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DOI: 10.1039/D0CC04739B

COMMUNICATION

Weak Coordinated Nitrogen Functionality Enabled Regioselective C–H Alkynylation via Pd(II)/Mono-N-Protected Amino Acid Catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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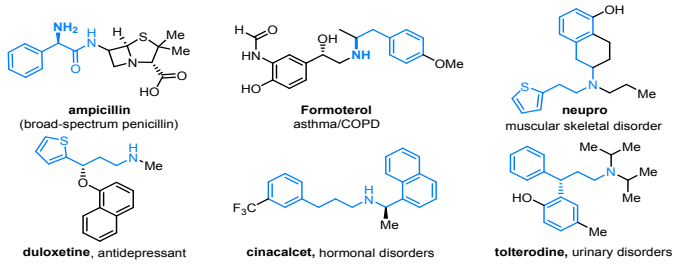
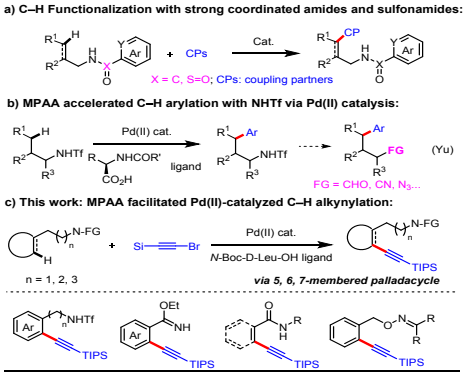
The exploration of weak coordinated amine derivatives enabled regioselective C–H functionalization remained challenging due to the elusive achievement of reactivity and selectivity simultaneously. Herein, regioselective C–H alkynylation of various readily transformable nitrogen functionality, was developed with great efficiency, with the assistance of mono-N-protected amino acid (MPAA) ligand under Pd(II) catalysis proceed via 5, 6 and 7-membered palladacycle intermediates.

Amines serves as versatile building blocks and ubiquitous structural skeletons in pharmaceuticals, material and life science. For instance, besides amino acids, benzylamines, phenylethylamines, benzedrines also act as vital precursors of pharmaceuticals, such as ampicillin, sensipar, sertraline, venlafaxine and cinacalcet, which exhibited great bioactivities as drugs (Scheme 1).[1] The great utility of amines has stimulated continuous development of general strategies for their efficient construction and rapid manipulation, e.g., reductive amination, cross-couplings and direct C–H amination.[2]



Scheme 1. Selective amines skeletons in pharmaceuticals.

Considering the atom and step-economy of the overall process, direct C–H functionalization of amine derivatives has emerged as a reliable platform enabled concise construction of functionalized amine libraries.[3] In this context, to well balance the reactivity of the metal catalyst and regioselectivity of the amine substrates, great efforts have been devoted in the catalytic system and ligand design, which led to fruitful accomplishment. However, strong directing strategy with rigid and intrinsic functionality, *et. al*., quinolone or pyridine derived amides and sulfonamides, would be hard to remove or for the further transformation (Scheme 2). To omit the tedious procedure for the additional introduction and removal of directing groups, the use of readily available and transformable amine derivatives held great synthetic practicality.



Scheme 2. C–H Functionalization of amine derivatives.

To this end, key challenges and limitations lied in the acquisition of practical C–H transformations mainly included: 1) with readily available substrates, and delivering to easily decorative products,[4] which would make the overall process in a concise manner, enabling the practical delivery of complex molecular libraries; 2) proximal directing strategy was often used for the achievement of regioselectivity in the C–H functionalization, while the development of remote control cyclometalation intermediates, would be synthetically useful and highly desirable.[5]

Our continuous efforts toward the efficient construction of functionalized alkynes,[6] recently, we have developed weak coordination functionalities, such as ketones, esters and primary

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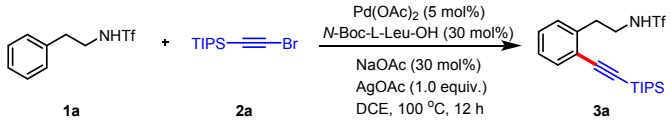
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

sulfonamides facilitated *ortho* C–H alkynylation via Ir(III) catalysis. Considering the synthetic utility of amines, and inspired by Yu's pioneer work on MPAA (mono-*N*-protected amino acids) accelerated C–H bond functionalizations,[7] we reported herein a versatile Pd(II)/MPAA catalytic system enabled regioselective C–H alkynylation of weak coordinated amine derivatives. Key feature of this transformation included: 1) amines, imines and amides could serve as readily accessible and transformable substrates, via possible 5, 6 and 7-membered palladacycle intermediates. 2) Amino acid could also enable regioselective C–H alkynylation of aryl aldehydes via transient directing strategy, the overall transformation served as reliable platform, leading to rapid construction of alkyne libraries.

