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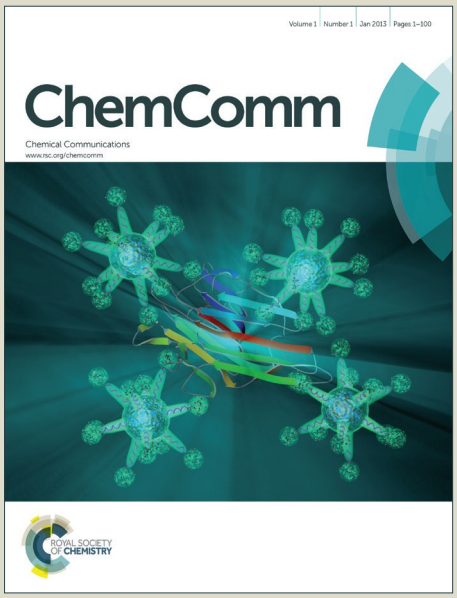

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Palladium-Catalyzed Oxalyl Amide Assisted Direct *ortho*-Alkynylation of Arylalkylamines Derivatives at δ and ε Positions

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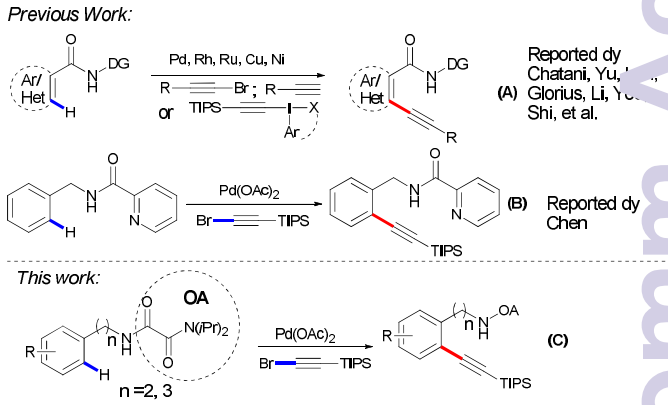
Palladium-catalyzed oxalyl amide directed *ortho*-alkynylation of arylalkylamine derivatives is first reported. A wide variety of *β*-arylethamine and *γ*-arylpropamine derivatives are compatible with this protocol. The method provides a general means to synthesize substituted alkynylarylalkylamine derivatives, highlighting the ability of oxalyl amide in promoting C–H functionalization at unique *δ* and *ε* positions.

Alkynes are special building blocks in synthetic chemistry and in materials chemistry because of their versatile transformation into multiple functional groups or linear structure motifs.[1] One of the most convenient methods for adding alkyne functionality is transition-metal-catalyzed Sonogashira–Hagihara coupling reaction combining aryl halide with terminal alkynes.[2] In recent years, transition-metal-catalyzed direct C–H functionalization reactions have become a rapidly expanding area in synthetic chemistry.[3] Oxidative coupling of C–H bonds with alkynyl halides, hypervalent iodine, or terminal alkynes has been developed in various studies. In 2007, Gevorgyan and co-workers reported a seminal example of palladium-catalyzed C–H alkynylation of electron-rich heterocycles with alkynyl halides, which represents a new approach for C(sp^2)–C(sp) bond formation.[4] Since this work, groups of Chatani,[5] Miura,[6] Su,[7] Chang,[8] Gevorgyan,[9] Li,[10] Loh,[11] Shi,[12] and others[13] expanded oxidative alkynylation to various C–H bonds with alkyne in the presence of transition-metal catalyst or alkyne reagents (Scheme 1A). Additionally, the well-developed bidentated directing group strategy[14-21] has also well applied in the oxidative alkynylation reactions. For example, Chen and co-workers reported picolinamide-promoted palladium-catalyzed *ortho*-alkynylation of benzylamine substrates with acetylenic bromide with high yields in 2012 (Scheme 1B).[22] Later, Chatani described the 8-aminoquinoline assisted *ortho*-alkynylation of aromatic carboxylic acid derivatives.[23] In 2014, Yu and coworkers reported from their seminal work a copper-catalyzed alkynylation of aryl C–H bonds with alkyne in good yields.[24] Very recently, Shi and co-workers developed the oxidative ethynylation of (hetero)aryl C–H bonds in the presence of catalysts by using an auxiliary agent, 2-(pyridin-2-yl)isopropylamine.[25] Despite significant progress in the realization of *ortho*-alkynylation of *β*-arylethamine and *γ*-arylpropamine derivatives, there are still no reports on this reaction. Herein, we report the palladium-catalyzed selective functionalization of ortho C–H bonds of arylalkylamine oxalyl amide derivatives with acetylenic bromide via a six- or seven-membered palladacycle intermediate.

