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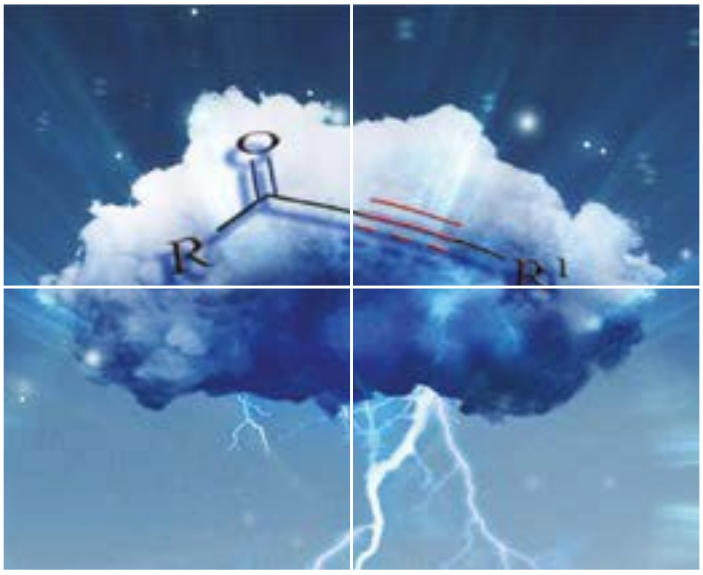

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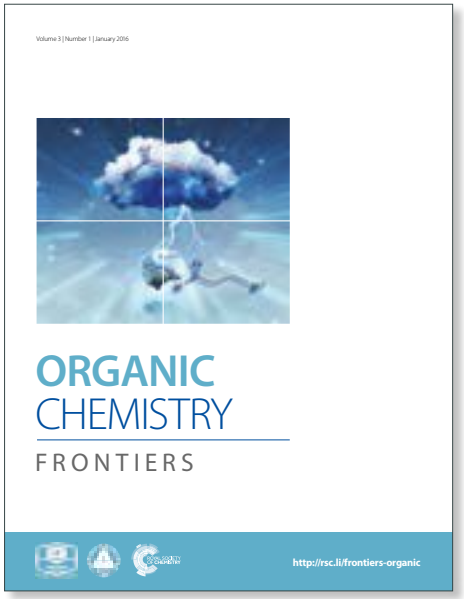

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COMMUNICATION

Room-temperature Pd(II)-catalyzed direct C–H TIPS-ethynylation of phenylacetic amides with terminal alkyne

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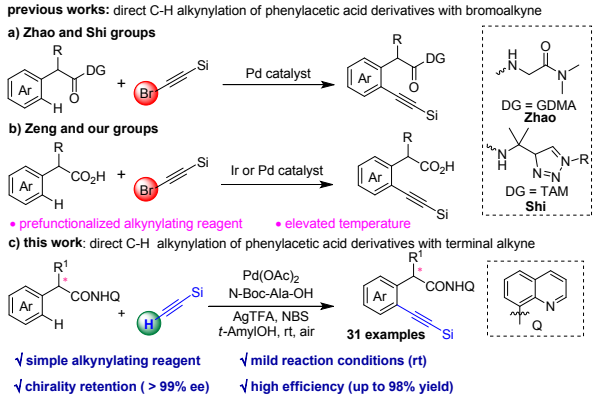
Ligand-promoted room-temperature Pd(II)-catalyzed direct C–H alkynylation of phenylacetic amides has been developed using commercially available TIPS-acetylene as an efficient alkynylating reagent, where 8-aminoquinoline was employed as a removable bidentate auxiliary, thus giving rise to optically pure *ortho*-alkynylated *α*-APA in a highly efficient manner.

