of cyclic substrates (**5i–l**) could be alkynylated under higher temperature. Cyclopropanecarboxylic acid amide (**5i**) could afford the alkynylated product in 65% total yield (mono:di = 2.5:1) after only 10 h. The present protocol was also found to be effective for the alkynylation of β -methyl C(sp³)–H bonds of substrates containing α -quaternary carbon centers (**5m–o**). AgOPiv and KF were used as the optimal additive and base for this type of substrates. Alkynylation of pivalic acid amide **5m** gave a mixture of mono- and di-functionalized products in 70% total yield, and the mono-alkynylated product was isolated in 50% yield. It is worth noting that α -quaternary substrates (**5k–o**) are not effective in our previously developed Pd(0)/*N*-heterocyclic carbene and Pd(0)/phosphine system^[8b] and also not compatible with other reported methods.^[8] In terms of the substrate without β -hydrogen atoms (**5p**), the use of **L16** could enable the alkynylation at the γ -position, albeit affording a moderate yield. Propionic acid-derived amide **5q** could also give the desired product in 38% yield (see SI).

The auxiliary group can be readily removed by the treatment with BF₃·Et₂O and transformed into methyl ester **7** (Scheme 4). The phthalimido group was removed in ethylenediamine solution to give the free amine **8** which was then protected with Boc₂O. After the removal of TIPS groups in the presence of TBAF, compound **9** could be easily converted into synthetically useful intermediate **10**, allowing for the synthesis of various unnatural amino acids. The terminal triple bond could be effectively transformed to triazole **11** by click chemistry.^[13] It could also couple with *tert*-butylimines of *o*-halo aldehydes followed by cyclization to form isoquinolines **12** and **13** (Scheme 5).^[14]

In conclusion, pyridine-based ligands have been utilized to enable alkynylation reactions of β -methyl as well as β -methylene C(sp³)–H bonds in carboxylic acid derivatives. The substrates containing α -quaternary carbon centers are successfully alkynylated in Pd catalysis for the first time. The development of chiral pyridine-based ligands to realize an enantioselective version of C(sp³)–H alkynylation is currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Diederich, F., Stang, P.J., Tykwinski, R.R. *Acetylene Chemistry: Chemistry, Biology and Material Science*. Wiley-VCH; Weinheim: 2005. b) Fürstner, A., Davies, P.W. *Chem Commun.* 2005. p. 2307c) Kolb HC, Finn MG, Sharpless KB. *Angew Chem Int Ed.* 2001; 40:2004.

