Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400007

Palladium/Copper Bimetallic System-Mediated Cross-Coupling of Alkynes and Alkenes: Two Strategies to Suppress β-H Elimination on Alkyl-Palladium Center

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Received: January 2, 2014; Revised: March 20, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400007.

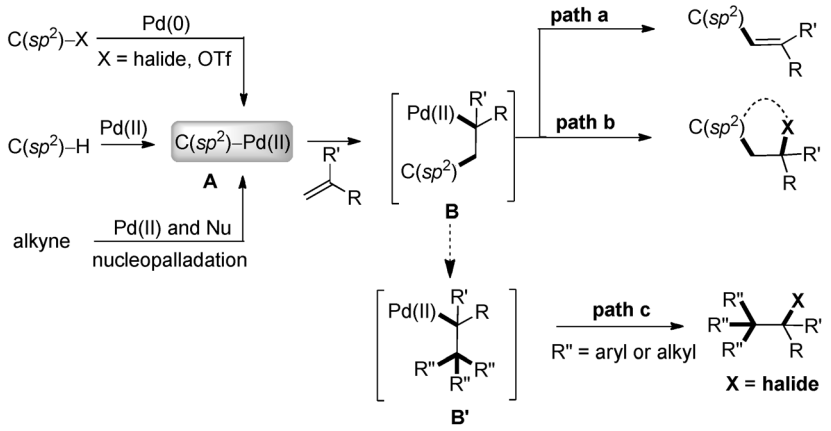
Abstract: This paper describes two efficient strategies to suppress β-H elimination during the palladium/copper bimetallic system-mediated cross-coupling between alkynamides and alkenes. Remote donor groups with the terminal olefins, such as toluenesulfonamide, phosphate, sulfone, etc., cooperate with the amide of alkynamides and chelate the palladium active center, to promote C(sp^3)–O bond formation by suppressing the β-H elimination. Another strategy uses the rigid structure of norbornene to make an intermediate without a *syn*-β-hydrogen to achieve reductive elimination of the C–Cl bond.

Keywords: bimetallic systems; cross-coupling; palladium; reductive elimination; suppression of β-H elimination

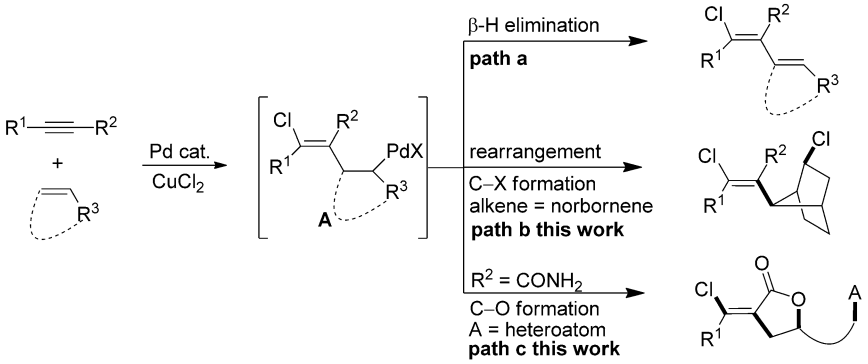
Palladium chemistry occupies a significant place in transition metal-catalyzed C–C and C–X bond formation reactions.[1] Traditionally, the carbon-palladium species could be formed through oxidative addition or cycloaddition of low valent Pd(0), transmetallation, C–H activation, decarboxylation and nucleopalladation of carbon-carbon multiple bonds with a Pd(II) center (Scheme 1). The C–Pd species captured by the alkenes through migratory insertion could afford the alkyl-Pd species **B**, which is the elementary intermediate in Heck-type reactions.[2–3] Two strategies were typically employed to quench the alkyl-Pd species **B**: (i) β-H elimination to get C=C double bonds like the Heck process (Scheme 1, path a);[4–9] (ii) reductive elimination when there was no hydrogen at the β position (Scheme 1, path c).[10–16] The reductive elimination, especially C–heteroatom reductive elimination, from C(sp^3)–Pd species usually needs strong oxidants to form Pd(IV) intermediates,[17–19] while the carbon-carbon multiple bonds are usually sensitive to strong oxidants. A key challenge which has attracted chemists' interest was how to suppress the fast β-H elimination and achieve reductive elimination to form a C–heteroatom bond under mild reaction conditions (Scheme 1, paths a and c).

