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Palladium(II)-catalyzed catalytic aminocarbonylation and alkoxycarbonylation of terminal alkynes: regioselectivity controlled by the nucleophiles

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The aminocarbonylation and alkoxycarbonylation reactions of terminal alkynes took place smoothly and efficiently using a catalyst system $Pd(OAc)_2$–dppb–*p*-TsOH–CH_3CN–CO under relatively mild experimental conditions. The catalytic system was tested and optimized using two different nucleophiles: alcohols and amines. Phenylacetylene (1a) was considered as an alkyne along with diisobutylamine ($2b_1$) and methanol ($2c_1$) as nucleophiles. The results showed significant differences in the conversion of 1a and in the selectivity towards the *gem* or *trans* unsaturated esters or amides with these nucleophiles. The effects of the type of palladium catalysts, the type of ligands, the amount of dppb and the solvents were carefully studied. With diisobutylamine ($2b_1$), excellent regioselectivity towards the 2-acrylamides (*gem* isomer, $3ab_1$) was almost always observed, while *trans*-α,β-unsaturated esters $4ac_1$ was the predominant product with methanol ($2c_1$) as a nucleophile. This remarkable sensitivity in the selectivity of the reaction indicates two different possible mechanistic pathways for these carbonylation reactions. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: alkynes; amines; alcohols; carbonylation; palladium; phosphine

Introduction

Palladium-catalyzed carbonylation reactions, carried out in the presence of various nucleophiles like amines and alcohols, are among the most widely used homogenous catalytic reactions in synthetic chemistry.[1] α,β-Unsaturated amides or esters can be prepared by a direct carbonylation of alkynes in the presence of appropriate nucleophiles such as amines (aminocarbonylation) or alcohols (alkoxycarbonylation).

Aminocarbonylation plays a special role in synthesizing carboxamides which are difficult to prepare via a conventional carboxylic acid–carboxylic halide–carboxamide route (e.g. with bulky substituents at the amide nitrogen) from easily available starting materials.[2] The acrylic ester derivatives produced by the above reaction are employed in a wide of organic reactions, including nucleophilic additions and cycloaddition reactions.[3] They are also extensively used in the synthesis of polymeric materials.[4] Cinnamic acids and their esters are important intermediates for the production of pharmaceuticals, fragrances, light-sensitive materials, electrically conductive materials and agrochemicals.[5] The development of more efficient aminocarbonylation and alkoxycarbonylation catalytic systems in terms of conversion, selectivity and diversity of synthesized products is still a challenging area for many scientists. It is well known that the ratio of products from aminocarbonylation and alkoxycarbonylation reactions depends strongly on the catalytic system and the reaction conditions employed.[6,7] The regioselective synthesis of the *gem*-α,β-unsaturated esters has been achieved easily by various methods.[8–10] However, the research reports that describe the regioselective synthesis of the *trans*-α,β-unsaturated esters are still limited.[6,11] Many aminocarbonylation reactions of alkynes have been reported in the literature.[12–14] Nevertheless, only limited work has been done towards the selective aminocarbonylation of terminal alkynes using primary and secondary alkylamines; high regioselectivities and yields for the target products were achieved under relatively mild conditions.[13,15,16] The use of the same catalytic system for the aminocarbonylation and alkoxycarbonylation of terminal alkynes has been reported before.[2a,17] However, no apparent change on the selectivity of the reaction was observed by changing the type of nucleophile. In the present paper, we wish to report the new results of our investigations of the comparative study of the aminocarbonylation and alkoxycarbonylation of terminal alkynes using the same catalyst system $Pd(OAc)_2$–dppb–*p*-TsOH–CH_3CN–CO. A careful screening of the various reaction conditions including the type of catalyst, the type and amount of dppb, the amount of additive, the type of solvent and the type of amines or alcohols has been made.

Results and Discussion

The aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**), adopted as a model alkyne, using diisobutylamine ($\mathbf{2b_1}$) and methanol ($\mathbf{2c_1}$) was carried out using the system $Pd(OAc)_2$–dppb–*p*-TsOH–CO–CH_3CN (Table 1). Excellent conversion and regioselectivity towards the formation of *gem* isomer

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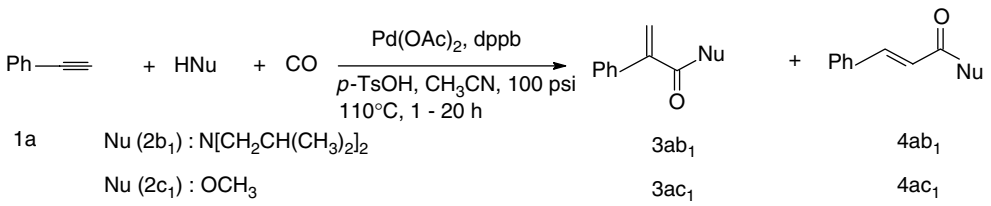
Table 1. Palladium(II)-catalyzed aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) and methanol (**2c$_1$**). Effect of the type of palladium catalyst[a]