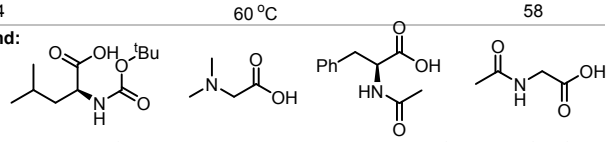
Table 1. Optimization of reaction conditions. [a]



1a 2a 3a

Entry	Variation of standard condition	Yield (%)[b]
1	Standard condition	83
2	$PdCl_2$ as the catalyst	79
3	$NiCl_2$ as the catalyst	n.r.
4	$[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst	n.r.
5	$[RhCp^*Cl_2]_2$ as the catalyst	n.r.
6	with N,N-Dimethylglycine as the ligand	n.r.
7	with Ac-Phe-OH as the ligand	55
8	with Ac-Gly-OH as the ligand	64
9	without $Pd(OAc)_2$	n.r.
10	without AgOAc	26
11	$Cu(OAc)_2$ instead of AgOAc	< 10
12	Addition of PivOH (0.5 equiv.)	22
13	Toluene or DMF as the solvent	< 10
14	60 °C	58

Ligand:

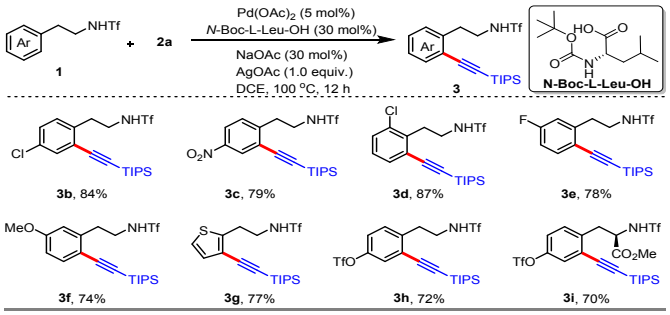


N-Boc-L-Leu-OH **N,N-Dimethylglycine** **Ac-Phe-OH** **Ac-Gly-OH**

[a] Standard conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), NaOAc (20 mol%), AgOAc (30 mol%), *N*-Boc-D-Leu-OH (10 mol%), DCE (1 mL), air, 100 °C, 12 h.

To commence our study on amine directed *ortho* C–H alkynylation, we selected sulfonamide **1a** as the model substrate,[8] and with bromoalkyne **2a** as the alkynylation reagent,[9,10] under various metal catalysis. The results revealed that Pd(II) exhibited great reactivity with the assistance of mono-*N*-protected amino acid *N*-Boc-D-Leu-OH, and $Pd(OAc)_2$ exhibited better performance than $PdCl_2$ (entry 2). Notably, the use of Ni(II), Rh(III), Ru(II) catalyst led to no desired alkyne product **3a** (entries 3-5). Notably, the addition of *N*-protected amino acid derivatives significantly facilitate this transformation (entries 6-8), and *N*-Boc-D-Leu-OH as ligand gave the optimal yield of the *ortho* C–H alkynylation product **3a**. Control experiments showed that Pd(II) and AgOAc were critical for the generation of the desired *ortho* alkynylation product **3a** (entries 9,10), while the use of Cu(I) or Cu(II) salt instead of Ag(I) led to no desired product (entry 11). Addition of protonic acid such as PivOH led to poor yield of product **3a** (entry 12), solvent such as DMF or toluene gave inferior results (entry 13). And lower the temperature to 60 °C gave moderated yield of **3a** (entry14).

With the optimal conditions in hand, we next explored the synthetic generality of aryl ethylamines in this regioselective C–H alkynylation under MPAA/Pd(II) catalysis (Scheme 3). Halides such as chloro at *para* or *ortho* position of arenes (**3b**, **3d**), were compatible, which could be further modified via metal-catalyzed cross-couplings. Aryl ethylamines with readily transformable groups, e.g., nitro, on the arenes, also showed great efficiency (**3c**). Notably, this transformation was sensitive to steric hindrance, when exposure *meta*-substituted phenyl ethylamines to the standard reaction conditions (**3e**, **3f**), this C–H alkynylation took place exclusively at less hindered position. Heterocycles were also suitable substrates in this reaction, when with 2-ethylamine substituted thiophene under Pd(II)/MPAA catalysis, directing ability of weak coordinated NHTf transcended the innate chemoselectivity, and C–H alkynylation proceeded at C3 position without the observation of C5–H alkynylation product (**3g**). Amino acid derivatives, e.g., L-Tyrosine, (**3i**), could well participate in this C–H alkynylation.