Alkynes are an exceptionally versatile functional group and are ubiquitous in pharmaceuticals, organic materials, and natural products.[1] Therefore, the development of efficient synthetic methodologies to construct alkyne motifs is greatly attractive. In recent years, with the rapid progress in transition-metal-catalyzed C–H functionalization,[2] direct C–H alkynylation of arenes has received much attention due to its advantages in atom-economy, step-economy and environmental benignity.[3-6] To address the homocoupling issue of terminal alkynes under oxidative conditions,[7] preactivated alkynylating reagents such as alkynyl halides[3] and benziodoxolone-based hypervalent iodine reagents[4] were successfully explored as coupling partners in C–H activation reactions. Despite these advances, it would be ideal to take advantage of ubiquitous terminal alkynes as the alkynylating reagent, which would provide a straightforward and step-economy procedure. Although great progress have been made on transition-metal catalysed C-H alkynylation of activated substrates with terminal alkynes,[5] the direct alkynylation reaction with unprefunctionalized alkynylated reagents via inert C-H bond activation is underdeveloped.[8] Thus, it is highly desirable to develop mild and efficient alkynylation systems to broaden the current limited substrate scope.

Phenylacetic acids and α-aryl propionic acids (α-APAs) are significantly important organic skeletons in medicinal chemistry and organic synthesis.[9] In past few years, significant progress has been made in direct C–H alkynylation of phenylacetic acid and α-APA derivatives.[10]



Scheme 1 Direct C–H alkynylation of phenylacetic acid derivatives

In 2016, Zhao[10a] and Shi[10b] groups reported Pd(II)-catalyzed C–H alkynylation of phenylacetic acids and aryl acids with alkynylbromide using bidentate directing groups. In 2017, Zeng group developed the first carboxylate-directed iridium catalyzed C–H alkynylation of phenylacetic acids using bromoalkyne as reagent.[10c] Very recently, our group reported ligand-promoted Pd(II)-catalyzed direct C–H alkynylation of free phenylacetic acids with bromoalkyne.[10d] Nevertheless, there are still some drawbacks including the prebromination of terminal alkyne, and relative higher temperature need to be overcome. As our continuous endeavor on developing efficient and mild C–H functionalizations,[11] we herein describe a room-temperature Pd(II)-catalyzed direct C–H alkynylation of phenylacetic acid derivatives with simple terminal alkyne promoted by mono-protected amino acid ligands.

Initially, we selected *s*-2-(4-isobutylphenyl)propanoic amide (**1a**) as a model substrate and (triisopropylsilyl)acetylene **2** as a coupling reagent with the conditions previously established for Pd-catalyzed C–H alkynylation reaction with bromoalkyne.[10d]

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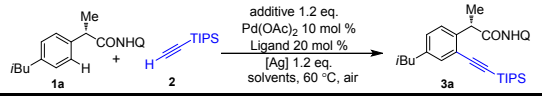
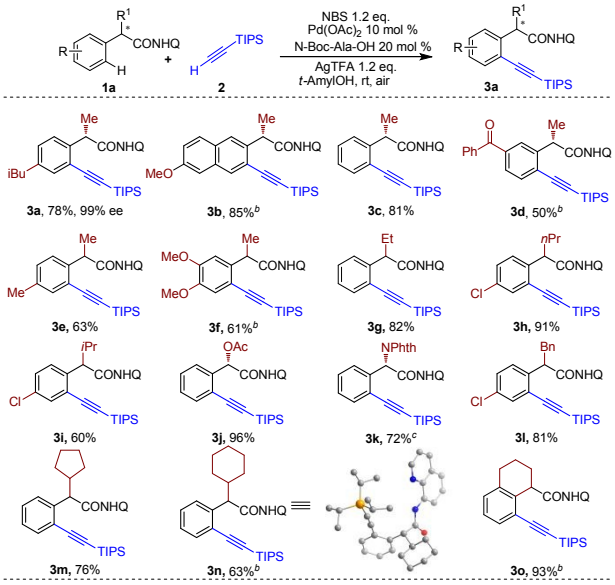
However, the alkynylated product **3a** was not detected (Scheme 2, entry 1). Reaction did not take place in other solvents such as DCE, and toluene (Scheme 2, entry 2, 3). To our delight, high yield of **3a** (77%) was obtained, when NBS was added to the reaction (entry 4). However, other additives such as NCS, NIS, and I_2 had low activities (entry 5-7). The NBS maybe play an important role in the generation of bromoalkyne in the presence of Ag salts. Then, we screened different silver salts. Silver nitrate is effective, giving the product in 63% yield (entry 8), but other silver salts such as Ag_2CO_3 and Ag_2O had little effect on this alkynylation reaction (entry 9, 10). At last, a series of acids are screened (Scheme 2, entry 11-15, 17, 18). Although most acid ligands could promote the reaction, *N*-Boc-Ala-OH gave the best result. To our delight, the reaction could proceed successfully even at room temperature, giving the desired product in 78% yield and 99% ee (entry 16). Considering that palladium catalysts usually possess high reactivity in C–H activation, 5 mol% of $Pd(OAc)_2$ was used in this reaction, only giving the product **3a** in 35% yield. Based on these optimization studies, we confirmed that 10 mol % $Pd(OAc)_2$, 20 mol % *N*-Boc-Ala-OH, 1.2 equiv of AgTFA and 1.2 equiv of NBS in *t*-AmylOH at room temperature offer the best reaction conditions for this C–H alkynylation reaction.