Pd/Cu bimetallic catalysis has made great progress in the Sonogashira process[20–25] and decarboxylative cross-coupling.[26–30] And as a part of our interest in Pd/Cu bimetallic system-mediated oxidative alkyne–alkene cross-couplings,[31–34] we herein report the development of two routes to suppress the β-H elimination from intermediate **A** (Scheme 2). Under such a scenario, the complex **A** usually serves as the key intermediate, followed by β-H elimination to form the C=C bond (Scheme 2, path a).[33–34] Recently, Lautens and Tong independently reported the Pd-catalyzed intramolecular carbohalogenation of α-substituted olefins through C(sp^3)-halogen bond reductive elimination.[10–16] Inspired by this seminal work and our bromoalkynylation of norbornene,[35] we have achieved C–Cl bond formation when norbornene was used as the substrate in this cross-coupling, due to its rigid structure norbornene is able to prevent the corresponding β-H elimination (Scheme 2, path b).

Besides, the lack of a *syn*-β-hydrogen could suppress the β-H elimination from intermediate **A**, and the coordinative saturation of the Pd center represents another established strategy to suppress β-H elimination.[3] Some coordinating groups in the terminal olefins, such as NHTs, vinyl, $PO(OEt)_2$, SO_2Ph, were used to cooperate with alkynamide to make the Pd center coordinatively full and so promote the reductive elimination (path c in Scheme 2). Herein, we



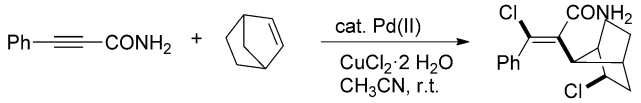
Scheme 1. Three typical strategies to form C–C or C–X bonds.



Scheme 2. Nucleopalladation-initiated oxidative cross-coupling between alkynes and alkenes.

report the Pd-catalyzed Kaneda-type reaction of alkynamides with norbornene to construct C-7 functionalized norbornylalkenes (path b in Scheme 2) and lactonization of the alkenes bearing coordinated groups with alkynamides to construct α-methylene-γ-lactones (path c in Scheme 2).

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	$CuCl_2 \cdot 2H_2O$ (equiv.)	Temp. [°C]	Yield [%]
1	$PdCl_2$	2	50	73
2	$Pd(OAc)_2$	2	50	63
3	$PdCl_2(MeCN)_2$	2	50	68
4	$PdCl_2$	3	50	83
5	$PdCl_2$	4	50	78
6	$PdCl_2$	3	r.t.	88

[a] *Reaction conditions:* **1a** (0.5 mmol) and **2a** (0.6 mmol), Pd catalyst (5 mol%), $CuCl_2 \cdot 2H_2O$ (2–4 equiv.) and 0.5 mL of acetonitrile for 12 h. Yields of isolated products are given.

During the optimization of the reaction conditions, we focused our attention on the cross-coupling of 3-phenylpropiolamide **1a** and norbornene **2a** (Table 1). After exploring a wide array of conditions, we determined that CH_3CN was the best solvent for this transformation (see the Supporting Information for details). When **1a** and **2a** were treated with 5 mol% $PdCl_2$ and 2 equiv. of $CuCl_2 \cdot 2H_2O$ in CH_3CN under air at 50 °C for 14 h, a satisfying isolated yield of 73% of **3a** could be obtained (Table 1, entry 1). And the structure of **3a** was confirmed by X-ray crystallographic analysis (Figure 1).[36] The screening of various Pd catalysts led to very similar results and $PdCl_2$ was found to be best for this reaction (Table 1, entries 2–4). A higher isolated yield (83%) could be obtained by increasing the amount of $CuCl_2 \cdot 2H_2O$ to 3 equiv. (Table 1, entries 4 and 5). Gratifyingly, a use of a lower reaction temperature (room temperature) gave **3a** in 88% yield (Table 1, entry 6). However, the reaction using $CuBr_2$ instead of $CuCl_2$ gave a *trans*-dibrominated alkene product exclusively upon addition of bromide to the alkynyl group of **1a**. Therefore, the best condition consisted of 5 mol% $PdCl_2$, 3 equiv. of

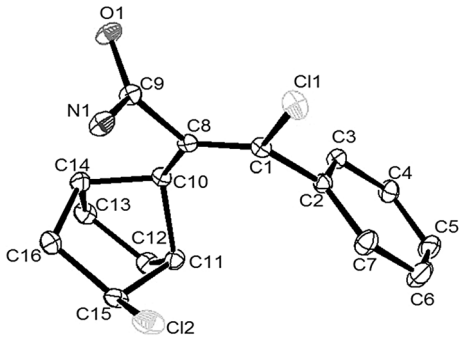
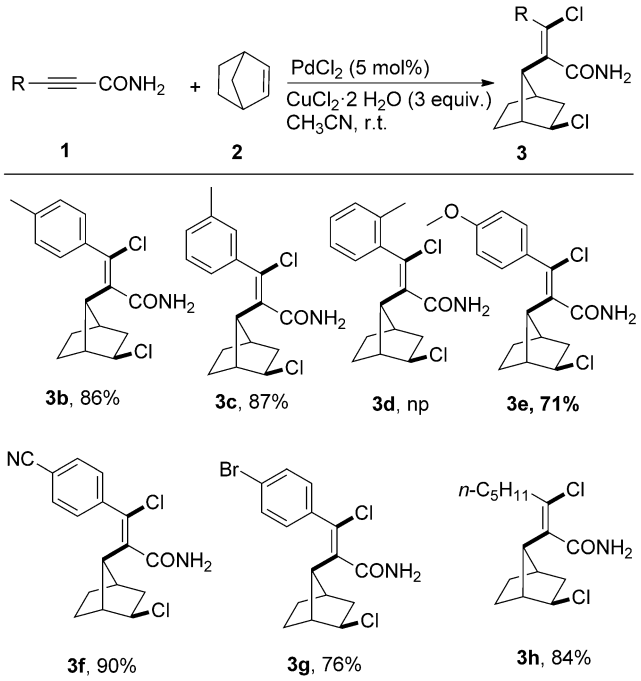


Figure 1. X-ray structure of **3a**.

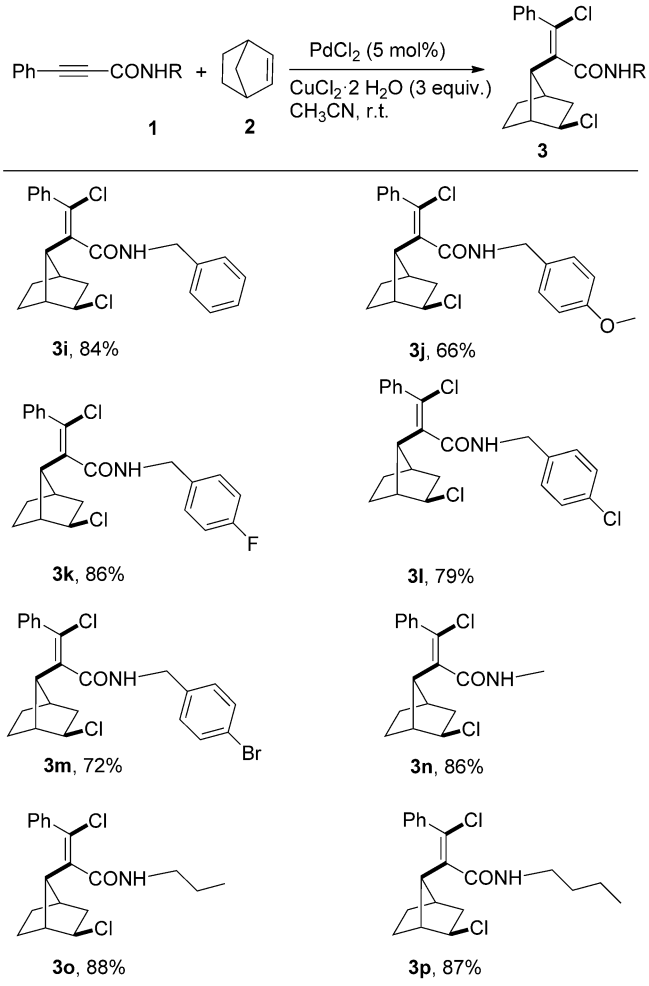
$CuCl_2 \cdot 2H_2O$, in CH_3CN at room temperature for 12 h.

With the optimized reaction conditions in hand, we next expanded the substrate scope of the Pd-catalyzed cross-couplings between alkynamides and norbornene (Scheme 3). Alkynamides substituted with electron-donating groups, such as methyl and methoxy, afforded the corresponding products in good yields (Scheme 3, **3b**, **3c**, **3e**). The 4-CN-substituted alkynamide could be converted into the corresponding C-7 functionalized norbornylalkene in excellent yield (Scheme 3, **3f**). Bromide on the aromatic ring was well tolerated, which provides the possibility for further functionalization (Scheme 3, **3g**). In contrast with the *para*- and *meta*-substituted alkynamides, the *ortho*-substituted substrate failed to convert to the product (Scheme 3, **3d**). When oct-2-ynamide was used in this transformation, the corresponding product was obtained in good yield (Scheme 3, **3h**).

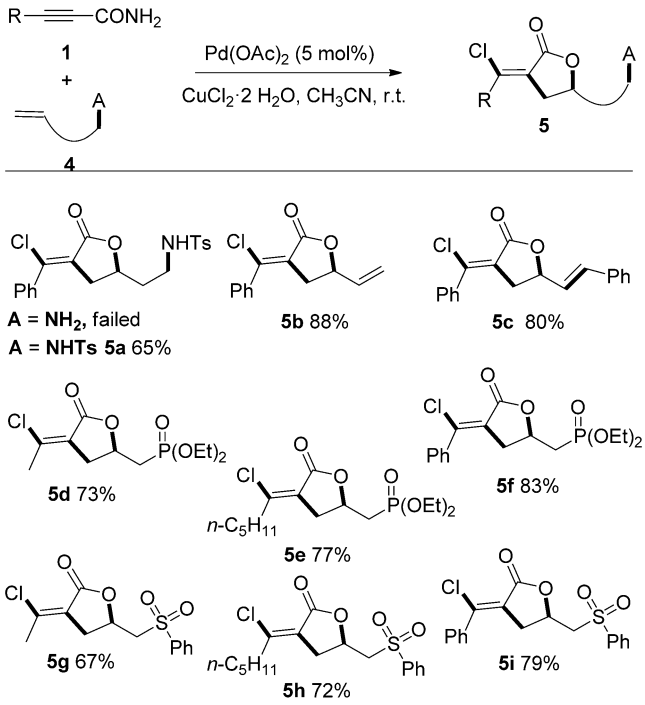
Encouraged by these promising results, we further applied these conditions to Pd-catalyzed cross-coupling of *N*-substituted alkynamides (Scheme 4). A series of *N*-benzyl-substituted alkynamides could be transformed to the corresponding products in good yields. For example, **3i** and **3j** were smoothly obtained in 84% and 66% yields, respectively (Scheme 4). In addition, halide functional groups, such as F, Cl, Br, were tolerated in this transformation and the corresponding products were obtained in moderate yields (Scheme 4, **3k–3m**). *N*-substituted alkynamides with alkyl groups, such as methyl, propyl and *n*-butyl, also



Scheme 3. Pd-catalyzed cross-coupling of alkynamides with norbornene. *Reaction conditions:* the reactions were carried out with norbornene (0.6 mmol), alkynamide (0.5 mmol), $PdCl_2$ (5 mol%), $CuCl_2 \cdot 2H_2O$ (3 equiv.) in 0.5 mL of acetonitrile at room temperature for 12 h. Yields of isolated products are given.



Scheme 4. Pd-catalyzed coupling of *N*-substituted alkynamides with norbornene. *Reaction conditions:* the reactions were carried out with norbornene (0.6 mmol), alkynamide (0.5 mmol), $PdCl_2$ (5 mol%), $CuCl_2 \cdot 2H_2O$ (3 equiv.) in 0.5 mL of acetonitrile at room temperature for 12 h. Yields of isolated products are given.



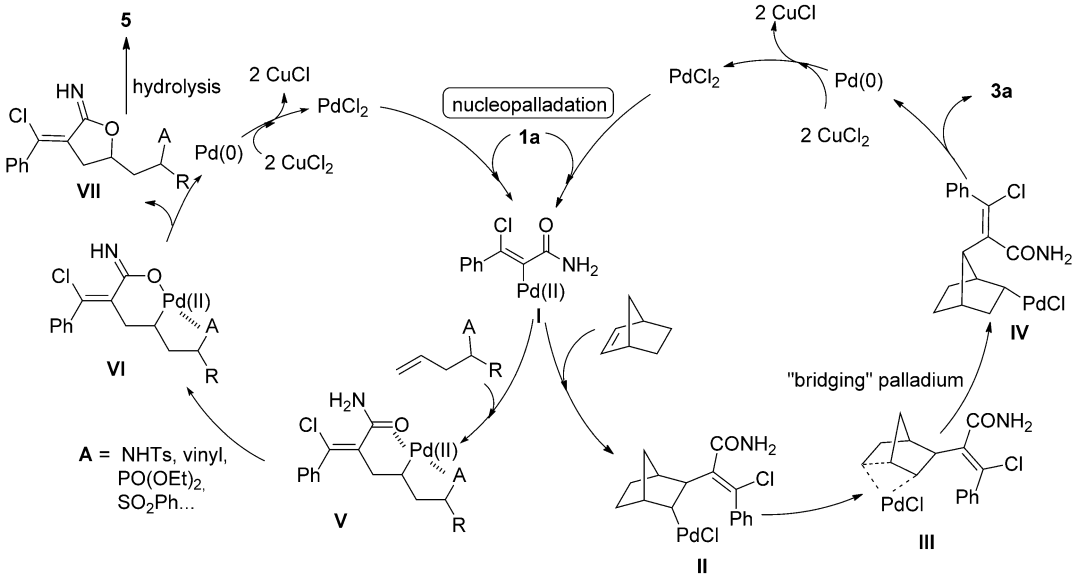
Scheme 5. Pd-catalyzed lactonization of electronically nonbiased olefins with alkynamides. *Reaction conditions:* the reactions were carried out with norbornene (0.6 mmol), alkynamide (0.5 mmol), $PdCl_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (3 equiv.) in 0.5 mL of acetonitrile at room temperature for 12 h. Yields of isolated products are given.

afforded the respective products in satisfying isolated yields (Scheme 4, **3n–3p**).

On the other hand, some terminal olefins were evaluated under the optimized conditions for the Pd-catalyzed lactonization with alkynamides (Scheme 5).

Firstly, but-3-en-1-amine was chosen for this transformation. Unfortunately, a complicated result was obtained, and no target product could be isolated (Scheme 5). However the *N*-Ts-substituted but-3-en-1-amine was a suitable coupling partner with alkynamide to afford the corresponding α-methylene-γ-lactone **5a** with 65% yield. Buta-1,3-dienes also reacted well, giving **5b** and **5c** in high yields. Delightfully, diethyl allylphosphonate could react well with alkynamides to generate the corresponding products (Scheme 5, **5d–5f**). It is known that the increasing importance of phosphorus compounds in organic synthesis, materials science, and biology demands efficient methods to functionalize phosphorus compounds.[37,38] Furthermore, the chelate effect of sulfone was proven to be feasible for these transformations (Scheme 5, **5g–5i**). A structural motif bearing both α-methylene-γ-lactone and sulfone units would be a useful synthetic intermediate and a privileged medicinal target.[39–44]

On the basis of the above results, a possible reaction mechanism for this Pd-catalyzed cross-coupling was proposed (Scheme 6). The righthand pathway was initiated by *trans*-halopalladation of alkynamide, which gave the vinylpalladium intermediate **I**. Subsequently, **I** was captured by the norbornene through migratory insertion to produce intermediate **II**. The isomer **IV** was generated through the "bridging" palladium intermediate **III**.[35,45,46] Then reductive elimination of **IV** afforded the product **3a**. The Pd(II) active species was regenerated *via* oxidation by Cu(II). For the lefthand pathway, **I** was captured by alkene to produce intermediate **V**. The amide of the alkynamide cooperated with group A [NHTs, vinyl, $PO(OEt)_2$, SO_2Ph] in the olefin to chelate the Pd center. It is known that the coordinative saturation of



Scheme 6. Proposed mechanism.

the metal center represents one established strategy to suppress β-H elimination. The five- or six-membered palladacycle intermediate **V** was transformed to the intermediate **VI** by isomerization, which was followed by C(sp^3)–O bond formation and hydrolysis to give the five-membered lactones. Finally, the Pd(II) active species was regenerated *via* oxidation by Cu(II).

In conclusion, we have developed two efficient methods to suppress the β-H elimination during construction of C-7 functionalized norbornylalkenes and α-methylene-γ-lactone *via* Pd-catalyzed cross-coupling reactions between alkynamides and alkenes. This transformation features high reactivity under mild conditions from easily available materials. Furthermore, the highly functionalized α-methylene-γ-lactone is an important moiety existing in numerous natural products with biological activities, which also illustrates that the remote group-assisted strategy is highly interesting and useful. Therefore, the search for methods to suppress β-H elimination is still attractive and further study is underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Pd/Cu-Catalyzed Cross-Coupling of Alkynes and Alkenes

The mixture of alkynamide (0.5 mmol), $PdCl_2$ (5 mol%) or $Pd(OAc)_2$ (5 mol%), olefin (0.6 mmol), $CuCl_2{\cdot}2H_2O$ (3 equiv.) and acetonitrile (0.5 mL) was stirred at room temperature for 12 h. After completion, the reaction was quenched by the addition of water (10 mL), and the mixture was extracted with ethyl acetate (3×10 mL), the combined extract was dried with $MgSO_4$ and the solvent was evaporated under vacuum. The residue was separated by chromatography on silica gel to give the pure product.

Acknowledgements

The authors thank the National Natural Science Foundation of China (21172076 and 21202046), the National Basic Research Program of China (973 Program; 2011CB808600), Guangdong Natural Science Foundation (10351064101000000 and S2012040007088) and the Fundamental Research Funds for the Central Universities (2014ZP0004 and 2014ZZ0046) for financial support.

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