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Silver-Free Palladium-Catalyzed sp^3 and sp^2 C−H Alkynylation Promoted by a 1,2,3-Triazole Amine Directing Group

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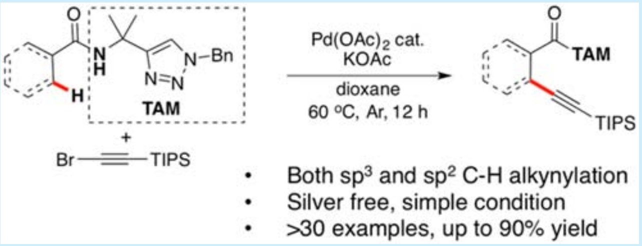
Ⓢ *Supporting Information*

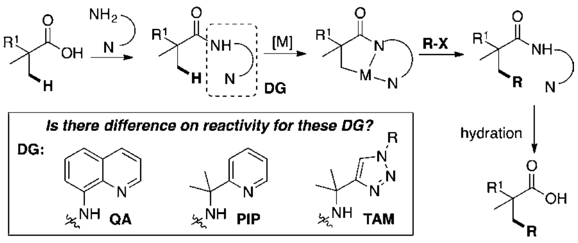
ABSTRACT: Triazole amine was identified as an effective directing group in promoting C−H alkynylation under silver-free conditions. No other external oxidant was required, and the alkynylation products were received in good to excellent yields. X-ray crystallographic analysis confirmed a direct C−H activation intermediate. Other typical directing groups, including pyridine amine (PIP) and 8-aminoquinoline (QA), gave almost no reaction under identical conditions, which highlighted the unique reactivity of the triazole directing group in direct C−H functionalization.



During the past decade, transition-metal-catalyzed C−H activation has been widely applied as an efficient approach in complex molecule synthesis.[1] Recently, the directing group (DG) strategy has gained increased attention due to its ability to achieve excellent site-selectivity. To target the more challenging inactive sp^3 C−H bond, various directing groups have been developed.[2] Among the reported systems, the bidentate directing groups have been extremely effective due to their ability to form chelation with metal complexes.[3] Two representative examples are 8-aminoquinoline (QA)[4] and α,α-dimethyl-2-pyridinemethanamine (PIP),[5] which have been used to modify substrates containing a COOH group through amide formation (Scheme 1).

Our group has been working on the development of transition-metal catalysts using 1,2,3-triazole ligands during the last several years.[6] These efforts have led to the thought of using 1,2,3-triazole derivatives as potential directing groups in C−H activation.[7] Meanwhile, the Ackermann group first reported the use of triazole-amine directing group (TAM) in 2014 for a successful iron-catalyzed C−H functionalization.[8] Considering the reactivity difference among these various heteroaromatic structures, we wondered whether the unique electronic nature of 1,2,3-triazole could provide new reactivity to achieve challenging transformations that do not proceed well with QA and PIP directing groups.[9] Herein, we report the utilization of TAM directing group in promoting sp^3 and sp^2 C−H alkynylation under silver-free conditions. In this study, the C−H activation intermediate was isolated, and its structure was confirmed by X-ray crystallography. Importantly, both QA and PIP derivatives gave almost no reaction under identical conditions, which highlighted the unique properties of the TAM directing group in selective C−H activation.

Scheme 1. Removable DG for Selective C−H Activation



Alkynes are one of the most common and widely applied building blocks for chemical, medicinal, and material research. Sonogashira coupling has been the dominant approach for sp^2−sp C−C cross coupling.[10] However, metal-catalyzed sp^3−sp bond formation was a challenge due to competitive β-hydride elimination when alkyl halide was applied. Thus, metal-catalyzed C−H alkynylation would offer an alternative method to install alkyne group on sp^3 C−H bond with high efficiency.[11] Chatani and co-workers reported the first example of sp^3 C−H alkynylation using 8-aminoquinoline (QA) as the chelating directing group.[12] Under their optimal conditions, a stoichiometric amount of silver salt was required. According to the author, silver salt served a dual role as both terminal oxidant and halide scavenger (Scheme 2A). The major limitation of this method was the reaction substrate scope, in which only the methylene sp^3 C−H bond (CH_2) was compatible. Terminal CH_3 afforded no product under identical conditions. Later, Chen improved this method using the same directing group and extended the scope to β-substituted α-amino acids derivatives.[13] However, silver salt was still required. Yu also reported a similar transformation with the Yu−Wasa auxiliary as a directing group. In that work, a special