Entry	Ligand (20 mol %)	[Ag]	Additive	Solvent	Yield[a] of **3a**
1	*N*-Boc-Ala-OH	AgTFA	/	DCE	0%
2	*N*-Boc-Ala-OH	AgTFA	/	toluene	0%
3	*N*-Boc-Ala-OH	AgTFA	/	*t*-AmylOH	0%
4	*N*-Boc-Ala-OH	AgTFA	NBS	*t*-AmylOH	77%
5	*N*-Boc-Ala-OH	AgTFA	NCS	*t*-AmylOH	< 5%
6	*N*-Boc-Ala-OH	AgTFA	NIS	*t*-AmylOH	< 5%
7	*N*-Boc-Ala-OH	AgTFA	I_2	*t*-AmylOH	20%
8	*N*-Boc-Ala-OH	$AgNO_3$	NBS	*t*-AmylOH	63%
9	*N*-Boc-Ala-OH	Ag_2CO_3	NBS	*t*-AmylOH	< 5%
10	*N*-Boc-Ala-OH	Ag_2O	NBS	*t*-AmylOH	< 5%
11	PivOH	AgTFA	NBS	*t*-AmylOH	61%
12	$AdCO_2H$	AgTFA	NBS	*t*-AmylOH	62%
13	*N*-Boc-Val-OH	AgTFA	NBS	*t*-AmylOH	64%
14	*N*-Boc-Ile-OH	AgTFA	NBS	*t*-AmylOH	62%
15	*N*-Ac-Ala-OH	AgTFA	NBS	*t*-AmylOH	66%
16[b]	*N*-Boc-Ala-OH	AgTFA	NBS	*t*-AmylOH	78%[c] (99% ee)
17	CH_3CO_2H	AgTFA	NBS	*t*-AmylOH	58%
18	CF_3CO_2H	AgTFA	NBS	*t*-AmylOH	60%
19[d]	*N*-Boc-Ala-OH	AgTFA	NBS	*t*-AmylOH	35%

Scheme 2 Optimization of the reaction conditions. [a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), [Ag] (0.12 mmol), additive (0.12 mmol), solvent (1 mL), at 60 °C for 24 h under air. Isolated yields. [b]mono:di = 5:1. [c]Conducted at rt. [d]$Pd(OAc)_2$ (5 mol %) was used.

With the optimized reaction conditions in hand, we probed its versatility in the C(sp^2) –H alkynylation of α-aryl propionic amides and α-tertiary phenylacetic amides (Scheme 3). As expected, other chiral α-aryl propionic amide (**3b, 3c, 3d**) could successfully generate the *ortho*-alkynylated products in good yields, which proved high versatility and efficiency of this method for the synthesis of optically pure *ortho*-alkynylated α-aryl propionic acids. The racemic α-aryl propionic amide substrates with methyl and methoxyl substituents could also give the target product in moderate yields (**3e, 3f**). To our delight, other alkyl substituents at α-position of phenylacetic acids were amenable to this reaction condition, thus generating the products in good to excellent yields (**3g-3i, 3l-3o**). The steric hindrance of substituent has a significant effect on the reactivity of substrates. When the substituent group is an isopropyl group (**1i**) having a relatively large sterically hindered structure, only 60% yield was obtained. The substrates with cyclopentyl and cyclohexyl substituent at α-position, could give the desired products in 76% (**3m**) and 63% (**3n**), respectively. The structure of product **3n** was characterized by single-crystal X-ray diffraction.[12] It is worth noting that the protected (*s*)-mandelic acid (**1j**) and (*s*)-α-phenylglycine (**1k**) could smoothly produce the *mono*-alkynylated product in 96% and 72% yields, respectively.