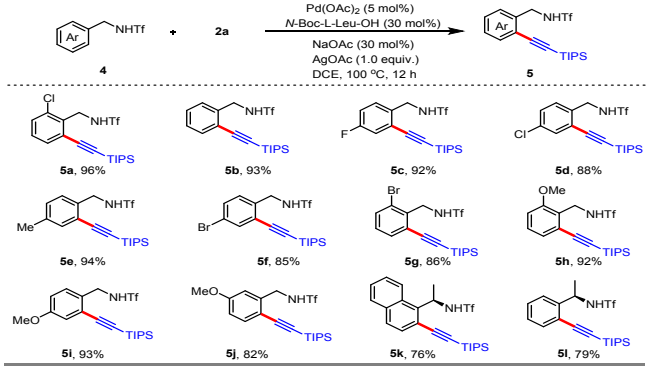


Scheme 3. Regioselective C–H alkynylation of aryl ethylamines.

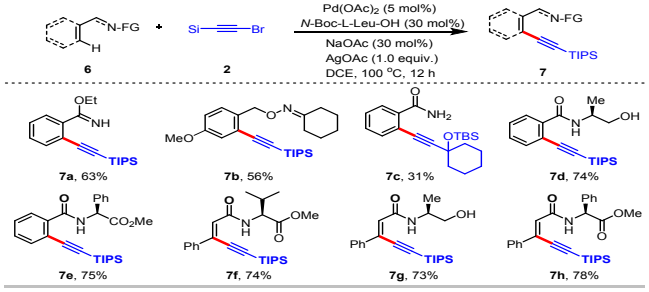
The above regioselective C–H alkynylation of aryl ethylamines, which might proceed via 6-membered iridacycle intermediates, encouraged us to further investigate the synthetic potential in C–H alkynylation of benzyl amines via a possible 5-membered organometallic intermediates. As depicted in Scheme 4, halides such as fluoro (**5c**), chloro (**5a**, **5d**), bromo (**5f**, **5g**) could be compatible, affording to the corresponding C–H alkynylation products in high yields. Electron-donating groups, e.g., methyl, methoxyl substituted benzyl amines (**5b**, **5e**, **5i**) exhibited relatively higher yields to that of electron-withdrawing groups. Notably, this regioselective C–H alkynylation showed no significant position effect, for instance, with *ortho*, *meta* and *para*-methoxyl group substituted benzyl amines (**5h**, **5i**, **5j**), proceeded smoothly. Great efficiency was also observed in the regioselective C–H alkynylation with (*R*)-1-(naphthalen-1-yl)ethan-1-amine and (*R*)-1-phenylethan-1-amine (**5k**, **5l**).

Readily transformable imidate esters, which have been demonstrated to serve as traceless directing groups in C–H

activation,[11] could also well participate in this regioselective C–H alkynylation (**7a**). The alcohol derived ketoxime **6b** could also furnish the desired C–H alkynylation product **7b** under this versatile Pd(II)/MPAA catalytic system via a possible 6-membered palladacycle intermediate. Notably, sterically hindered alkyl substituted bromoalkyne was also suitable alkynylation reagent, which enabled regioselective C–H alkynylation of primary amide, leading to alkyne product **7c**. Inspired by this amino acid ligand facilitated regioselective C–H alkynlation, amino alcohols and amino acids derived amides could well undergo this reaction with great regioselectivity (**7d**, **7e**). Notably, stereoselective construction of conjugated enynes (**7f**, **7g**, **7h**), which serve as key skeletons in pharmaceutical and advanced materials, were also realized.