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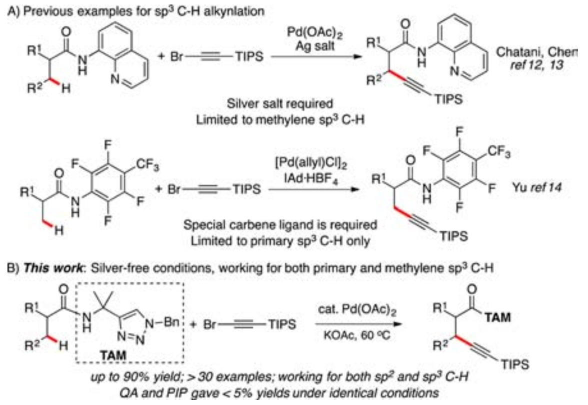
Scheme 2. Removable DG for Selective C−H Activation



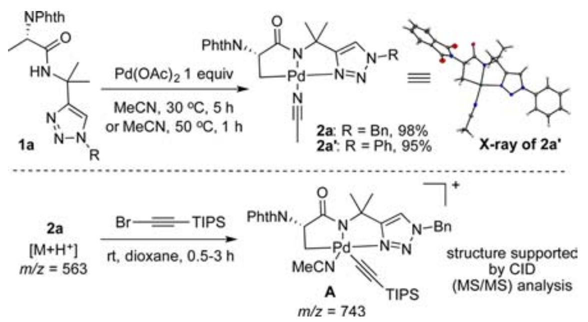
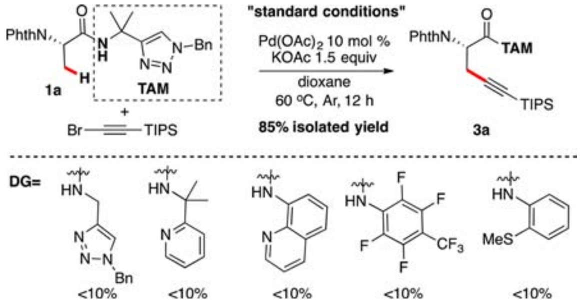


Figure 1. TAM-promoted C−H activation.

Table 1. Optimization of the Reaction Conditions[a,b]



entry	variations from the “standard” conditions	conv of **1a** (%)	yield of **3a** (%)
1	w/o $Pd(OAc)_2$	0	0
2	w/o KOAc	<10	<10
3	AgOAc instead of KOAc	92	70
4	NaOAc instead of KOAc	20	12
5	K_2CO_3 instead of KOAc	90	77
6	DCE as solvent	92	80
7	toluene as solvent	62	52
8	O_2 instead of Ar	100	80
9	5% $Pd(OAc)_2$	85	79
10	50 °C	65	59

[a] Conditions: **1a** (0.1 mmol), bromoalkyne (0.15 mmol), $Pd(OAc)_2$ 10 mol %, and additives in the solvent (0.3 mL). [b] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as internal standard.

IAd−carbene ligand was required to enhance the reactivity of the Pd catalyst.[14] As a result, the reaction only worked for the primary sp^3 C−H bond. It is clear that the development of new conditions to promote direct C−H alkynylation with a broader reaction scope and mild conditions (silver free) is highly desirable.

As shown in Scheme 1, the directed C−H functionalization typically involves three key steps: (1) C−H activation, (2) oxidative addition, and (3) reductive elimination.[15] To explore the feasibility of TAM in promoting sp^3 C−H activation, we prepared TAM-modified compound **1a**. A stoichiometric amount of $Pd(OAc)_2$ was used to react with **1a**,and the reaction was monitored by NMR.[16] A very clean reaction was observed with complex **2a** obtained in nearly quantitative yield under mild conditions (Figure 1). The structure of **2a**′ was unambiguously confirmed by X-ray crystallography.

Notably, complexes **2a** and **2a**′ were formed under very mild conditions, emphasizing the strength of the TAM directing group in promoting sp^3 C−H activation. With the goal of achieving C−H alkynylation, our next question was whether a bromoalkyne could serve as an oxidant to promote the oxidation of **2a** to the Pd(IV) intermediate without the assistance of silver salt. To explore this process, complex **2a** was used to react with the bromoalkyne. With CH_3CN as the solvent, no reaction had occurred after 24 h at 60 °C. Interestingly, when the solvent was switched to dioxane, a complex mixture was observed by NMR while the reaction was heated at 50 °C for 5 h. Monitoring the reaction with ESI-MS indicated the formation of Pd-containing ion **A** ($m/z = 743$). The structure was supported from the MS/MS studies (Figure 1, see details in the SI). These MS results provided strong evidence that, with the TAM directing group, the Pd(II) complex **2a** could be further oxidized to Pd(IV) by bromoalkyne alone without requiring other external oxidants, such as silver salts. Combining these results, we postulated that TAM should be a good directing group for direct C−H alkynylation under the silver-free conditions. To test this hypothesis, we conducted detailed condition screening with a catalytic amount of $Pd(OAc)_2$. The results are summarized in Table 1.