1a — Nu (2b$_1$) : $N[CH_2CH(CH_3)_2]_2$ — 3ab$_1$ — 4ab$_1$

Nu (2c$_1$) : OCH_3 — 3ac$_1$ — 4ac$_1$

Entry	Catalyst	Conversion **1a** (%)[b]		Product distribution[c] (%)	
		2b$_1$	**2c$_1$**	**3ab$_1$: 4ab$_1$**	**3ac$_1$: 4ac$_1$**
1	$Pd(OAc)_2$	99	99	97 : 3	12 : 88
2	$PdCl_2$	100	27	95 : 5	25 : 75
3	$PdCl_2(PPh_3)_2$	91	7	97 : 3	100 : 0
4	$Pd(PhCN)_2Cl_2$	88	4	97 : 3	100 : 0
5	$Pd(CN)_2$	38	22	97 : 3	35 : 65
6	$PdSO_4$	56	99	96 : 4	62 : 38
7	Pd – C (5%)	34	97	97 : 3	13 : 87

[a] Reaction conditions: catalyst (0.02 mmol), dppb (0.08 mmol), phenylacetylene (2.0 mmol), diisobutylamine (**2b$_1$**) (2.0 mmol) or methanol (**2c$_1$**) (8.0 mmol), CO (100 psi), *p*-TsOH (0.3 mmol), CH_3CN (10 ml), 110 °C, 20 h (**1a** + **2b$_1$**) and 1 h (**1a** + **2c$_1$**).
[b] Determined by GC based on phenylacetylene.
[c] Determined by GC and ^{1}H NMR.

3ab$_1$ (2-acrylamide) was obtained with the alkylamine **2b$_1$**, while *trans* isomer **4ac$_1$** (cinnamate ester) was the predominant product with methanol (**2c$_1$**) as nucleophile. The reaction conditions were optimized and the effect of various reaction parameters on the activity and selectivity was determined.

Effect of the Type of Palladium Complexes

The presence of metal catalyst is essential for the catalytic carbonylation of alkynes. No reaction was observed in the absence of palladium catalysts. We have considered various palladium complexes in the aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) and methanol (**2c$_1$**). The results are summarized in Table 1. No significant change in the selectivity of the reaction was observed in the aminocarbonylation experiments by changing the type of palladium catalysts (Table 1, entries 1–7), where the *gem* isomers **3ab$_1$** were obtained as major products. Different ratios of products (**3ac$_1$: 4ac$_1$**) were obtained in the alkoxycarbonylation experiments using different palladium catalysts (Table 1, entries 1–7). It seems that the presence of ligands having higher binding ability such as chloride or cyanide (Table 1, entries 2–5) reduces the availability of the coordination sites around palladium, hence leading to lower catalytic activity in alkoxycarbonylation of terminal alkynes.[18,19] With methanol as a nucleophile, low yields (7–27%) were obtained with $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PhCN)_2Cl_2$ and $Pd(CN)_2$, while lower selectivity (**3ac$_1$: 4ac$_1$**=62 : 38) was observed with $PdSO_4$.

Effect of the Type of Ligand

The effect of the type of the ligand on the carbonylative coupling of phenylacetylene (**1a**) with diisobutylamine (**1b$_1$**) and methanol (**2c$_1$**) was investigated. Different bidentate phosphine ligands with wide range of bite angles and also monodentate phosphine ligands were used in the study. The results summarized in Table 2

Table 2. Palladium(II)-catalyzed aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) and methanol **(2c$_1$**). Effect of the type of ligand[a]

Entry	Ligand	Conversion **1a** (%)[b]		Product distribution[c] (%)	
		2b$_1$	**2c$_1$**	**3ab$_1$: 4ab$_1$**	**3ac$_1$: 4ac$_1$**
1	PPh_3	0	99	–	14 : 86
2	$P(OPh)_3$	0	0	–	–
3	dppe	12	0	85 : 15	–
4	dppp	59	0	97 : 3	–
5	dppf	78	12	97 : 3	62 : 38
6	dppb	99	99	97 : 3	11 : 89

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), ligand (0.08 mmol) except PPh_3, and $P(OPh)_3$ (0.16 mmol), phenylacetylene (2.0 mmol), diisobutylamine (**2b$_1$**) (2.0 mmol) or methanol (**2c$_1$**) (8.0 mmol), CO (100 psi), *p*-TsOH (0.3 mmol), CH_3CN (10 ml), 110 °C, 20 h (**1a** + **2b$_1$**) and 1 h (**1a** + **2c$_1$**).
[b] Determined by GC based on phenylacetylene.
[c] Determined by GC and ^{1}H NMR.

showed no catalytic activity in the aminocarbonylation reaction of phenylacetylene and an excellent activity in alkoxycarbonylation reaction when monodentate ligand PPh_3 was used (Table 2, entry 1). The use of $P(OPh)_3$ ligand inhibits completely both reactions (Table 2, entry 2). A correlation between diphosphine ligand bite angle, rate and selectivity has been observed for the two studied reactions. For example, an increase in the bite angle of the diphosphine ligand used resulted in an increase in both activity and selectivity to produce selectively **3ab$_1$** and **4ac$_1$** in the aminocarbonylation and alkoxycarbonylation reactions, respectively (Table 2, entries 3–6). A similar correlation between diphosphine ligand bite angle, catalytic efficiency and selectivity was also observed in palladium-catalyzed alkoxycarbonylation of phenylacetylene,[11] and palladium-catalyzed cross coupling

reactions of Grignard reagents with organic halides.[20] Extended Huckel calculations indicate that, in the diphosphine complexes with small ligand bite angles, the electron density is shifted to the hydride ligand. Therefore, the increase in the bite angle of the ligand increases the hydride ligand acidity, hence the basicity of the following ligands increases in the order: dppe > dppp > dppb. This order suggests a possible reason for the reduced activity of dppe in alkoxycarbonylation of (**1a**).[21] In the alkoxycarbonylation mechanism, the hydropalladation process exhibits high regioselectivity, resulting in *cis*-addition of Pd hydride complex to a less hindered carbon atom, which finally yields the *trans* isomer **4ac$_1$**.[22,23] Our postulation about the early coordination of amine and diphosphine ligand to the active palladium center can be used to explain the insensitivity for the type of phosphine ligand on the selectivity of the aminocarbonylation reaction (Table 2, entries 3–6).