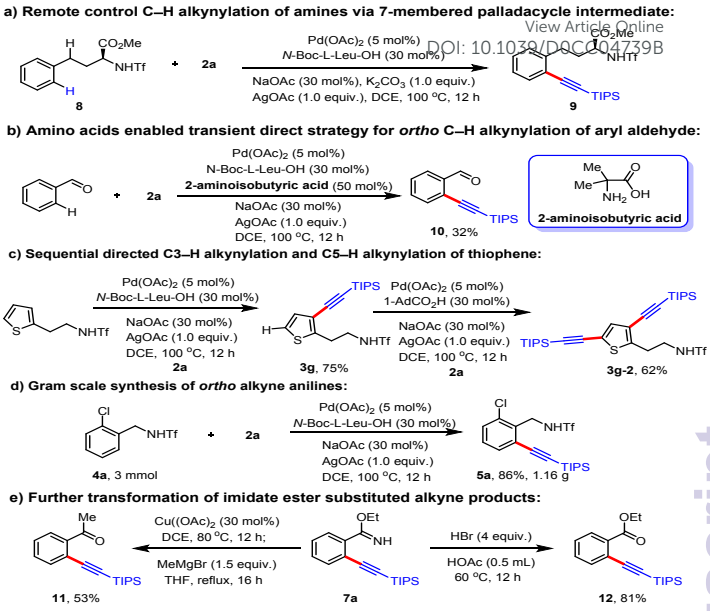


Scheme 4. Regioselective C-H alkynylation of benzyl amines.



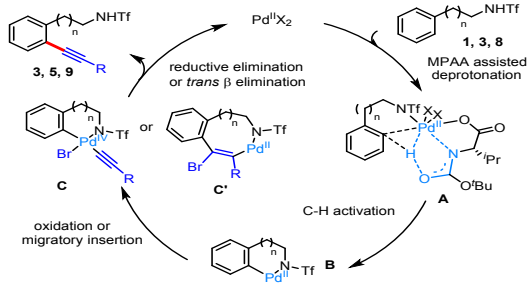
Scheme 5. Regio- and stereo-selective C–H alkynylation.

Remote control of regioselectivity in the weak coordination facilitated C–H functionalization held great synthetic promise.[5] Delightfully, this NHTf directed Pd(II)/MPAA catalysis could also enable *ortho* C–H alkynylation of *L*-Homophenylalanine derivative, via possible 7-membered palladacycle intermediate (Scheme 6-a). Notably, by using transient directing strategy,[12] and with the assistance of 2-aminoisobutyric acid in this Pd(II)/MPAA catalysis, *ortho*-selective C–H alkynylation of benzaldehyde was also achieved (Scheme 6-b). This Pd(II)/MPAA catalysis also enabled sequential C3–H and C5–H alkynylation of 2-(thiophen-2-yl)ethan-1-amine (Scheme 6-c). Gram scale synthesis of alkyne product **5a** was feasible (Scheme 6-d). Significantly, the obtained imidate ester directed C–H alkynylation products could be readily transformed to the corresponding ketone and ester **11** and **12** (**Scheme 6-e**), which serve as key precursors for the rapid construction of complex skeletons via Diels-Alder reaction.[13]



Scheme 6. Synthetic transformations.

According to the literature and experimental observations, it was proposed that ligand exchange of Pd(II) catalyst to the amine substrates initiated this transformation (Scheme 7). Notably, with the assistance of MPAA, deprotonation took place with lower activation barrier, delivering to the corresponding 5, 6 and 7-membered palladacycle intermediate **B**. Further oxidation of the palladacycle intermediate with bromoalkyne might procced to give Pd^{IV} species **C**, which underwent subsequent reductive elimination[14] to afford the desired alkynes. Alternatively, alkyne migratory insertion into the palladacycle **B** led to the palladacycle species **C'**, which followed by *trans* β elimination to release the desired alkynes.[8, 15-17]



Scheme 7. Proposed mechanism.

In summary, we have developed herein a versatile and regioselective C–H alkynylation of weak coordination nitrogen functionality, enabled by Pd(II)/MPAA catalysis. Key features included various benzylamines, arylethyl amines and benzedrines could well serve as suitable substrates, via possible 5, 6 and 7-membered palladacycle intermediates. Moreover, readily transformable imines and amino acid/alcohols derived amides could also enabled this regioselective C–H alkynylation. Further synthetic application

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DOI: 10.1039/D0CC04739D

of this Pd(II)/MPAA catalysis in C–H functionalization of weak coordination is underway.

We are grateful for the financial supported by the National Natural Science Foundation of China (21602032, 21502066), the Natural Science Foundation of Guangdong Province (No. 2014a030310113), the Program for Innovative Research Team of Huizhou University, the Open Fund of the Key Laboratory of Functional Molecular Engineering of Guangdong Province (No.2018kf02, South China University of Technology).

Conflicts of interest

There are no conflicts to declare.

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Graphic abstract

MPAA facilitated Pd(II)-catalyzed C-H alkynylation: