C–H Activation

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Ligand-Enabled Alkynylation of C(sp^3)–H Bonds with Palladium(II) Catalysts

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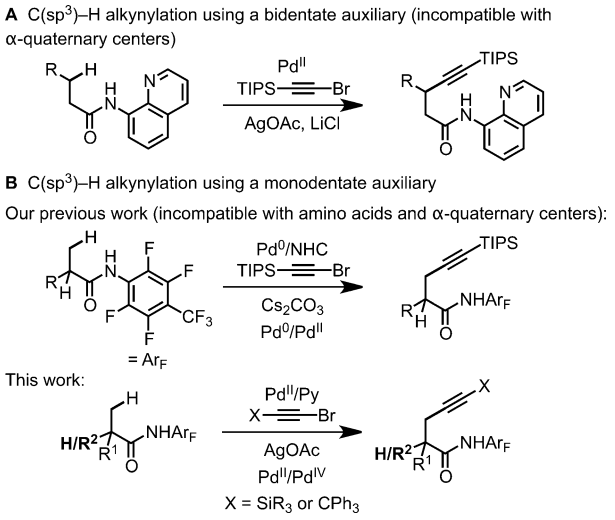
Abstract: *The palladium(II)-catalyzed β- and γ-alkynylation of amide C(sp^3)–H bonds is enabled by pyridine-based ligands. This alkynylation reaction is compatible with substrates containing α-tertiary or α-quaternary carbon centers. The β-methylene C(sp^3)–H bonds of various carbocyclic rings were also successfully alkynylated.*

Alkynes are important synthetic moieties in materials science and organic synthesis as they can be utilized as pivotal handles for further transformations.[1] Aside from the palladium(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, the alkynylation of C(sp^2)–H bonds has been achieved using a number of transition-metal catalysts.[3–7] In sharp contrast, the alkynylation of inert C(sp^3)–H bonds remains underdeveloped, and only a few examples have been reported.[8–10] Chatani and co-workers reported a palladium(II)-catalyzed alkynylation of methylene C(sp^3)–H bonds using a bidentate auxiliary (Scheme 1 A).[8a] Our group also developed a distinct approach for the alkynylation of β-methyl C(sp^3)–H bonds using Pd^0/phosphine and Pd^0/N-heterocyclic carbene (NHC) catalysts (Scheme 1 B).[8b] Despite the success with the palladium-catalyzed alkynylation of amide substrates containing α-hydrogen atoms, amides derived from aliphatic acids bearing α-quaternary carbon centers gave poor reactivity.[8] Cobalt- and nickel-catalyzed β-alkynylation reactions that involve the use of a bidentate auxiliary have also been developed, but are limited to amide substrates containing quaternary carbon centers.[9] To broaden the substrate scope of 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 by Pd^{II}/Pd^{IV} catalysis (Scheme 1, bottom). This reaction is compatible with a wide range of carboxylic acid derivatives, including α-amino acid substrates as well as α-quaternary and cyclic amide substrates.



Scheme 1. Palladium-catalyzed C(sp^3)–H alkynylation of amides.

Encouraged by our recent finding that pyridine- and quinoline-based ligands facilitate C(sp^3)–H arylation through 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. A preliminary test was carried out by reacting **1a** with triisopropyl (TIPS) protected ethynyl bromide (2.0 equiv) in the presence of Pd(OAc)$_2$ (10 mol%), AgOAc (1.0 equiv), and pyridine **L1** (12 mol%) in toluene at 110°C for 20 h (Table 1). To our delight, the desired alkynylated product **3aa** was obtained in 28% yield, along with 5% of cyclized product **4aa**. Control experiments revealed that both the pyridine ligand and AgOAc were required (see the 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 containing a methyl group at the 2-position and alkyl substituents at other positions (**L3**, **L5**, **L8**, and **L9**) further increased the yield to 66%. In contrast, 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 the desired product **3aa** in 85% yield, with no detectable side product **4aa**. Quinoline- and isoquinoline-based ligands did not further increase the yield of **3aa**.

With optimized reaction conditions in hand, we then explored the scope of alkynyl bromides using **L14** as the ligand (Table 2). TIPS-protected ethynyl bromide afforded

