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Monoprotected Amino Acid (MPAA) Ligand Enabled C−H Alkynylation of Phenyl Acetic Acid

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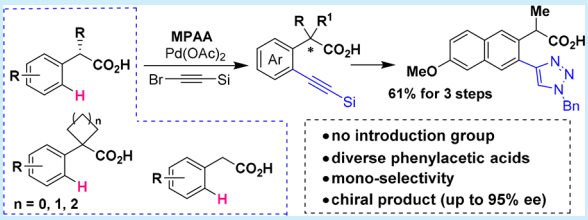
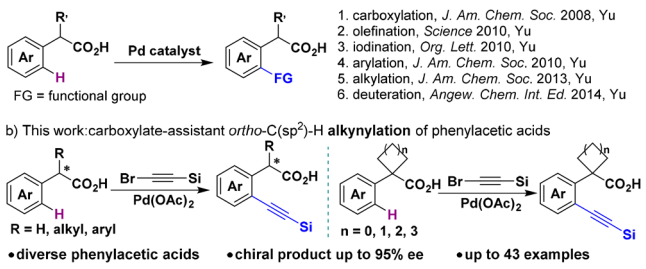
Supporting Information

ABSTRACT: A weakly carboxylate-directed palladium(II)-catalyzed *ortho*-C−H alkynylation of diverse phenylacetic acids promoted by monoprotected amino acid ligand enabled is reported. The reaction has a broad substrate scope including α-secondary, tertiary, and quaternary phenylacetic acids. Notably, the direct *ortho*-C−H alkynylation of α-quaternary phenylacetic acids and chiral α-tertiary phenylacetic acids was achieved for the first time. Moreover, this method could be used for simple and efficient gram-scale synthesis and diversification of an anti-inflammatory drug.



The phenylacetic acids are common motifs in drug molecules.[1] For example, naprofen and ibuprofen are commonly used anti-inflammatory drugs.[2] Thus, development of efficient methods for modification of phenylacetic acids has received considerable attention in synthetic chemistry. Traditional methods for derivatization of phenylacetic acids at the α-H atom and carboxyl group have been well established. In contrast, modification of phenylacetic acids at unactivated positions remains of great challenge in synthesis. Over the past decade, the transition-metal-catalyzed C−H bond activation strategy has emerged as a powerful tool for direct functionalization of organic molecules due to its advantages in atom economy, step economy, and environmental benignity.[3] Such procedures can provide simple, efficient, and functional-group-tolerable methods for direct functionalization of phenylacetic acids via C−H bond cleavage (Scheme 1a).[4] The Yu group has conducted a series of seminal work on weakly coordination-assistant *ortho*-C−H carboxylation,[4a] olefination,[4b−h] iodination,[4h−j] arylation,[4k,l] alkylation,[4m] deuteration,[4n] and acetoxylation[4h] of phenylacetic acid substrates.

Scheme 1. Palladium(II)-Catalyzed *Ortho*-C−H Functionalization of Free Phenylacetic Acids



However, the site-selective *ortho*-C−H alkynylation of phenylacetic acids is largely underexplored due to the challenge of overcoming strong coordination of an alkyne reagent with transition metal catalysts and the subsequent cyclization of the resulting *ortho*-alkynylated product. Despite success with *ortho*-C−H alkynylation of phenylacetic acid derivatives by using bidentate assisting groups,[5] critical drawbacks of preinstallation and removal of the directing group are inevitable, which limit its wide application. Therefore, the development of simple and efficient methods for direct *ortho*-C−H alkynylation of phenylacetic acids using carboxylic acid as an intrinsic directing group is highly desirable, but challenging.

Recently, Zeng and co-workers reported the first weakly coordination-assisted *ortho*-C(sp^2)−H alkynylation of aryl carboxylic acids with iridium catalysis, but the reaction proceeded with low efficiency for phenylacetic acid substrates (32−47% yields).[6] Moreover, the substrate scopes of these methods are limited to α-secondary and tertiary phenylacetic acids. To date, direct *ortho*-C(sp^2)−H alkynylation of α-quaternary phenylacetic acids and chiral α-tertiary phenylacetic acids have not yet been solved. Herein, we describe a weakly carboxylate-assisted *ortho*-C(sp^2)−H alkynylation of diverse phenylacetic acids under $Pd(OAc)_2$ catalysis, achieving the direct *ortho*-C−H alkynylation of α-quaternary phenylacetic acids and chiral α-tertiary phenylacetic acids for the first time (Scheme 1b). The reaction is also applicable to α-secondary and tertiary phenylacetic acids with a broad substrate scope.