As shown in Table 1, under optimal conditions (10% $Pd(OAc)_2$, KOAc as base, dioxane as solvent, and argon protection), the desired sp^3 C−H alkynylation product **3a** was obtained in 85% isolated yields. KOAc was found to be pivotal. Notably, as expected, silver acetate could also promote the reaction, though with slightly lower yield at 60 °C. These results implied that the function of silver salts might be more than a simple oxidant as proposed in previous examples. Further investigations are necessary to elucidate the role of silver salts in this reaction. Among the tested solvents, dioxane gave the best results. Reducing the catalytic loading (5%) or reaction temperature (50 °C) caused the incomplete conversion of starting material.

It is important to note that C−H alkynylation on the triazole ring (at triazole C-5 position) was not observed in this case, highlighting the mild conditions of this C−H alkynylation process.[17] To further evaluate the reactivity of this TAM directing group, substrates containing other common directing groups were prepared and applied under identical conditions. Surprisingly, the popular QA and PIP directing group could not promote this transformation. Both the Yu−Wasa auxiliary[18] and thio ether[3f] were also ineffective for this transformation under this mild, silver-free condition. To evaluate the reaction scope, various TAM modified acid derivatives were prepared and charged with the optimal conditions. The results are summarized in Scheme 3.

As shown in Scheme 3, both primary and secondary sp^3 C−H bond could be activated using the TAM directing group. To the best of our knowledge, this is the first example of an effective directing group that could achieve C−H alkynylation of both types of C−H bonds. Similar to other C−H activation reactions, the primary sp^3 C−H bond is more reactive than the secondary sp^3 C−H bond, giving the corresponding alkyne product in good

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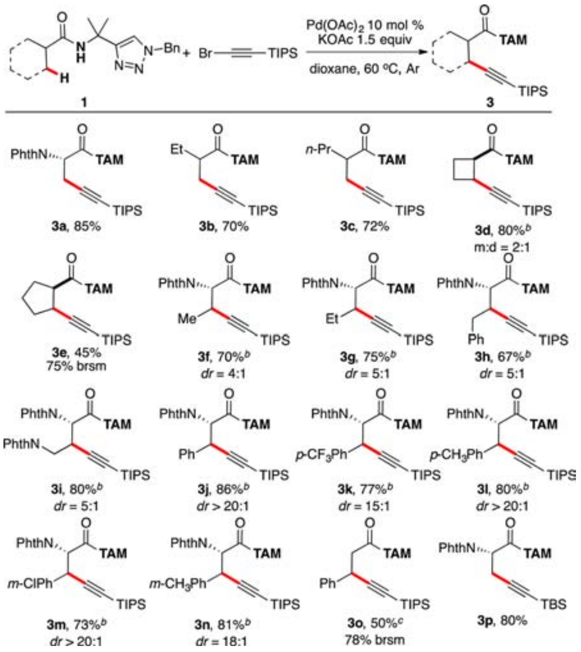
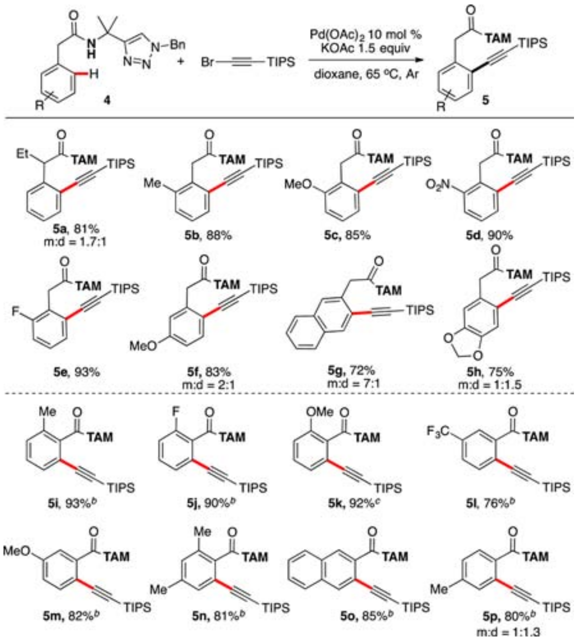
Scheme 3. Reaction Scope for sp^3 C−H Alkynylation[a,d,e]



