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# Pd-catalyzed hydroaminocarbonylation of alkynes with aliphatic amines and its mechanism study

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Dong-Liang Wang, Wen-Di Guo, Lei Liu, Qing Zhou, Wen-Yu Liang, Yong Lu and Ye Liu*

**This work described the hydroaminocarbonylation of alkynes with aliphatic amines without the addition of any acid additive. The excellent conversion and regioselectivity toward the formation of branched amide were obtained over dppp-based Pd-catalytic system. The catalytic mechanism was studied and disclosed that the carbamoylpalladium complex intermediate instead of the widely accepted palladium-hydride (Pd-H) species was the active catalytic species for this reaction.**

## Introduction

Carbonylation of alkenes or alkynes in the presence of the nucleophile such as amines or alcohols has been wildly utilized for the construction of high value-added carbonyl compounds.[1–14] Many studies revealed that the use of Brönsted acid, [15–21] $H_2O$,[22] or $H_2$[23,24] as additive was usually required to produce palladium-hydride (Pd-H) species responsible for the catalytic transformations.[25–27] However, unlike applied alcohols for hydroalkoxycarbonylation in which Pd-H catalytic species can authentically survive under non-alkali conditions, organic amines especially aliphatic amines with strong basicity greatly inhibit the generation of the active Pd-H species through rapidly quenching proton in hydroaminocarbonylation.[28] In order to solve this problem, various methods have been developed to fulfil hydroaminocarbonylation of alkenes/alkynes. For example, in 2015, Huang and his co-workers have reported a novel palladium-catalyzed hydroaminocarbonylation of alkenes with aminals instead of aliphatic amines to grantee the generation of Pd-H species.[29] In the same year, they also applied the weak acid ($NH_2OH{\cdot}HCl$) as a basicity-mask to overcome the basicity barrier.[30] Later on, Beller and co-workers developed an elegant strategy by using amine hydrochlorides instead of basic amines. With the involvement of an elaborate monophosphine, the palladium-catalyzed hydroaminocarbonylation of olefins proceeded smoothly affording the branched amides in good yields.[31] But so far, the limited strategies have been achieved towards the hydroaminocarbonylation of alkynes with aliphatic amines for the synthesis of $\alpha,\beta$-unsaturated amides. In 2006, Yu and his co-workers reported the hydroaminocarbonylation of alkynes with aliphatic amines in the ionic liquid of [bmim][$NTf_2$] without the addition of acid additive.[32] In 2009, El Ali and co-workers reported an Pd-catalyzed hydroaminocarbonylation of terminal alkynes using *p*-TsOH as acidic additive to promote the generation of Pd-H species.[33]

Herein, we found that even with the presence of aliphatic amines, the palladium-catalyzed hydroaminocarbonylation of alkynes could proceed smoothly without the addition of any acid additive while the diphosphine of dppp was applied as a chelating ligand, which suggested that the catalytic mechanism of hydroaminocarbonylation focusing on the generation of Pd-H species be still open to debate. Based on such fact, the mechanism of hydroaminocarbonylation of alkynes under basic condition was investigated carefully through the activity evaluation of the as-synthesized carbamoylpalladium intermediate complex as well as FT-IR characterization.

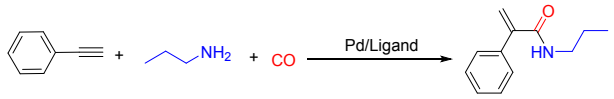
## Results and Discussion

The hydroaminocarbonylation of phenylacetylene with propylamine was investigated as a model reaction without addition of the auxiliary additive. The various bidentate phosphines with different bite angles were firstly examined for this reaction (Table 1, entries 1-7). It was found that in the presence of a catalytic amount of $Pd(OAc)_2$ (1 mol%) under 1 MPa of CO in $CH_3CN$ at 120 °C, the excellent conversion of phenylacetylene and 100% selectivity to the branched amide were obtained in 2 h with the involvement of dppp at P/Pd molar ratio of 2 (Entry 3). The other bidentate phosphines like dppe and dppb with the similar natural bite angle of ca. 90 °

[a] *Address here.*
[b] *Address here.*
[c] *Address here.*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

just corresponded to the moderate yields to the target amide (Entries 2 and 4). In contrast, the uses of phosphines with the bite angle much larger or less than 90 ° corresponded to the completely inhibited transformation (Entries 1 and 5-7). Upon further screening the reaction parameters such as CO pressure and the reaction time (Entries 8-10), the highest yield of the product (99%) was obtained under 0.5 MPa of CO in 1 h (Entry 10 @ 120 °C, $Pd(OAc)_2$ 1 mol%, P/Pd=2:1). It was found that the decrease of CO pressure dow to 0.1 MPa compleltely stopped the reaction (Entry 9).