2. a) Sonogashira K, Tohda Y, Hagihara N. *Tetrahedron Lett.* 1975; 16:4467. b) Sonogashira K. *J Organomet Chem.* 2002; 653:46.
3. For selected examples of Pd-catalyzed C(sp²)-H Alkynylation, see :a) Seregin IV, Ryabova V, Gevorgyan V. *J Am Chem Soc.* 2007; 129:7742. [PubMed: 17539646] b) Gu Y, Wang X. *Tetrahedron Lett.* 2009; 50:763. c) Kim SH, Chang S. *Org Lett.* 2010; 12:1868. [PubMed: 20337427] d) Yang L, Zhao L, Li CJ. *Chem Commun.* 2010; 46:4184. e) Kim SH, Yoon J, Chang S. *Org Lett.* 2011; 13:1474. [PubMed: 21348492] f) Shibahara F, Dohke Y, Murai T. *J Org Chem.* 2012; 77:5381. [PubMed: 22612569] g) Dudnik AS, Gevorgyan V. *Angew Chem, Int Ed.* 2010; 49:2096. h) Tobisu M, Ano Y, Chatani N. *Org Lett.* 2009; 11:3250. [PubMed: 19555067] i) Kim SH, Park SH, Chang S. *Tetrahedron.* 2012; 68:5162. j) Ano Y, Tobisu M, Chatani N. *Org Lett.* 2012; 14:354. [PubMed: 22148889] k) Brand JP, Waser J. *Chem Soc Rev.* 2012; 41:4165. [PubMed: 22513709] l) Tolnai GL, Ganss S, Brand JP, Waser J. *Org Lett.* 2013; 15:112. [PubMed: 23249277]
4. For selected examples of Rh-catalyzed C(sp²)-H Alkynylation, see: a) Zhang X, Qi Z, Gao J, Li X. *Org Biomol Chem.* 2014; 12:9329. [PubMed: 25325793] b) Yang XF, Hu XH, Feng C, Loh TP. *Chem Commun.* 2015; 51:2532. c) Xie F, Qi Z, Yu S, Li X. *J Am Chem Soc.* 2014; 136:4780. [PubMed: 24593822] d) Wang H, Xie F, Qi Z, Li X. *Org Lett.* 2015; 17:920. [PubMed: 25650718] e) Jeong J, Patel P, Hwang H, Chang S. *Org Lett.* 2014; 16:4598. [PubMed: 25141216] f) Feng C, Loh TP. *Angew Chem Int Ed.* 2014; 53:2722. g) Feng C, Feng D, Luo Y, Loh TP. *Org Lett.* 2014; 16:5956. [PubMed: 25383914] h) Feng C, Feng D, Loh TP. *Chem Commun.* 2014; 50:9865. i) Collins KD, Lied F, Glorius F. *Chem Commun.* 2014; 50:4459.
5. For selected examples of Cu-catalyzed C(sp²)-H Alkynylation, see: a) Li ZP, Li CJ. *J Am Chem Soc.* 2004; 126:11810. [PubMed: 15382913] b) Li ZP, MacLeod PD, Li CJ. *Tetrahedron: Asymmetry.* 2006; 17:590. c) Shang M, Wang HL, Sun SZ, Dai HX, Yu JQ. *J Am Chem Soc.* 2014; 136:11590. [PubMed: 25087720]
6. For a rare example of Au-catalyzed C(sp²)-H Alkynylation, see: Brand JP, Waser J. *Org Lett.* 2012; 14:744. [PubMed: 22260441]
7. For selected examples of Ni-catalyzed C(sp²)-H Alkynylation, see: a) Matsuyama N, Hirano K, Satoh T, Miura M. *Org Lett.* 2009; 11:4156. [PubMed: 19739688] b) Brachet E, Brion JD, Alami M, Messaoudi S. *Chem Eur J.* 2013; 19:15276. [PubMed: 24108443] c) Liu Y, Liu YH, Yan SY, Shi BF. *Chem Commun.* 2015; 51:6388.
8. For rare examples of Pd-catalyzed C(sp³)-H alkylation, see: a) Ano Y, Tobisu M, Chatani N. *J Am Chem Soc.* 2011; 133:12984. [PubMed: 21790123] b) He J, Wasa M, Chan KSL, Yu JQ. *J Am Chem Soc.* 2013; 135:3387. [PubMed: 23406445] c) Wang B, Lu C, Zhang SY, He G, Nack WA, Chen G. *Org Lett.* 2014; 16:6260. [PubMed: 25412205] d) Wang B, He G, Chen G. *Sci China Chem.* 2015; 58:1345. e) Ye X, Xu C, Wojtas L, Akhmedov NG, Chen H, Shi X. *Org Lett.* 2016; 18:2970. [PubMed: 27267908]
9. a) Zhang J, Chen H, Lin C, Liu Z, Wang C, Zhang Y. *J Am Chem Soc.* 2015; 137:12990. [PubMed: 26389708] b) Luo FX, Cao ZC, Zhao HW, Wang D, Zhang YF, Xu X, Shi ZJ. *Organometallics.* 2016; doi: 10.1021/acs.organomet.6b00529
10. Tang S, Wang P, Li H, Lei A. *Nat Commun.* 2016; 7:11676. [PubMed: 27339161]
11. For selected examples of pyridine-based ligand promoted C(sp³)-H activation reactions via a Pd(II)/Pd(IV) catalytic cycle, see: a) He J, Li S, Deng Y, Fu H, Laforteza BN, Spangler JE, Homs A, Yu JQ. *Science.* 2014; 343:1216. [PubMed: 24626923] b) Deng Y, Gong W, He J, Yu JQ. *Angew Chem Int Ed.* 2014; 53:6692. c) Zhu RY, He J, Wang XC, Yu JQ. *J Am Chem Soc.* 2014; 136:13194. [PubMed: 25208210] d) He J, Takise R, Fu H, Yu JQ. *J Am Chem Soc.* 2015; 137:4618. [PubMed: 25822198]
12. He J, Wasa M, Chan KSL, Shao Q, Yu JQ. *Chem Rev.* 2017; doi: 10.1021/acs.chemrev.6b00622
13. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew Chem Int Ed.* 2002; 41:2596.
14. Roesch KR, Larock RC. *Org Lett.* 1999; 1:553.