[a]Conditions: **1a** (0.2 mmol), bromoalkyne (0.3 mmol), Pd(OAc)$_2$ 10 mol %, and KOAc (0.3 mmol) in solvent (0.3 mL). [b]Bromoalkyne (0.4 mmol) and KOAc (0.4 mmol) were used at 85 °C. [c]Bromoalkyne (0.4 mmol), KOAc (0.4 mmol), and Ag$_2$CO$_3$ (0.04 mmol) were used at 85 °C. [d]dr was determined by ^{1}H NMR. [e]Isolated yields. [f]Aryl- and alkyl-substituted bromoalkynes gave very messy reaction.

Scheme 4. Reaction Scope for sp^2 C−H Alkynylation[a,d]



[a]Conditions: **1a** (0.2 mmol), bromoalkyne (0.3 mmol), Pd(OAc)$_2$ 10 mol %, and KOAc (0.3 mmol) in the solvent (0.3 mL). [b]85 °C. [c]100 °C. [d]Isolated yield.

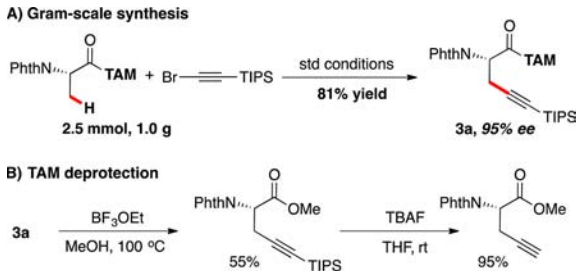


Figure 2. Synthetic application and substrate derivatives.

yields (**3a**−**c**). Moreover, with cyclic substrate, excellent stereoselectivity was achieved, giving the *cis* isomer (confirmed by NMR analysis, see the SI) as the major products (**3d** and **3e**), which was consistent with the proposed mechanism. Other N-protected amino acid derivatives (**3f**−**n**) were also prepared. Good to excellent yields were obtained in all cases, suggesting the potential applications of this method in complex molecule synthesis. For the more hindered methylene C−H, a higher temperature (85 °C) was needed to achieve full conversion. Notably, carbonyl *α*-substitution was important. No reaction was observed for phenylethyl acid derivatives **3o** under the optimal conditions. Interestingly, with the addition of 20% Ag$_2$CO$_3$, the desired product **3o** was obtained in 50% yield. This result implied the special role of silver salts in C−H activation as observed in other reported systems. Overall, the broad substrate scope of this reaction highlighted not only the efficiency of this new strategy for the synthesis of complex molecules but also the unique reactivity of TAM directing group. To further demonstrate the utility of this new method, sp^2 C−H alkynylation was performed, and the results are summarized in Scheme 4.

Both phenyl acetic acid and benzoic acid derivatives are suitable for this transformation. With more reactive sp^2 C−H (relative to sp^3 C−H), generally higher yields were obtained. Both EDG- (**5b** and **5c**) and EWG-modified (**5d** and **5f**) arenes were suitable for this reaction. Modest regioselectivity was observed for the *meta*-substituted benzenes (**5h**) with less hindered *ortho*-alkynylation as major products. Generally, higher temperature was required for the benzoic acid derivatives (**5i**−**p**), likely due to the increased steric hindrance on the metal center. Similar to the phenylacetic acid derivatives, substituent groups on the aromatic ring showed little influence on the reactivity: both EDG and EWG modified substrates gave good to excellent yields. Remarkably, excellent regioselectivity was observed for the *meta*-substituted benzenes (**5l**,**m**), with substitution occurring at the less hindered C−H bond.

A 2.5 mmol gram-scale reaction was performed, giving the desired alkyne product in 81% isolated yield with excellent chirality retention (Figure 2A). The sequential deprotection of TAM and Tips afforded *β*-alkynyl amino acid derivatives (Figure 2B). These reactions further demonstrate the mild conditions and high efficiency of this method.

In summary, we have demonstrated 1,2,3-triazole amine (TAM) as a unique directing group in promoting the selective C−H alkynylation. The efficient C−C bond formation was enabled through homogeneous Pd catalysis with C−H bond activation on both sp^2 and sp^3 carbon atoms. This study revealed a new practical approach with the assistance of a triazole directing group under silver free conditions, which highlighted the unique nature of the triazole directing group. Detailed studies regarding the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01319.

Experimental procedures, characterization data, and NMR spectra (PDF)
X-ray data for **2a′** (CIF)

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Notes

The authors declare no competing financial interest.

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