The study of the effect of different dppb : Pd ratios is found to have significant effect on the catalytic activity and product distribution of the alkoxycarbonylation reaction (Fig. 1), while significant improvement in catalytic activity was only observed for the aminocarbonylation catalyst system (Fig. 2). No change in the activity and the selectivity for both reactions was observed at the ratios of dppb : Pd = 3–4. However, in the aminocarbonylation experiments, the use of excess amounts of dppb ligand (>0.08 mmol) resulted in lowered rate of the reaction, which could be explained by competition of dppb ligands with the reactant molecules for coordination, causing decrease in activity, but with no effect on the product distribution.

Effect of the Solvent

The study of the effect of solvent is extremely important in the aminocarbonylation and alkoxycarbonylation reactions of alkynes (Table 3). The results showed no clear correlation between the dielectric constant of the solvent and the outcome of the reactions. Various polar and non-polar solvents tested with alkoxycarbonylation of phenylacetylene led to excellent conversions (except *n*-hexane) producing mainly the *gem* isomer as predominant product, except with acetonitrile where *trans*-α, β-unsaturated ester **4ac$_1$** was the major product. This lower activity for *n*-hexane (Table 3, entry 5) compared with other solvents employed in this reaction is probably due to the fact that this non-polar solvent favors the association between the complex cation and the counter ion, so that could compete with the reacting molecule for coordination.[18] The opposite regioselectivity of the alkoxycarbonylation reaction was only achieved when CH_3CN was used as solvent (Table 3, entry 7). The reason for the high selectivity for the *trans* isomer **4ac$_1$** exclusively in acetonitrile as a solvent is not yet very clear, but it is possible that acetonitrile acts both as a solvent and a co-ligand.[5]

The drastic increase in the catalytic activity in the aminocarbonylation reaction was only observed with acetonitrile as the solvent. The change in the reaction rate was also accompanied by excellent selectivity of the reaction (Table 3, entry 7).

Effect of the Amount of *p*-TsOH Additive

The reaction of carbonylative coupling of phenylacetylene (**1a**) with diisobutylamine (**2b$_1$**) and methanol (**2c$_1$**) catalyzed by Pd : dppb in acetonitrile was carried out in the presence of different amounts of *p*-TsOH additive. The results of the aminocarbonylation reaction (Fig. 3) clearly showed that the presence of acid additive is not crucial for the reaction, since a conversion of 27% of phenylacetylene was obtained in the absence of *p*-TsOH. This yield was increased to 44% by elongating reaction time to 36 h. However, the addition of *p*-TsOH led to a significant increase in the activity (93%) and a slight increase in the selectivity of the reaction towards *gem* isomer **3ab$_1$** (97%). It seems that acid as additive is not an essential part of the active starting catalytic species, and its role appears as a promoter in the process of formation of the active catalytic species, or in the successive transformation of catalytic intermediates in the catalytic cycle. Also, the acid can create a free site at the metal center as well as reducing the concentration of acetate ion in solution.[5] Unlike aminocarbonylation, the presence of acid additive in the alkoxycarbonylation reactions is absolutely necessary to form the active species; no reaction occurred in the

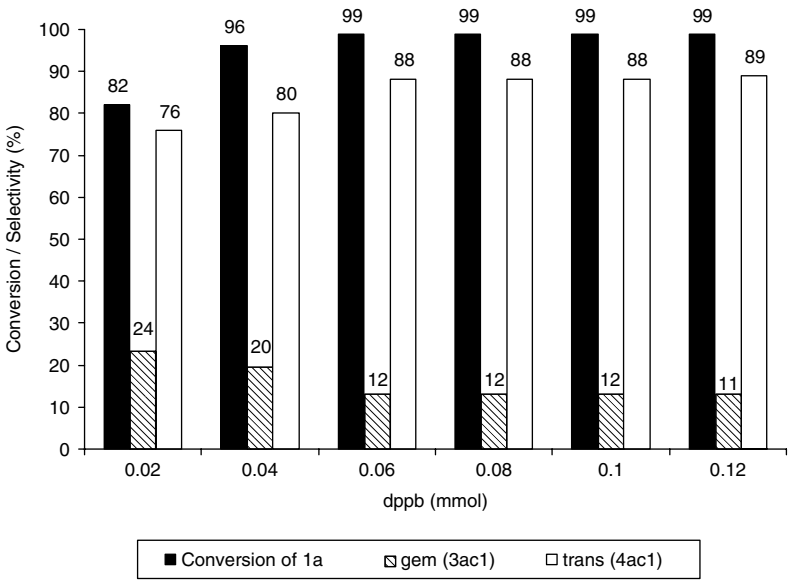


Figure 1. Alkoxycarbonylation of phenylacetylene (**1a**) using methanol (**2c$_1$**) by $Pd(OAc)_2$–dppb–*p*-TsOH. Effect of the amount of dppb. Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), **1a** (2.0 mmol), **2c$_1$** (8.0 mmol), CO (100 psi), *p*-TsOH (0.30 mmol), CH_3CN (10 ml), 110 °C, 1 h.