A C(sp³)-H Alkynylation using a Bidentate Auxiliary (incompatible with α -quaternary centers)

B C(sp³)-H Alkynylation using a Monodentate Auxiliary

Our previous work (incompatible with amino acids and α -quaternary centers):

This work:

Scheme 1.

Pd-catalyzed C(sp³)-H alkynylation of amides.

Scheme 2. Alkynylation of amino acid bearing α -quaternary carbon centers.

Scheme 4.

Removal of auxiliary and TIPS. a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.0 equiv), MeOH, 100 °C, 30 h. b) ethyldiamine (5.0 equiv), MeOH/DCM = 1/1, 40 °C, 4 h. c) $(\text{Boc})_2\text{O}$ (1.5 equiv), DCM, rt. d) TBAF (1.05 equiv), THF, 0 °C, 0.5 h.

Scheme 5.

Transformation of the alkynyl amino acid. a) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (1.0 mol%), sodium ascorbate (5 mol%), $\text{H}_2\text{O}/t\text{-BuOH}$, 2:1, rt, overnight. b) 1) $\text{PdCl}_2(\text{PPh}_3)_2$ (2.0 mol%), CuI (1.0 mol%), NEt_3 , 55 °C, 3 h; 2) CuI (10 mol %), DMF, 100 °C. c) 1) $\text{PdCl}_2(\text{PPh}_3)_2$ (2.0 mol%), CuI (1.0 mol%), NEt_3 , 55 °C, 5 h; 2) CuI (10 mol %), DMF, 100 °C.

Table 1

Screening of ligand.^[a,b]

without ligand				
3aa, 0% 4aa, 0%	3aa, 38% 4aa, 5%	3aa, 58% 4aa, 0%	3aa, 65% 4aa, 0%	3aa, 34% 4aa, 0%
3aa, 66% 4aa, 0%	3aa, 40% 4aa, 18%	3aa, 50% 4aa, 17%	3aa, 66% 4aa, 7%	3aa, 66% 4aa, 11%
3aa, 42% 4aa, 20%	3aa, 58% 4aa, 0%	3aa, 58% 4aa, 0%	3aa, 38% 4aa, 20%	3aa, 85% 4aa, 0%
3aa, 55% 4aa, 0%	3aa, 70% 4aa, 0%	3aa, 70% 4aa, 0%	3aa, 52% 4aa, 0%	3aa, 58% 4aa, 0%

^[a] **1a** (0.1 mmol), Pd(OAc)₂ (0.01 mmol), AgOAc (0.1 mmol), TIPS alkynyl bromide (0.2 mmol), ligand (0.012 mmol), toluene (1.0 mL), 110 °C, 24 h.

^[b] Yield determined by NMR spectroscopy with CH₂Br₂ as the internal standard.

Table 2

Alkynylation of amino acid amides.^[a,b]

^[a] **1a** (0.1 mmol), alkyne bromide (0.2 mmol), Pd(OAc)₂ (0.01 mmol), AgOAc (0.1 mmol), ligand **L14** (0.012 mmol), toluene (1.0 mL), 110 °C, 20 h. TIPS = Si(*i*-Pr)₃, TBS = Si(*t*-Bu)Me₂, TBDPS = Si(*t*-Bu)Ph₂.

^[b] Isolated yield.

Table 3

Alkynylation of aliphatic amides.^[a,b]

^[a] **5** (0.1 mmol), TIPS alkynyl bromide (0.2 mmol), Pd(OAc)₂ (0.01 mmol), AgOAc (0.1 mmol), KHCO₃ (0.4 mmol), ligand **L3** (0.01 mmol), DCM (1.0 mL), 70 °C, 36 h.

^[b] Isolated yield.

^[c] toluene (1.0 mL), 100 °C.

^[d] 100 °C.

^[e] AgOPiv (0.1 mmol), KF (0.2 mmol), 100 °C.

^[f] Ag₂CO₃ (0.2 mmol), ligand **L16** (0.02 mmol), *t*-AmylOH (1.0 mL), 80 °C, 10 h.