**Table 1** Pd-catalyzed hydroaminocarbonylation of phenylethyne with n-propylamine[a]



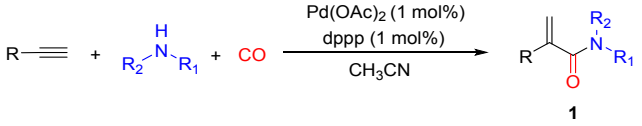

2-phenyl-*N*-propylacrylamide

| Entry | Ligand | Natural bite angle(°) [b] | Conv. (%)[c] | Sel. $_{B\text{-amide}}$ (%)[c] |
|---|---|---|---|---|
| 1 | dppm | 73 | 0 | -- |
| 2 | dppe | 86 | 75 | 100 |
| 3 | dppp | 91 | 99 | 100 |
| 4 | dppb | 94 | 40 | 100 |
| 5 | dppf | 99 | trace | -- |
| 6 | Xantphos | 108 | 0 | -- |
| 7 | Nixantphos | 114 | 0 | -- |
| 8[d] | dppp | 91 | 99 | 100 |
| 9[e] | dppp | 91 | trace | -- |
| 10[f] | dppp | 91 | 99 | 100 (90[g]) |

[a] Reaction conditions: phenylacetylene (2.0 mmol), $Pd(OAc)_2$ (1 mol%), P/Pd=2:1 (molar ratio), *n*-propylamine (2.5 mmol), $CH_3CN$ (2 ml), CO (1 MPa), 2 h, 120 °C; [b] Nature bite angles are taken from ref 34; [c] Determined by GC. $Sel._{B\text{-amide}}$ represents the selectivity to the branched product of 2-phenyl-N-propylacrylamide; [d] CO (0.5 MPa); [e] CO (0.1 MPa); [f] CO (0.5 MPa), 1h; [g] The isolated yield of the branched product.

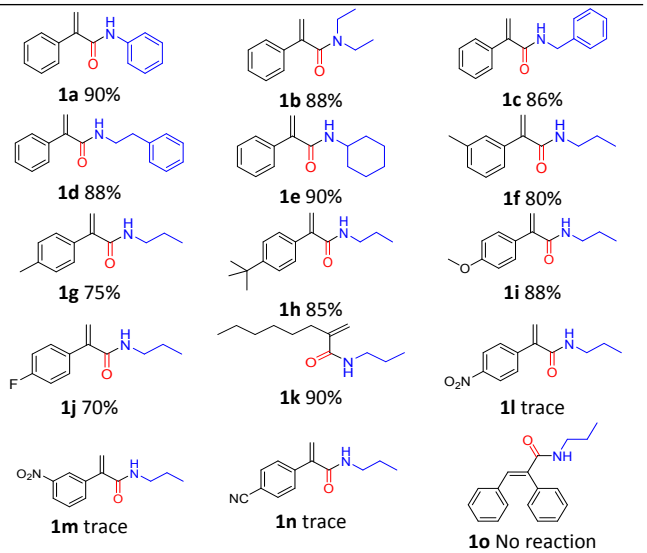
With the optimized reaction conditions in hand, we examined the substrate scope for the synthesis of the branched amides over dppp-based Pd-system. The results were summarized in Table 2. A variety of amines were initially surveyed. Both aliphatic amines and aryl amines were compatible with this transformation (**1a-1e**). In addition, a series of phenylacetylene derivatives with the electron-donating substituents like methyl, tert-butyl, and methoxy in phenyl ring were efficiently transformed, giving the corresponding branched amides in good yields (**1f-1i**, 75~88%). It was noted, 1-ethynyl-4-fluorobenzene with the strong electron-withdrawing substituent of –F also gave a good product yield (**1g**, 70%), which implied that the reactivity of the corresponding alkynes showed no obvious discrimination to the electronic effect of the substituent. Aliphatic alkynes 1-octyne was also suitable for this reaction to give the corresponding branched amides in 90% isolated yield (**1k**). However, when the aromatic alkyne with $–NO_2$ or -CN was applied, only trace amounts of the desired products were detected (**1l-n**), which was mainly attributed to the competitive coordination of such substituent with the alkynyl group toward Pd-center. The internal alkyne like diphenylacetylene showed the poor reactivity even when the reaction time was prolonged (**1o**).