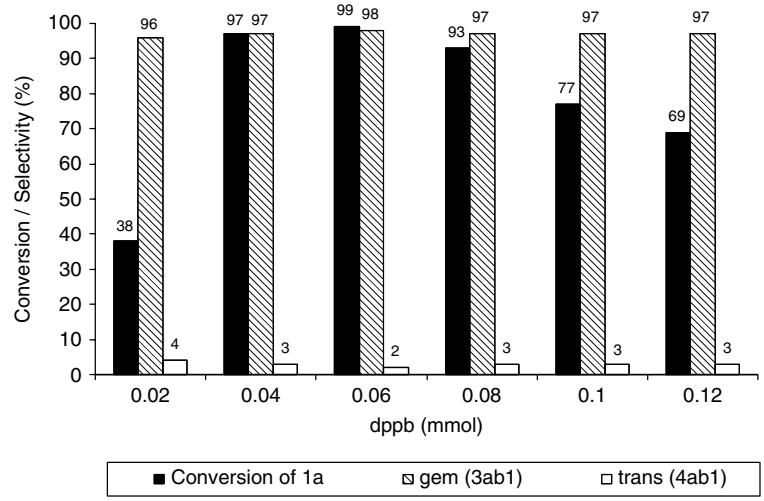


Figure 2. Aminocarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) by Pd(OAc)$_2$ – dppb – *p*-TsOH. Effect of the amount of dppb. Reaction conditions: Pd(OAc)$_2$ (0.02 mmol), **1a** (2.0 mmol), **2b$_1$** (2.0 mmol), CO (100 psi), *p*-TsOH (0.30 mmol), CH_3CN (10 ml), 110 °C, 20 h.

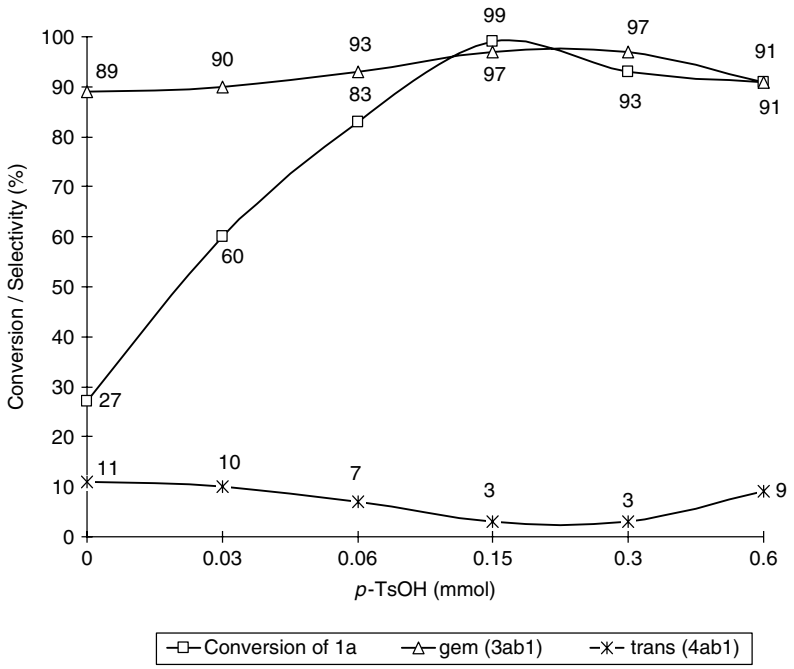


Figure 3. Aminocarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) by Pd(OAc)$_2$ – dppb – *p*-TsOH. Effect of the amount of *p*-TsOH. Reaction conditions: Pd(OAc)$_2$ (0.02 mmol), dppb (0.08 mmol), **1a** (2.0 mmol), **2b$_1$** (2.0 mmol), CO (100 psi), CH_3CN (10 ml), 110 °C, 20 h.

absence of *p*-TsOH. The effect of the concentration of *p*-TsOH on the catalytic activity and the selectivity is shown in Fig. 4. The acid may react by forming metal hydride species through protonation of the electron-rich Pd(0) species, which is formed from *in situ* reduction of Pd(II).[24] These species are electron-rich and known to form Pd – H in the presence of strong acid. The selectivity is not affected by change in *p*-TsOH concentration, which suggests that OTs^- may not be very strongly coordinated to the Pd center.[18]

Effect of the Reaction Temperature

The effect of temperature was also carefully studied. Similar reaction conversions were obtained with the aminocarbonylation and the alkoxycarbonylation reactions at 90 °C (Table 4, entry 1). The 10 °C increment in the reaction temperature resulted in almost complete conversion for alkoxycarbonylation system, and a doubling of the activity for the aminocarbonylation reaction (Table 4, entry 2). Maximum conversion of the aminocarbonylation reaction was obtained at 120 °C (Table 4, entry 4), but the catalyst partially decomposed and Pd black precipitated was formed. The selectivity of both reactions was hardly affected by the change of the reaction temperature.