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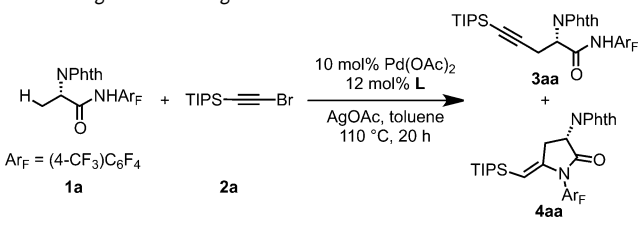
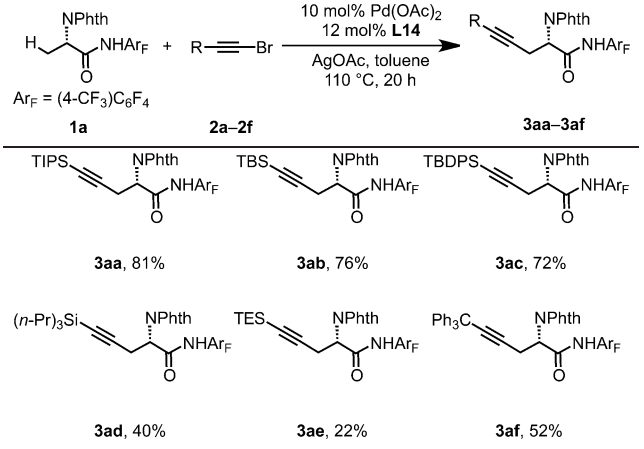
Table 1: Ligand screening.[a]



without ligand	L1	L2	L3	L4
3aa, 0% **4aa**, 0%	**3aa**, 38% **4aa**, 5%	**3aa**, 58% **4aa**, 0%	**3aa**, 65% **4aa**, 0%	**3aa**, 34% **4aa**, 0%
L5	**L6**	**L7**	**L8**	**L9**
3aa, 66% **4aa**, 0%	**3aa**, 40% **4aa**, 18%	**3aa**, 50% **4aa**, 17%	**3aa**, 66% **4aa**, 7%	**3aa**, 66% **4aa**, 11%
L10	**L11**	**L12**	**L13**	**L14**
3aa, 42% **4aa**, 20%	**3aa**, 58% **4aa**, 0%	**3aa**, 58% **4aa**, 0%	**3aa**, 38% **4aa**, 20%	**3aa**, 85% **4aa**, 0%
L15	**L16**	**L17**	**L18**	**L19**
3aa, 55% **4aa**, 0%	**3aa**, 70% **4aa**, 0%	**3aa**, 70% **4aa**, 0%	**3aa**, 52% **4aa**, 0%	**3aa**, 58% **4aa**, 0%

[a] Reaction conditions: **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. Yields determined by NMR spectroscopy with CH_2Br_2 as the internal standard. Phth = phthaloyl.

Table 2: Alkynylation of amino acid amides.[a]

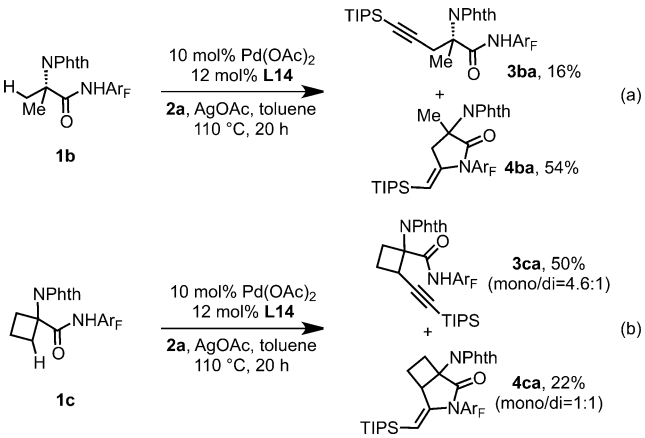


3aa, 81%	**3ab**, 76%	**3ac**, 72%
3ad, 40%	**3ae**, 22%	**3af**, 52%

[a] **1a** (0.1 mmol), alkynyl bromide (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOAc (0.1 mmol), **L14** (0.012 mmol), toluene (1.0 mL), 110 °C, 20 h. Yields of isolated products are given. TBDPS = Si(*t*-Bu)Ph_2, TBS = Si(*t*-Bu)Me_2, TES = $SiEt_3$, TIPS = Si(*i*-Pr)$_3$.

the desired alkynylated product in 81 % yield after isolation, and the reaction could be scaled up to 5.0 mmol without a decrease in yield. TBS- and TBDPS-protected ethynyl bromide gave the corresponding products in 76 % and 72 % yield, respectively. The sterically less demanding tripropyl- and TES-protected ethynyl bromides could also be used as coupling partners, but resulted in lower yields. Alkynylation with trityl ethynyl bromide gave the final product **3af** in 52 % yield.

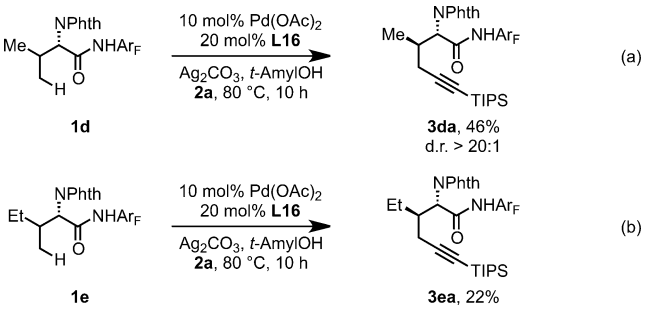
Using TIPS-protected ethynyl bromide as the coupling partner, we then studied the alkynylation of other types of amino acid derived amides. In the alkynylation of α-quaternary substrates (**1b** and **1c**), the corresponding products were prone to cyclization, providing **4ba** and **4ca**, respectively, possibly owing to the Thorpe–Ingold effect from the α-substituents (Scheme 2). This method can also be applied



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

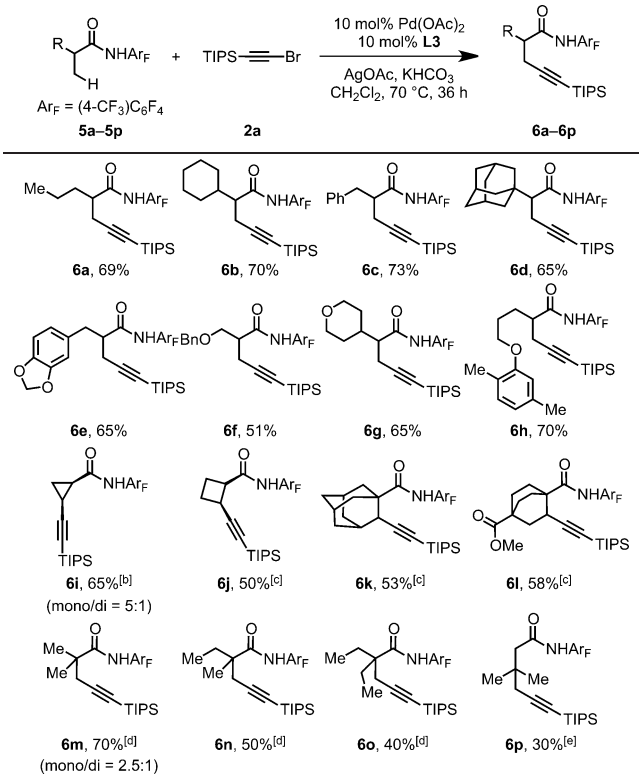
to remote γ-C(sp^3)–H alkynylation. For example, the alkynylation of valine-derived *N*-aryl amide **1d** with TIPS-protected ethynyl bromide in *t*-AmylOH afforded γ-alkynylated product **3da** in 46 % yield when **L16** and Ag_2CO_3 were used as ligand and oxidant, respectively (Scheme 3 a). Isoleucine derivative **1e** also provided the γ-alkynylated product in 22 % yield (Scheme 3 b).

Under slightly modified reaction conditions (see the Supporting Information), we systematically tested the scope of the reaction with respect to aliphatic amides using **L3** as the optimal ligand (Table 3). For amides containing α-hydrogen atoms (**5a**–**5h**), the alkynylated products (**6a**–**6h**) were obtained in good yields. When both β-methyl and β-methylene C(sp^3)–H bonds were present in the substrate (**5a**, **5c**, **5e**, **5f**, and **5h**), the β-methyl C(sp^3)–H bonds were



Scheme 3. γ-C(sp^3)–H alkynylation of α-amino acid amides.

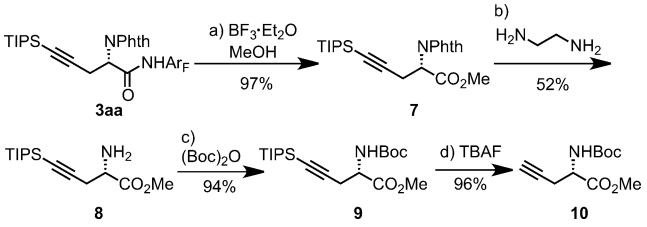
Table 3: Alkynylation of aliphatic amides.[a]



[a] Reaction conditions: **5** (0.1 mmol), TIPS-protected alkynyl bromide (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOAc (0.1 mmol), $KHCO_3$ (0.4 mmol), **L3** (0.01 mmol), CH_2Cl_2 (1.0 mL), 70 °C, 36 h. Yields of isolated products are given. [b] Toluene (1.0 mL), 100 °C. [c] 100 °C. [d] AgOPiv (0.1 mmol), KF (0.2 mmol), 100 °C. [e] Ag_2CO_3 (0.2 mmol), **L16** (0.02 mmol), *t*-AmylOH (1.0 mL), 80 °C, 10 h.

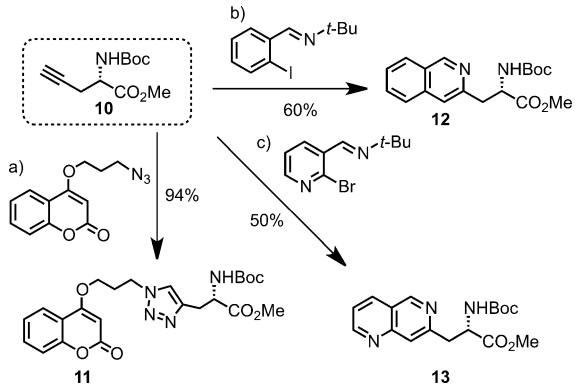
selectively alkynylated over the methylene C(sp^3)–H bonds. Encouragingly, the β-methylene C(sp^3)–H bonds of cyclic substrates (**5i**–**5l**) could be alkynylated at higher temperatures. Cyclopropanecarboxylic acid amide **5i** afforded the alkynylated product in 65% overall yield (mono/di = 2.5:1) after only 10 h. The present method was also found to be effective for the alkynylation of β-methyl C(sp^3)–H bonds of substrates containing α-quaternary carbon centers (**5m**–**5o**). 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 the mono- and difunctionalized products in a total yield of 70%, and the monoalkynylated product was isolated in 50% yield. It is worth noting that α-quaternary substrates (**5k**–**5o**) were not compatible with our previously developed Pd^0/NHC and Pd^0/phosphine systems[8b] nor with other reported methods.[8] For a substrate without β-hydrogen atoms (**5p**), the use of **L16** enabled alkynylation at the γ-position, albeit in moderate yield. Propionic acid derived amide **5q** also gave the desired product in 38% yield (see the Supporting Information).

The auxiliary can be readily removed by treatment with $BF_3{\cdot}Et_2O$ to transform **3aa** into methyl ester **7** (Scheme 4). The phthaloyl group was removed in ethylenediamine solution to give the free amine **8**, which was then protected with Boc_2O. After removal of the TIPS group in the presence



Scheme 4. Removal of the auxiliary and TIPS moieties. Reaction conditions: a) $BF_3{\cdot}Et_2O$ (2.0 equiv), MeOH, 100 °C, 30 h; b) ethylenediamine (5.0 equiv), $MeOH/CH_2Cl_2$ (1:1), 40 °C, 4 h; c) $(Boc)_2O$ (1.5 equiv), CH_2Cl_2, RT; d) TBAF (1.05 equiv), THF, 0 °C, 0.5 h. Boc = *tert*-butoxycarbonyl, TBAF = tetrabutylammonium fluoride.

of TBAF, compound **9** could be easily converted into synthetically useful intermediate **10**, which allows for the synthesis of various unnatural amino acids. The terminal triple bond could be effectively transformed into a triazole to give compound **11** in a click reaction (Scheme 5).[13] It could also be coupled with the *tert*-butyl imines of *ortho*-halogenated aldehydes to form isoquinolines **12** and **13** after cyclization.[14]



Scheme 5. Transformations of alkynyl amino acid **10**. a) $CuSO_4{\cdot}5H_2O$ (1.0 mol%), sodium ascorbate (5 mol%), H_2O/*t*-BuOH (2:1), RT, overnight; b) 1) $PdCl_2(PPh_3)_2$ (2.0 mol%), CuI (1.0 mol%), NEt_3, 55 °C, 3 h; 2) CuI (10 mol%), DMF, 100 °C; c) 1) $PdCl_2(PPh_3)_2$ (2.0 mol%), CuI (1.0 mol%), NEt_3, 55 °C, 5 h; 2) CuI (10 mol%), DMF, 100 °C.

In conclusion, pyridine-based ligands have been utilized to enable alkynylation reactions of β-methyl as well as β-methylene C(sp^3)–H bonds in carboxylic acid derivatives. Substrates containing α-quaternary carbon centers were successfully alkynylated by palladium catalysis for the first time. The development of chiral pyridine-based ligands to realize an enantioselective version of this C(sp^3)–H alkynylation is currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynylation · amino acids · C–H activation · palladium · pyridine

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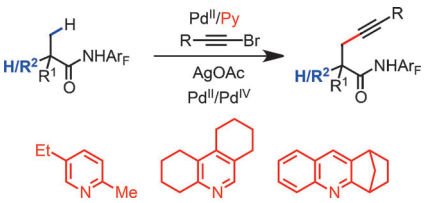
Communications

C–H Activation

H. Fu, P.-X. Shen, J. He, F. Zhang, S. Li, P. Wang, T. Liu, J.-Q. Yu* ——— ■■■–■■■

Ligand-Enabled Alkynylation of C(sp^3)–H Bonds with Palladium(II) Catalysts



Pyridine-enabled: The palladium(II)-catalyzed β- and γ-alkynylation of amide C(sp^3)–H bonds is enabled by pyridine-based ligands. This alkynylation reaction is compatible with substrates containing α-tertiary or α-quaternary carbon centers. The β-methylene C(sp^3)–H bonds in various carbocyclic rings were also successfully alkynylated.