Scheme 3 Scope of α-tertiary phenylacetic amides. [a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), *N*-Boc-Ala-OH(20 mol %), AgTFA (0.12 mmol), NBS (0.12 mmol), *t*-AmylOH (1 mL), at rt for 24 h under air. Isolated yields are presented. [b]Conducted at 60 °C. [c]Conducted at 80 °C.

This mild and efficient Pd(II)-catalyzed C–H alkynylation reaction was not limited to α-aryl propionic acid and α-tertiary phenylacetic acid substrates. Diverse phenylacetic acid derivatives with various functional groups were also well tolerated, giving the *ortho*-alkynylated products in good to excellent isolated yields (Scheme 4). Both electron-donating and electron-withdrawing groups at the *ortho*- (**5a-5d**), *meta*- (**5e-5j**), and *para*- (**5k-5t**) positions are well-tolerated. Additionally, the reaction showed good compatibility with a wide range of valuablefunctional groups, including fluoro (**5b, 5g, 5m**), chloro (**5c**, **5h, 5n**), bromo (**5o**), iodo (**5q**), alkyl (**5a, 5e, 5k, 5r**), methoxyl (**5f, 5l, 5t**), acetylamino (**5p**), nitro (**5s**),

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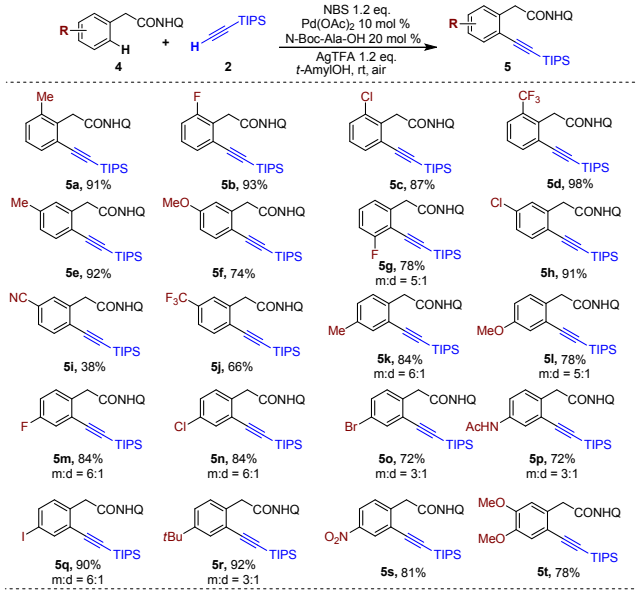
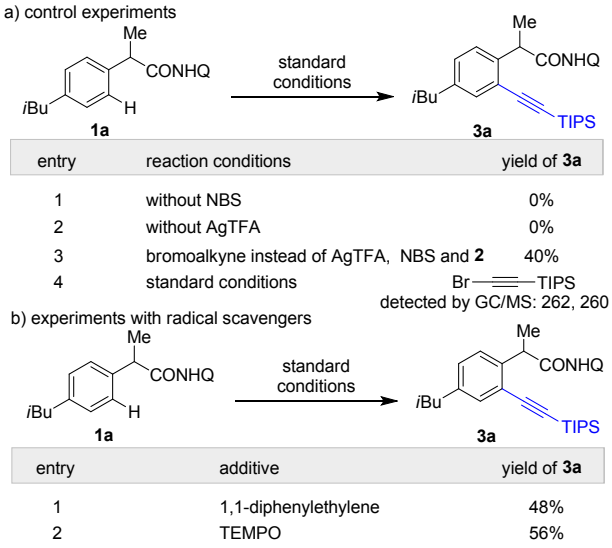
cyano (**5i**), and trifluoromethyl (**5d, 5g**) substituents. Interestingly, substrates bearing methyl, methoxyl, chloro, trifluoromethyl, and cyano at *meta*-position, respectively, offered the corresponding alkynylation product with high regioselectivity and good yields. However, the substrates with *para*- positions have low regioselectivity, producing mono- and di-alkynylated product (**5k-5r**). Nevertheless, the *meta*-fluoro derivatives gave a mixture of mono- and di-alkynylated products in good yield but the alkynylation of *meta*-fluoro phenylacetic amide (**4g**) reacted at the *ortho*-position of fluoro group probably because of different acidity of C–H bond. These results revealed that the nature of the substituent at the meta-position played a vital role in determining the outcome of the reaction. Notably, polysubstituted substrate, such as (3,4-dimethoxylphenylacetic amide) (**4t**), is also applicable to deliver the desired product in 78% yield. To better define the scope of this reaction, we further explored other terminal alkynes such as phenylacetylene and methyl propiolate. However, no expected coupling products were observed, indicating that the presence of a TIPS substituent was crucial for this reaction.