Effect of the Type of Nucleophiles

The carbonylative coupling of phenylacetylene (**1a**) with a variety of primary and secondary amines **2b$_{1-6}$** and alcohols **2c$_{1-4}$** was studied. The results are presented in Tables 5 and 6. In the aminocarbonylation reaction, no correlation was found between the catalytic activity and the basicity of the amines employed in

Table 3. Palladium(II)-catalyzed aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) or methanol (**2c$_1$**). Effect of the type of solvent[a]

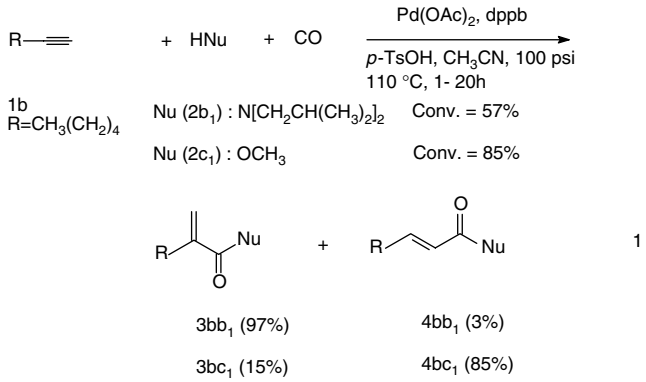
Entry	Solvent	Conversion **1a** (%)[b]		Product distribution[c] (%)	
		2b$_1$	**2c$_1$**	**3ab$_1$: 4ab$_1$**	**3ac$_1$: 4ac$_1$**
1	DMF	Traces	93	–	82 : 18
2	DMSO	28	99	67 : 33	87 : 13
3	DCM	19	99	94 : 6	75 : 25
4	THF	Traces	99	–	90 : 10
5	*n*-Hexane	22	72	89 : 11	69 : 31
6	Toluene	14	100	42 : 58	79 : 21
7	CH_3CN	93	99	97 : 3	12 : 88

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), phenylacetylene (2.0 mmol), diisobutylamine (**2b$_1$**) (2.0 mmol) or methanol (**2c$_1$**) (8.0 mmol), CO (100 psi), *p*-TsOH (0.3 mmol), solvent (10 ml), 110 °C, 20 h (**1a** + **2b$_1$**) and 1 h (**1a** + **2c$_1$**).
[b] Determined by GC based on phenylacetylene.
[c] Determined by GC and ^{1}H NMR.

the carbonylative reactions. Moderate to complete conversion was obtained with different alkyl amines affording the *gem* isomers **3ab$_{1-4}$** in excellent regioselectivity (Table 5, entries 1–4). Surprisingly, the employment of aromatic amines **2b$_{5-6}$** with the same catalytic system afforded the *trans* isomer **4ab$_{5-6}$** as a major product. Reversing the selectivity of the reaction by changing the type of amine is reported for the first time in this paper for the aminocarbonylation of terminal alkynes. The results obtained with aromatic amines **2b$_{5-6}$** leading to the regioselectively formation of *trans* isomer **4ab$_{5-6}$** were similar to data already published by our laboratory.[10]

For alkoxycarbonylation reaction, neither conversion nor selectivity was significantly changed by modifying the type of alcohol used (Table 6). Complete conversion and excellent selectivity towards the *trans* isomer **4ac** were obtained with alcohols **2c$_{1-4}$** with different numbers of carbon atoms. This method provides advantages in terms of both catalytic activity and regioselectivity compared with the systems described in the literature. It seems that the alkoxy mechanism is playing a minor role in this process because the initial formation of palladium carboalkoxy decreased with the increase in number of carbons of alcohols.[25–27]

It is also important to note that the aminocarbonylation and alkoxycarbonylation reactions take place not only with terminal aromatic alkynes but also selectively with terminal alkyl alkynes, for example, 1-heptyne **1b** [equation (1)].



Proposed Mechanisms

The mechanism of the addition of alcohols and amines to terminal alkynes catalyzed by $Pd(OAc)_2$–dppb–*p*-TsOH–CO is not yet well understood. Based on the literature and the present experimental observations, we tentatively propose two mechanisms for the alkoxycarbonylation and aminocarbonylation of terminal alkynes to amines and alcohols (Schemes 1 and 2). Claver and co-wokers

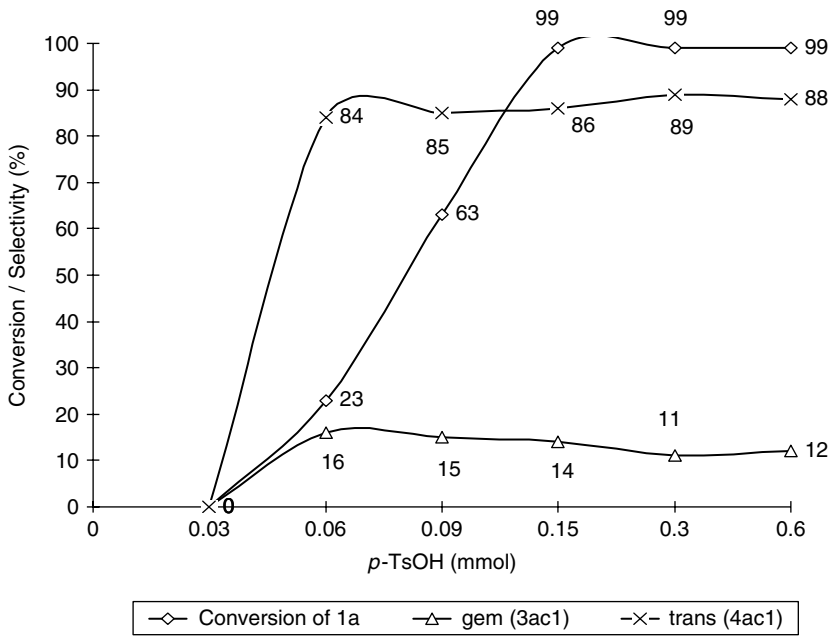
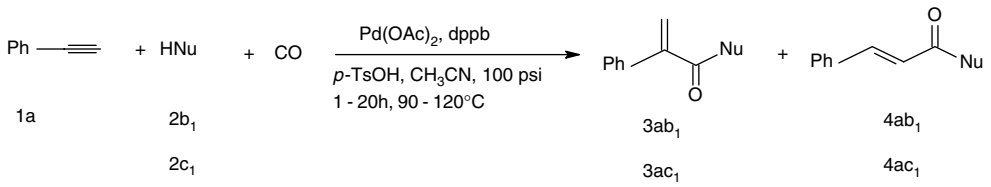