Scheme 1 Synthesis of Aryl Alkynes by Transition-Metal-Catalyzed C–H Alkynylation.



With these considerations in mind, we initially treated oxalyl amide protected **1a** with bromoalkyne **2** in the presence of $Pd(OAc)_2$, stoichiometric AgOAc, pivalicacid, and toluene under aerobic conditions at 100 °C for 24 h. The desired alkynylated products **3a** was obtained at 67% yield (Table 1, entry 1). Upon further evaluation of the reaction conditions, we discovered that only acetic salt could be employed to instead of expensive silver salt in promoting this palladium-catalyzed oxalyl amide assisted alkynylation reaction. Among the acetic acid salts tested, CsOAc

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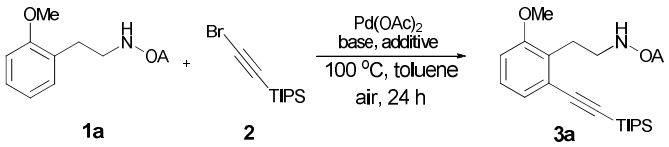
Table 1 Optimization of Reaction Conditions[a]

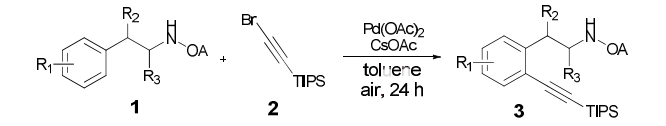


1a 2 3a

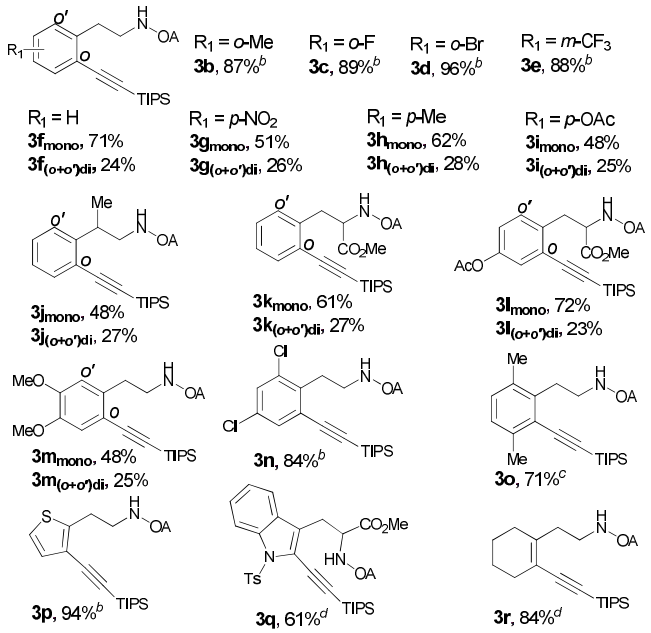
Entry	$Pd(OAc)_2$ (mol %)	Base	Additive (equiv)	Yield (%)
1	5	–	AgOAc (2) PivOH (0.3)	67
2	5	LiOAc	–	4
3	5	NaOAc	–	31
4	5	KOAc	–	62
5	5	CsOAc	–	93(**85**[b])
6	5	Na_2CO_3	–	22
7	5	K_2CO_3	–	36
8	5	$KHCO_3$	–	56
9	5	Na_2CO_3	PivOH (0.3)	47
10	5	K_2CO_3	PivOH (0.3)	36
11	5	CsOAc	PivOH (0.3)	51
12	–	CsOAc	–	NR

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.12 mmol), $Pd(OAc)_2$ (5 mol %), base (2 equiv), toluene (0.5 mL), 100 °C, air, 24 h. Yield was based on LC using acetophenone as the internal standard. [b]Isolated yield at 0.2 mmol scale.