Initially, we selected *s*-2-(4-isobutylphenyl)propanoic acid (**1a**) as a model substrate and (triisopropylsilyl)ethynyl bromide **2** as a coupling reagent. Reaction conditions such as solvent, inorganic base, oxidant, and ligand have been

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extensively screened (see the Supporting Information (SI) for details). It is noteworthy that without the *N*-Boc-Phe-OH the yield decreased dramatically to 36% (see SI Table S1). The yield in the presence of KOAc is 72% and that of NaOAc is 75%, suggesting similar reactivity regarding these two salts (see SI Table S2). We were delighted to find that the *ortho*-C(sp^2)−H alkynylated product **3a** could be obtained in 75% isolated yield and 95% ee under the following conditions: $Pd(OAc)_2$ (10 mol %), *N*-Boc-Phe-OH (20 mol %), AgOAc (2.0 equiv), and NaOAc (2.0 equiv) in 1,2-dichloroethane under air at 60 °C for 24 h.

With the optimized reaction conditions in hand, we probed its versatility in the *ortho*-C(sp^2)−H alkynylation of α-tertiary phenylacetic acids (Figure 1). As expected, chiral α-phenyl-

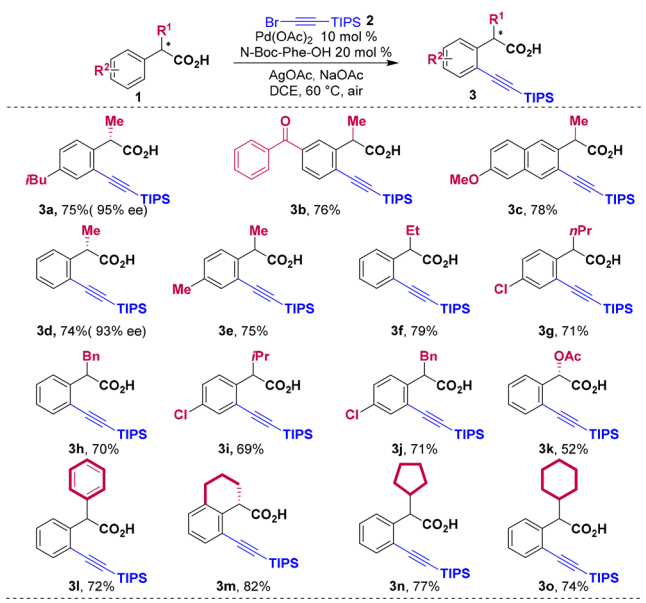

Figure 1. Scope of α-tertiary phenylacetic acids. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), *N*-Boc-Phe-OH (20 mol %), AgOAc (0.20 mmol), NaOAc (0.20 mmol), DCE (1 mL), at 60 °C for 24 h under air. Isolated yields are presented.

propionic acid (**1d**) could successfully generate the *ortho*-alkynylated product (**3d**) in 74% yield and 93% ee, which proved the high versatility and efficiency of this method for the synthesis of optically pure *ortho*-alkynylated α-tertiary phenylacetic acids. The racemic α-arylpropionic acid substrates could also give the target product in moderate to good yields (**3b**, **3c**, **3e**). To our delight, other substituents such as alkyl and aryl groups, at the α-position of phenylacetic acid, were amenable to this reaction condition, thus generating the products in moderate yields (**3f**−**3j**, **3l**−**3o**). The steric hindrance of substituents has a significant effect on the reactivity of substrates. When the substituent group is an isopropyl group having a relatively large sterically hindered structure, only a 69% yield was obtained. For the substrates with cyclopentyl and cyclohexyl substituents at the α-position, higher yields of 77% (**3n**) and 74% (**3o**), respectively, are obtained, as the steric hindrance is slightly less than that of the isopropyl group. It is worth noting that the acetoxyl protected mandelic acid (**1k**) which is a useful bioactive molecule[4h] could smoothly produce the *ortho*-alkynylated product **3k** in 52% yield. The structures of product **3c** (CCDC 1868406) and **3m** were characterized by single-crystal X-ray diffraction (see SI).