Figure 4. Alkoxycarbonylation of phenylacetylene (**1a**) to methanol (**2c$_1$**) by $Pd(OAc)_2$–dppb–*p*-TsOH. Effect of the amount of *p*-TsOH. Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), **1a** (2.0 mmol), **2c$_1$** (8.0 mmol), CO (100 psi), CH_3CN (10 ml), 110 °C, 1 h.

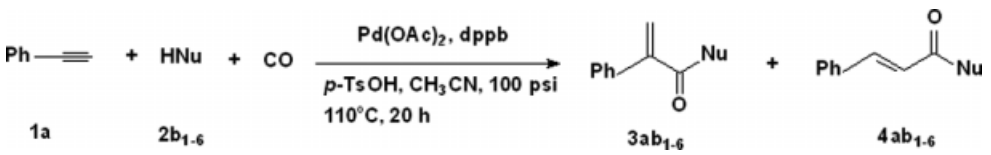
Table 4. Palladium(II)-catalyzed aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**) using diisobutylamine (**2b$_1$**) and methanol (**2c$_1$**). Effect of the temperature[a]



Entry	Temperature (°C)	Conversion **1a** (%)[b]		Product distribution[c] (%)	
		2b$_1$	**2c$_1$**	**3ab$_1$: 4ab$_1$**	**3ac$_1$: 4ac$_1$**
1	90	30	30	88 : 12	10 : 90
2	100	57	99	97 : 3	11 : 89
3	110	93	99	97 : 3	12 : 88
4	120	99	99	96 : 4	14 : 86

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), phenylacetylene (2.0 mmol), diisobutylamine (**2b$_1$**) (2.0 mmol) or methanol (**2c$_1$**) (8.0 mmol), CO (100 psi), *p*-TsOH (0.3 mmol), CH_3CN (10 ml), 20 h (**1a** + **2b$_1$**) and 1 h (**1a** + **2c$_1$**).
[b] Determined by GC based on phenylacetylene.
[c] Determined by GC and ^{1}H NMR.

Table 5. Aminocarbonylation of phenylacetylene (**1a**) using various amines **2b$_{1-6}$**[a]



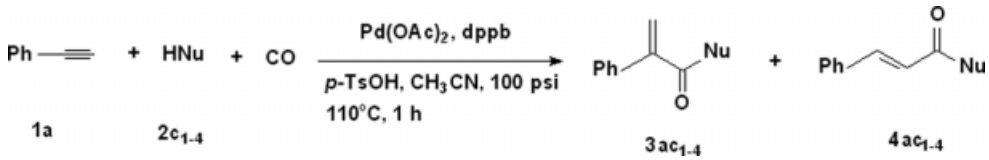
Entry	Amine **2b**	Conversion **1a** (%)[b]	Product distribution[c] (%)	
			3ab	**4ab**
1	Diisobutylamine	93	97	3
	2b$_1$		**3ab$_1$**	**4ab$_1$**
2	*n*-Hexylamine	56	95	5
	2b$_2$		**3ab$_2$**	**4ab$_2$**
3	Cyclohexylamine	63	96	4
	2b$_3$		**3ab$_3$**	**4ab$_3$**
4	Benzylamine	100	88	12
	2b$_4$		**3ab$_4$**	**4ab$_4$**
5	Aniline	100	34	66
	2b$_5$		**3ab$_5$**	**4ab$_5$**
6	*N*-methylaniline	100	44	56
	2b$_6$		**3ab$_6$**	**4ab$_6$**

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), amine (2.0 mmol), phenylacetylene (2.0 mmol), *p*-TsOH (0.3 mmol), CH_3CN (10 ml), CO (100 psi), 110 °C, 20 h.
[b] Determined by GC based on phenylacetylene.
[c] Determined by GC and ^{1}H NMR.

have suggested that high *gem* selectivity may proceed through a neutral catalytic cycle, while the *trans* preference follows a cationic catalytic cycle.[28]