Scheme 4 Scope of phenylacetic amides. Reaction conditions: **4** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), N-Boc-Ala-OH(20 mol %), AgTFA (0.12 mmol), NBS (0.12 mmol), *t*-AmylOH (1 mL), at rt for 24 h under air. Isolated yields are presented.

To gain insight into the reaction mechanism, preliminary mechanistic experiments were also performed. Firstly, control experiments were carried out. As shown in Scheme 4a, no product **3a** was detected in the absence of NBS or AgTFA under standard reaction conditions. However, the alkynylation product **3a** could be obtained in 40% yield with bromoalkyne as alkynylating reagent instead of terminal alkyne **2**, NBS and AgTFA (Scheme 4a). The control experiments show that NBS and AgTFA played crucial roles in the formation of bromoalkyne, which may be an important intermediate in this reaction. To further understand the detailed mechanism, the (bromoethynyl)triisopropylsilane was detected in situ by GC/MS analysis (262, 260) (See SI). Secondly, moderate yields of **3a** were obtained when the reaction was performed in the presence of radical scavengers, such as 1,1-diphenylethylene and TEMPO, indicating that a radical pathway might not be involved (Scheme 4b).

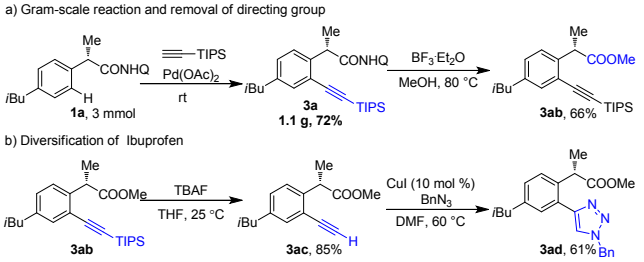


entry	reaction conditions	yield of **3a**
1	without NBS	0%
2	without AgTFA	0%
3	bromoalkyne instead of AgTFA, NBS and **2**	40%
4	standard conditions	Br—≡—TIPS detected by GC/MS: 262, 260

entry	additive	yield of **3a**
1	1,1-diphenylethylene	48%
2	TEMPO	56%

Scheme 4 Mechanistic studies

As shown in Scheme 5, a gram-scale synthesis was performed, giving the desired alkyne product in 72% isolated yield. The sequential removal of 8-aminoquinonline, esterification, and deprotection of TIPS group afford alkynylated ibuprofen derivatives in 66%, 85% isolated yield, respectively.[13]



Scheme 5 Synthetic application

In conclusion, we have developed a room-temperature Pd(II)-catalyzed direct C–H alkynylation of phenylacetic amides with terminal alkyne promoted by mono-protected amino acids. The reaction demonstrates broad substrate scope and good functional group tolerance. Notably, optically pure *ortho*-alkynylated *α*-APAs could be obtained with excellent chirality retention. The synthetic application of this protocol has been proved by gram-scale synthesis and diversification of drug molecule.

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KLSAOFM1702), the National Science Foundation for Distinguished Young Scholars of China (No. 21525101), and Hubei University are gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

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12 CCDC 1877769 (**3n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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