This versatile Pd(II)-catalyzed *ortho*-C−H alkynylation reaction was not limited to free α-tertiary phenylacetic acid substrates. Diverse α-secondary phenylacetic acids with various functional groups were also well tolerated, giving the *ortho*-alkynylated products in moderate to excellent yields (Figure 2). In general, both electron-donating and -withdrawing

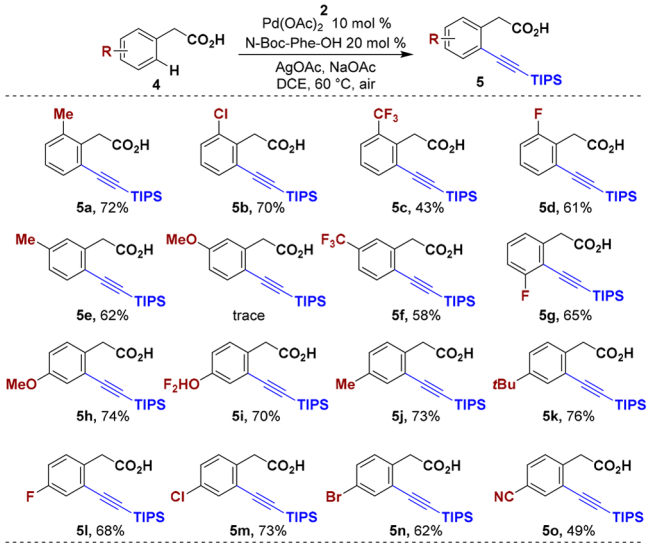

Figure 2. Scope of α-secondary phenylacetic acids. Reaction conditions: **4** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), *N*-Boc-Phe-OH (20 mol %), AgOAc (0.20 mmol), NaOAc (0.20 mmol), DCE (1 mL), at 60 °C for 24 h under air. Isolated yields are presented.

functional groups were well tolerated. Different functional groups such as methyl (**5a**, **5e**, **5j**), *tert*-butyl (**5k**), trifluoromethyl (**5c**, **5f**), difluoromethoxyl (**5i**), and methoxyl (**5h**) were compatible under the present alkynylation condition. To our disappointment, 3-methoxylphenylacetic acid gave very little *ortho*-alkynylated product. Substrates bearing a halogen group, e.g., fluoro (**5d**, **5g**, **5l**), chloro (**5b**, **5m**), and bromo (**5n**), remained intact during the Pd(II)-catalyzed *ortho*-C(sp^2)−H alkynylation reaction. Relatively lower yields were obtained when strong electron-withdrawing groups, such as trifluoromethyl or nitrile were tethered to the substrates (**5c**, **5f**, **5o**). Alkynylation of *meta*-functionalized free phenylacetic acids took place at the *para*-position of the functionalities (**5e**, **5f**). However, alkynylation of *meta*-fluoro phenylacetic acid reacted at the *ortho*-position of fluoro group (**5g**) and the other regioisomer was not isolated,[7] which is probably because of the different acidity of the C−H bond. The structures of **5c**, **5k**, and **5o** (CCDC 1867310, 1867309, and 1868316) were further confirmed by single-crystal X-ray crystallography (see SI).

With the *ortho*-C−H alkynylation of α-tertiary and secondary phenylacetic acids established, we turned our attention to the more challenging α-quaternary phenylacetic acids. We were pleased to find that the optimized conditions for *ortho*-C(sp^2)−H alkynylation of α-tertiary and secondary phenylacetic acids were also viable in the case of α-quaternary substrates, giving the desired *ortho*-alkynylated products in good yields (Figure 3). Substrates bearing different substituents on the phenyl ring reacted smoothly, providing the alkynylated products in moderate to good yields (**7g**−**7l**). It is noteworthy that α-cyclopropyl, cyclobutyl, and cyclopentyl

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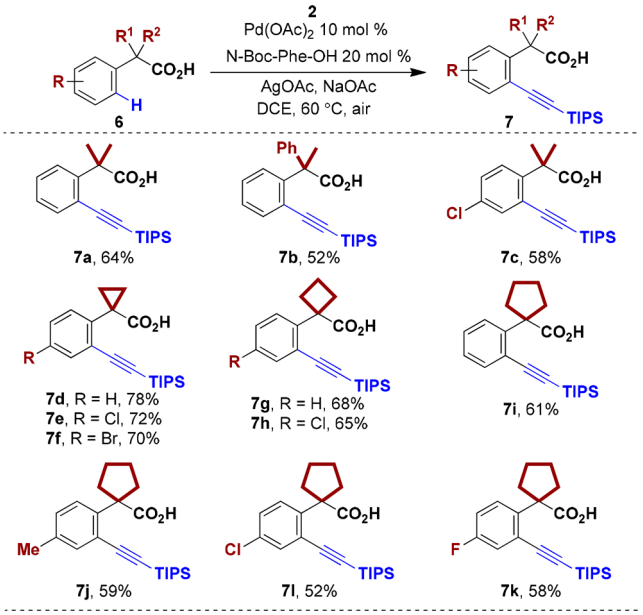
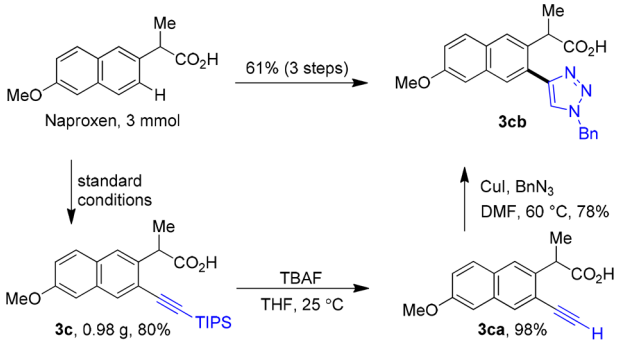


Figure 3. Scope of α-quaternary phenylacetic acids. Reaction conditions: **4** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), *N*-Boc-Phe-OH (20 mol %), AgOAc (0.20 mmol), NaOAc (0.20 mmol), DCE (1 mL), at 60 °C for 24 h under air. Isolated yields are presented.

phenylacetic acids could afford the *ortho*-alkynylated product in moderate yields (**7d**–**7l**). However, the reactivity of α-quaternary phenylacetic acids would decrease with increasing steric hindrance at the α-position (**7d**, 78%; **7g**, 68%; **7i**, 61%; **7e**, 72%; **7h**, 65%; **7l**, 52%). The structures of product **7i**, **7j**, and **7k** (CCDC 1867311, 1867314, and 1867316) were confirmed by single-crystal X-ray crystallography (see SI). To the best of our knowledge, it is the first example of *ortho*-C–H alkynylation of α-quaternary phenylacetic acids.

To highlight the synthetic utility of this procedure, a 3 mmol scale reaction was conducted using naproxen **1g** as the substrate, and the reaction proceeded smoothly to give the alkynylated product **3c** in 80% yield (Scheme 2). Furthermore,

Scheme 2. Scale-up and Diversification of Naproxen



the silyl group can be easily removed under mild reaction conditions to give the terminal alkyne **3ga**, which could be easily transformed into triazole compound **3cb** in 78% yield via a click reaction,[8] and the structure of **3cb** (CCDC 1867315) was confirmed by single-crystal X-ray crystallography (see SI).

In summary, we have developed a general and practical Pd(II)-catalyzed *ortho*-C(sp^2)–H alkynylation of free phenylacetic acids with a monoprotected amino acid (MPAA) ligand. Diverse α-secondary, tertiary, and quaternary phenylacetic acids were all tolerated in this protocol, giving the monoselective *ortho*-alkynylation products without further annulation. Notably, the more challenging alkynylation of α-quaternary phenylacetic acids as well as chiral α-tertiary phenylacetic acids are also achieved for the first time. Moreover, this protocol can be scaled-up for the synthesis and diversity modification of drug molecules. As a consequence, we expect this methodology will be rapidly adopted to prepare diverse, chiral α-arylpropionic acid derivatives for use in the development of new anti-inflammatory drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03182.

Experimental details and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1867309–1867311, 1867314–1867316, 1868316, and 1868406 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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