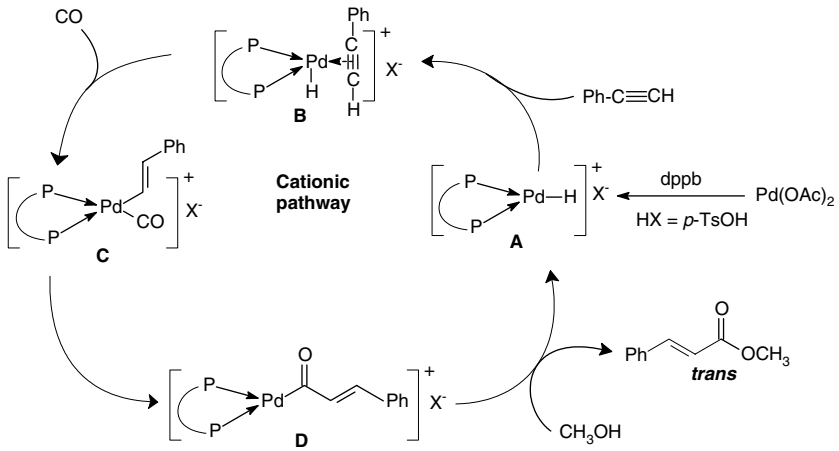
On the basis of the promoting effect of a hydride source such as *p*-TsOH, it is likely that this mechanism plays a major role with alcohol nucleophile.[11,29] The first step in the proposed mechanism is the formation of active cationic palladium hydride species **A** (Scheme 1). This intermediate is formed by the reaction of $Pd(OAc)_2$, dppb and acid.[7] The tosylate, in comparison with acetate, seems to be preferable for the formation of such species because it is a less coordinating ligand compared with acetate, so that the subsequent incorporation of alkynes proceeds smoothly.[30] Thus, the next proposed step is the coordination of alkyne on **A** to yield **B**. The formation of intermediate **C** includes the insertion of the coordinated alkyne into a Pd–H bond to give a (σ-vinyl)palladium complex followed by the coordination of CO molecule. Experimental results obtained in this study suggest three factors that control hydride addition to the triple bond to produce *trans* isomer: the nature of the catalyst precursor [$PdCl_2$; $Pd(OAc)_2$], the nature of the solvent and the steric and

Table 6. Alkoxycarbonylation of phenylacetylene (**1a**) using various alcohols **2c$_{1-4}$**[a]



Entry	Alcohol **2c**	Conversion **1a** (%)[b] (%)	Product distribution[c] (%) **3ac**	**4ac**
1	**MeOH**	100	11	89
	2c$_1$		**3ac$_1$**	**4ac$_1$**
2	***n*-BuOH**	100	11	89
	2c$_2$		**3ac$_2$**	**4ac$_2$**
3	***i*-BuOH**	100	15	85
	2c$_3$		**3ac$_3$**	**4ac$_3$**
4	***n*-PeOH**	100	13	87
	2c$_4$		**3ac$_4$**	**4ac$_4$**

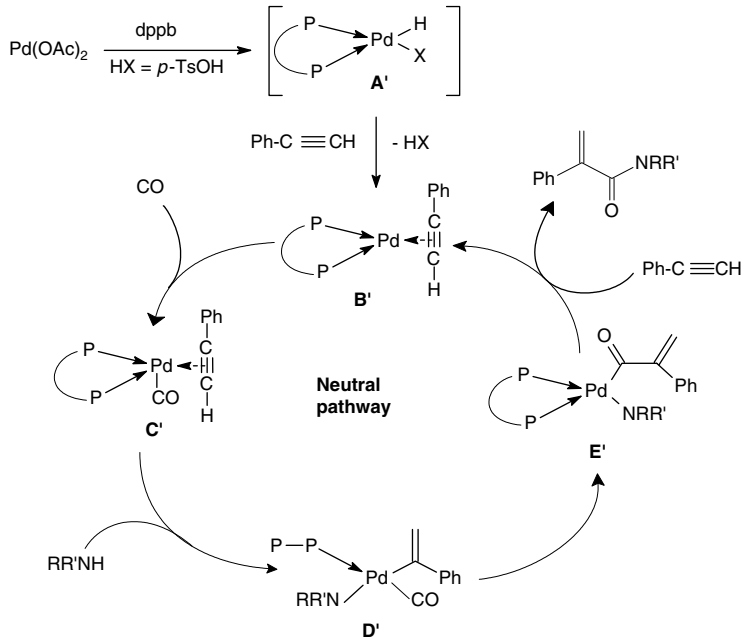
[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), alcohol (8.0 mmol), phenylacetylene (2.0 mmol), *p*-TsOH (0.30 mmol), CH_3CN (10 ml), CO (100 psi), 110 °C, 1 h.
[b] Determined by GC based on phenylacetylene.
[c] Determined by GC and ^1H NMR.



Scheme 1. Palladium-catalyzed alkoxycarbonylation of phenylacetylene. Cationic pathway leading to *trans*-α,β-unsaturated esters.

electronic effect of the ligand. Migration insertion of CO into the palladium–vinyl bond leads to the formation of intermediate **D**. Finally, the methanolysis of the acyl complex produces the *trans* isomer **4** and regenerates the hydride **A**. The charge distribution in phenylacetylene indicates that the terminal carbon is more nucleophilic than the internal carbon, because of the electron-withdrawing effect of the phenyl group. Theoretical calculation shows the charge distribution is −0.452 for the terminal carbon and 0.094 for the internal carbon; therefore, it is expected that the terminal carbon of the triple bond has more affinity for the cationic palladium than the internal; hence more *trans* isomer is formed via the cationic pathway rather then the neutral pathway.[11] Again, it is unlikely to be the palladium–carboxy mechanism that is operating here, since no change in the selectivity was observed by changing the type of alcohol (Table 6).