The successful hydroaminocarbonylation of alkynes with aliphatic amines or aryl amines (i.e. under the strong basic condition) without the addition of acid additive suggested that Pd-H species not be the active catalytic intermediate for this transformation. Instead, the carbamoylpalladium intermediate (**B**) upon reacting palladium(Ⅱ)-precursor with amine and CO

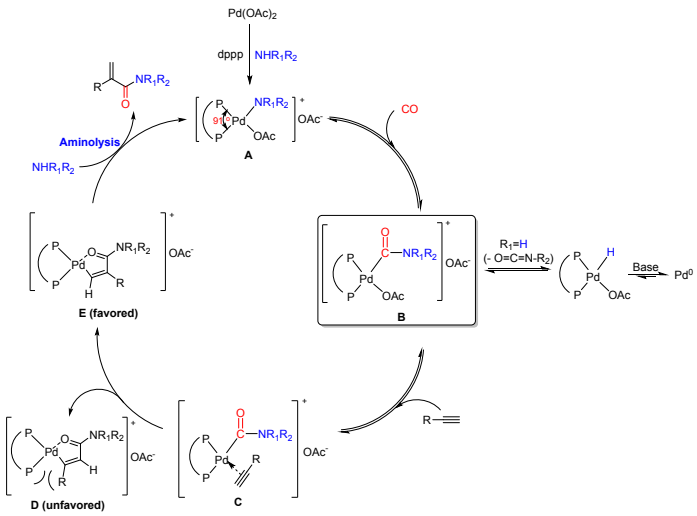



**1**

**Table 2** Pd-catalyzed hydroaminocarbonylation of alkyne with amine[a]




[a] Reaction conditions: alkyne (2.0 mmol), $Pd(OAc)_2$ (1mol%), dppp (1 mol%), amine (2.5 mmol), CO (0.5 MPa), $CH_3CN$ (2 ml), 120 °C, 2 h; The isolated yield to the branched product was indicated.



**Scheme 1** The alternative mechanism for hydroaminocarbonylation of alkynes with organic amines.

was believed to be crucial active species for the reaction with an amine to yield the corresponding amide. As proposed in Scheme 1, the carbamoylpalladium intermediate (**B**) was readily formed upon complexation of $Pd(OAc)_2$ with organic amine in CO atmosphere. The subsequent insertion of π-coordinated C≡C bond in Pd-C bond (**C**) led to the favored formation of (β-vinyl) carbamoylpalladium intermediate complex (**E**) due to steric effect. The later (**E**) irreversibly proceeded aminolysis to afford the branched α,β-unsaturated amide accompanied by the regeneration of carbamoylpalladium intermediate (**B**).

In order to verify the above mechanism, the carbamoylpalladium complex (**S1**) as a kind of intermediate **B** was synthesized purposely by reacting $PdCl_2(PPh_3)_2$ with $^{n}PrNH_2$ in CO atmosphere[35] and then applied as the active intermediate complex to react with phenylacetylene stoichiometryically and free of CO (Scheme 2, see ESI provided with the detailed reaction procedures). When the as-synthesized **S1** (0.1 mmol) reacted with phenylacetylene (0.1 mmol) at 120 °C in $CH_3CN$ (**eq. 2**), only styrene (Yield 90%) but not the desired amide was formed unexpectedly, along with the unreacted phenylacetylene. However, when $Et_3N$ was introduced to provide an alkaline environment, styrene was not formed anymore under the same conditions (**eq. 3**). The FT-IR spectra upon treating at 120 °C for 30 min (Fig. 1) showed that an intensive vibration at 1560 $cm^{-1}$ appeared obviously which was attributed to isocyanate group. These results indicated that, via β-H migration and propyl isocyanate elimination, **S1** was evolved to propyl isocyanate along with the release of the active Pd-H species (**eq. 4**). Herein, since CO was not introduced in the controlling experiment in **eq. 2**, the available Pd-H species derived from **S1** under non-alkaline condition ((heating at 120 °C in $CH_3CN$) just reacted with phenylacetylene to afford the hydrogenated product (styrene: yield 90%) instead of the desired amide. Whereas under the alkaline condition by adding $Et_3N$, the Pd-H species derived from **S1** susceptibly transformed to the inactive $Pd^0$ upon the capture of $H^+$ by the base as a driving force, leading to the termination of hydrogenation of phenylacetylene as observed in **eq. 3**. Accordingly, Pd-H species can be generated from **S1** as shown in **eq. 4**, which was absolutely unavailable under alkaline condition. Hence, it was believed that the successful hydroaminocarbonylation of alkynes with alkaline organic amines in this work was not driven by Pd-H species. Interestingly, when **S1** reacted with phenylacetylene in the presence of propylamine or aniline, the target amide was formed in good yields (**eqs. 5** and **6**). It was noted that upon completion of each control experiment (**eq. 2**, **5** or **6**), only the unreacted phenylacetylene and the target product were obtained. The other by-product or **S1** was not found. Without the presence of CO in **eqs. 5** and **6**, **S1** was not able to be regenerated after reacting with phenylacetylene and the amine in stoichiometry as the active agent. These results confirmatively supported that the carbamoylpalladium complex (**B**, similar to **S1**) was the real catalytic species as proposed in Scheme 1, which was compatible with the alkaline organic amines. Subsequently, the coordinate and insertion of the alkyne into **B** generates the corresponding (β-vinyl) carbamoylpalladium intermediate (**E**), which is aminolyzed by another amine to give the target branched amide along with the regeneration of **B** followed by CO insertion. Reasonably, the intermediate **B** also can evolve into Pd-H species which unavoidably converts to inactive $Pd^0$ with the presence of a base, leading to the deactivation of Pd(II)-catalyst as shown in Scheme 1.

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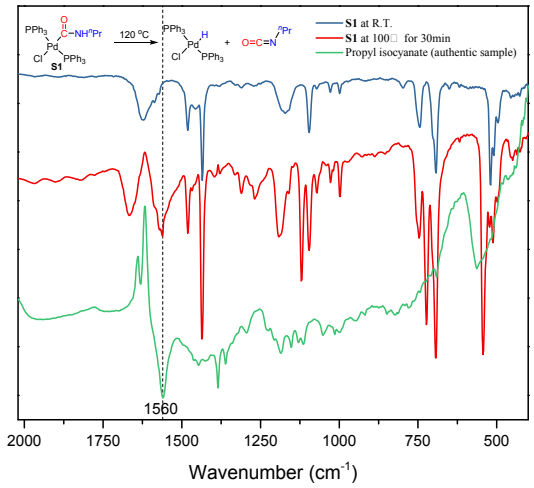
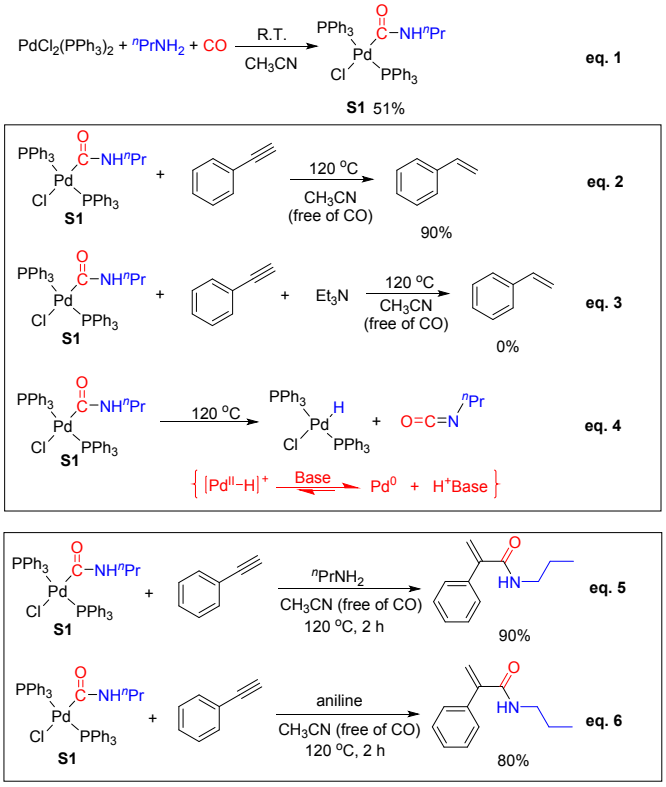



**Fig. 1** FT-IR spectra of **S1** and its derivative upon treating at 120 °C



**Scheme 2** Synthesis of carbamoylpalladium complex (**S1**) and its stoichiometric control reaction with phenylacetylene under different conditions free of CO

## Conclusions

The palladium-catalyzed aminocarbonylation of alkynes with aliphatic amines proceeds efficiently without any acid additive, yields the corresponding branch amides in excellent regioselectivity and good yields. In the presence of dppp with the natural bite angle of 91 °, the excellent conversion of phenylacetylene and 100% selectivity to the branched amide were obtained over $Pd(OAc)_2$. Dppp-based $Pd(OAc)_2$ system also exhibited wide generality to aminocarbonylation of alkynes with organic amines including the weak alkaline aryl amines and the strong alkaline aliphatic ones. The mechanism study proved that carbamoylpalladium intermediate but not palladium-hydride is the key catalytic species for this reaction under strong alkaline condition.

## Conflicts of interest

There are no conflicts to declare.

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