Table 2 Palladium-Catalyzed Oxalyl Amide Directed *ortho*-Alkynylation of Phenylethylamine Derivatives[a]



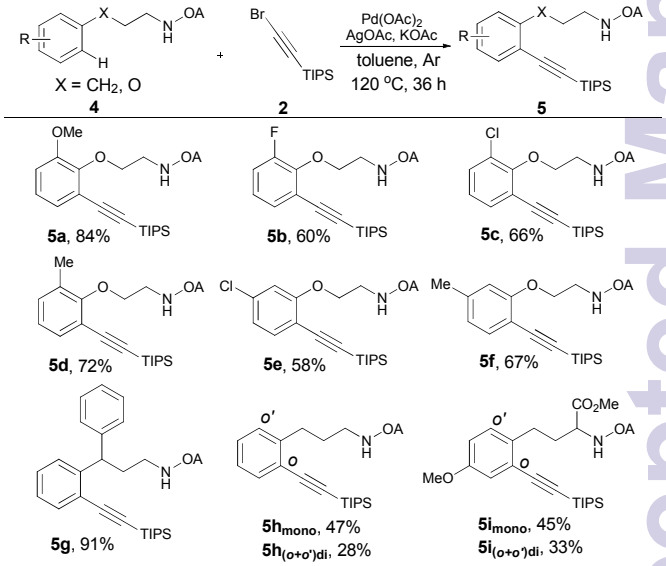
1 2 3



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (5 mol %), CsOAc (2 equiv), toluene (0.5 mL), 80 °C, air, 24 h. Isolated yields. [b]100 °C. [c]120 °C, 36h. [d]140 °C, 36h.

emerged as the best additive, as it produced **3a** in 93% yield. We hypothesized that the acetate ion might act as a proton shuttle during the catalytic cycle, as reported by Larock and Fagnou. Meanwhile, cesium ion behaved as a base by keeping the reaction in an alkaline environment. Several other bases such as K_2CO_3, $KHCO_3$, and Na_2CO_3 combined with pivalic acid were also screened; all tests afforded results slightly poorer than those of CsOAc. Control experiments revealed that the palladium catalyst was crucial for this alkynylation reaction (Table 1, entry 12).

Table 3 Palladium-Catalyzed Oxalyl Amide Directed *ortho*-Alkynylation of *γ*-Arylpropamine Derivatives[a]



[a]Reaction conditions: **4** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), AgOAc (2.0 equiv), KOAc (3.0 equiv), toluene (1 mL), Ar, 120 °C, 36h. Isolated yields.

With these optimized conditions, we proceeded to explore the substrate scope. Representative data for this study were shown in Table 2. Generally, both electron-donating and electron-withdrawing functional groups substituted oxalyl amide protected phenylethylamine derivatives in the reaction afforded the corresponding products in good to excellent yields. Various functional groups such as F, Cl, Br, CF_3, NO_2, Me, and OMe were compatible in this oxalyl amide assisted C–H transformation. *Para*-substituted substrates (**1g**–**1i**) gave a mixture of mono- and dialkynylated products at a ratio of 2:1 to 3:1 in good yields, which could be easily separated by silica gelchromatography (Table 2, **3g**–**3i**). Substitution of functional groups of CF_3 at the *meta*-position caused the alkynylation to favorless-hindered positions, resulting in *mono*-alkynylated products in good to excellent yield. However, the less steric functional group of Cl, Br, and MeO resulted in poor selectivity at the ortho position (See Supporting Information). Nevertheless, heterocycles were also tolerated in the reaction. For example, oxalyl amide protected 2-thiopheneethylamine gave the alkynylated product **3p** in excellent yield. The tryptophan derivative **1q** reacted with **2** at high temperature, selectively leading to **3q** in good yield. It is worth mentioning that palladium-catalyzed

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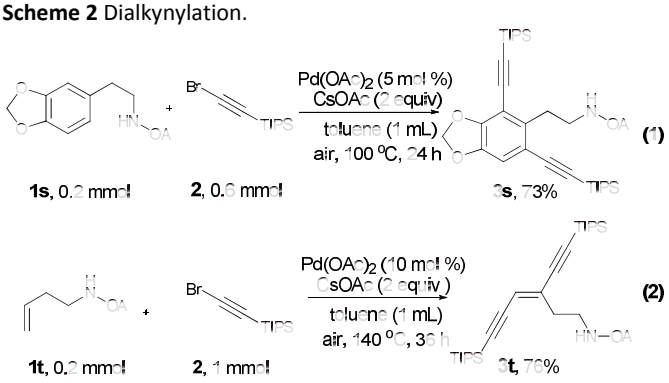
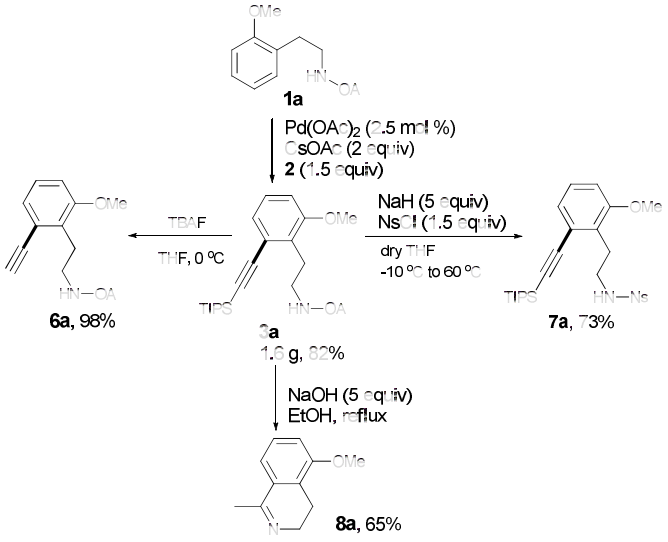
alkynylation favored vinylic bonds (**1r**), affording the important synthons 1,3-enynes in good yield.

Scheme 2 Dialkynylation.



Because of the successful alkynylation of *β*-arylethamine derivatives, we then proceeded to explore the difficult *ε*-C(sp^2)–H alkynylation via a seven-membered palladacycle intermediate. Alkynylation of oxalyl amide protected *γ*-arylpropamine derivatives using silver acetate instead of cesium acetate proceeded slowly, affording the *ε*-alkynylated products in good yields (Table 3). The substrates (Table 3, **4a–4i**) also gave the *ortho*-alkynylated products in moderate to good yields. Importantly, the steric effect in this developed protocol also resulted in highly regioselective products compared with *β*-arylethamine derivatives.

Scheme 3 Gram Scale Reaction and Synthetic Transformation of **3a**.



Subsequently, we performed another experiment to avoid the selective alkynylation at the ortho position of *β*-arylethamine (**1s**). Dialkynylation produced good yield upon increase of the number of acetylenic bromide equivalents to 3(Scheme 2, eq **1**). Interestingly, oxalyl amide protected 3-butenylamine was applicable to this protocol, giving products dialkynylated at *δ* and *γ* positions.

To highlight the synthetic utility of this synthetic approach, gram scale reaction with 2.5 mol % $Pd(OAc)_2$ was performed. This gave 1.6 g of product in 82% yield. Meanwhile, the oxalyl amide directing group could be easily removed by treating with 4-nitrobenzenesulfonyl chloride and sodium hydride. Importantly, alkynylated *β*-arylethamine oxalyl amide **3a** could be easily converted to the valuable synthon, dihydroisoquinoline derivative in good yield. The protecting group of TIPS could be readily removed with TBAF to afford the terminal alkyne, which could furnish a wide variety of alkynylated arylalkylamine derivatives.

In conclusion, we have developed palladium-catalyzed alkynylation of arylalkylamine derivatives via rare six- and seven-membered palladacycles using our developed oxalyl amide directing group. A wide variety of *β*-arylethamine and *γ*-arylpropamine derivatives are compatible with this synthetic method, which provides a general means to furnish alkynylated arylalkylamines derivatives under mild conditions. Direct conversion of the product to the useful synthetic synthons isoquinoline derivatives highlights the potential synthetic utility of this method.

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