The results of the aminocarbonylation of phenylacetylene are totally different in the presence of the same catalyst system and at the same experimental conditions. The *gem* α,β-unsaturated amides are formed as the major products. We believe that this reaction proceeds via a neutral mechanistic pathway (Scheme 2). While we proposed a plausible reaction mechanism, the stepwise details for this aminocarbonylation process are still open to debate and remain subject to further experimental and computational investigations. The presence of amine nucleophile inhibits the formation of any active cationic palladium species and subsequently suppresses the cationic pathway. This is supported by the fact that only amine is carbonylatively added to phenylacetylene when an equal amount (2.0 mmol) of diisobutylamine and methanol is added to reaction mixture. The key of our suggested mechanism will be the formation of active neutral species **B′** via the coordination of alkyne to the neutral species **A′**. The experimental results suggested the electronic effect of ligand to play an important role in determining the conversion and selectivity of the aminocarbonylation reaction. The neutral CO molecule then coordinated to the metal center forming intermediate **C′**. A vacant site on the metal center can



Scheme 2. Palladium-catalyzed aminocarbonylation of phenylacetylene. Neutral pathway leading to 2-acrylamides.

be created by de-coordination of one of the metal–phosphine bidentate bonds, which allows the oxidative addition of amine to the palladium center accompanied with the addition of the palladium center to the internal carbon of the double bond forming the intermediate **D**′. The experimental results for the effect of type of amine obtained in this study supported the assumption of early coordination of amine nucleophile. This type of coordination makes the electronic effect a predominant factor in determining the selectivity of the reaction. The isolation of traces amount of urea derivatives as byproducts in aminocarbonylation reaction gave more support for the existence of **D**′. Intermediate **E**′ was formed by the migratory insertion of CO into the palladium–vinyl bond. The final step will involve the reductive elimination of the *gem* product and the regeneration of **B**′. Another plausible pathway for the production of *gem* product will be the insertion of CO into the palladium–amine bond of the intermediate **D**′,[12] reconstruction of second palladium-phosphine ligand and finally the reductive elimination of *gem* product.

Conclusions

In conclusion, the regioselective control in the synthesis of 2-acrylamides **3ab** and cinnamate esters **4ac** was achieved by the aminocarbonylation and alkoxycarbonylation of phenylacetylene (**1a**) using various amines and alcohols, respectively. A simple catalytic system $Pd(OAc)_2$–dppb–*p*-TsOH–CH_3CN–CO under relatively mild experimental conditions was used. The selectivity of the reactions depends strongly on the type of nucleophile. However, the nature of the catalyst precursor, the type of solvent and the steric and electronic effects of the ligand also play a significant role. The results obtained showed great advantages in terms of both catalytic activity and regioselectivity in producing the 2-acrylamides **3ab** and cinnamate esters **4ac** compared with other systems reported in the literature. Computational study of the suggested mechanistic pathways is also underway.

Experimental Section

Introduction

Alkynes, amines, alcohols, palladium catalysts, phosphine ligands and *p*-toluenesulfonic acid (*p*-TsOH) are highly pure commercially available materials and were used without any purification. Dry solvents were used in all experiments. ^1H and ^{13}C NMR spectra were recorded on 500 MHz Jeol 1500 NMR machine. Chemical shifts (δ) were reported in ppm relative to tetramethyl silane (TMS) using $CDCl_3$. IR spectra were recorded on a Perkin–Elmer ^{16}F PC FT-IR spectrometer and reported in wave numbers (cm^{-1}). Gas chromatography (GC) analyses were realized on an Agilent GC 6890. The products of the reactions were also analyzed on GC-MS Varian Saturn 2000 equipped with 30 m capillary column (HP-5). Thin-layer chromatography (TLC) analyses were performed on silica gel Merck 60 F254 plates (250 µm layer thickness).

General Procedure for the Carbonylative Coupling of Phenylacetylene (1a) with Amines or Alcohols

A mixture of $Pd(OAc)_2$ (0.02 mmol), 1,4-bis(diphenylphosphino)butane (dppb; 0.08 mmol), *p*-TsOH (0.3 mmol), alkyne (2.0 mmol) and amine (2.0 mmol) or alcohol (8.0) in 10 ml acetonitrile was placed in the glass liner, equipped with a stirring bar, fitted in a 45 ml Parr autoclave. The autoclave was vented three times with CO and then pressurized at room temperature with 100 psi CO. The mixture was stirred and heated at 110 °C for the required time. After cooling, the pressure was released, the reaction mixture was filtered and a sample of this solution was immediately analyzed by GC and GC-MS. The solvent was then removed and the products were separated by preparative TLC (30% EtOAc–petroleum ether 40–70 °C). The products were identified by ^1H and ^{13}C NMR, FT-IR and GC-MS analyses. Compounds **3ab**$_{1-4}$ prepared in this study are new amides and their spectral data are given below, while the other products (**3ab**$_{5-6}$[14], **4ac**$_{1-4}$[31]) are known compounds.

Spectral and Analytical Data for some α,β-unsaturated Amides

*N,N-diisobutyl-2-phenylpropeneamide (**3ab$_1$**)*

Oil, IR ($CHCl_3$) ν (cm^{-1}) 1633 (CO); ^{1}H NMR δ ($CDCl_3$): 0.71 [d, 6H, CH($\underline{CH_3}$)$_2$, J = 5.0 Hz], 0.91 [d, 6H, CH($\underline{CH_3}$)$_2$, J = 5.0 Hz], 1.82 [m, 1H, $\underline{CH}(CH_3)_2$], 2.10 [m, 1 H, $\underline{CH}(CH_3)_2$], 2.99 (d, 2 H, NCH_2, J = 7.5 Hz), 3.31 (d, 2 H, NCH_2, J = 7.5 Hz), 5.28 (d, 1 H, $=CH_2$, J = 1.5 Hz), 5.64 (d, 1 H, $=CH_2$, J = 1.5 Hz), 7.22–7.45 (m, 5 H arom.); ^{13}C NMR δ ($CDCl_3$): 19.0 $(CH_3)_2$, 19.4 $(CH_3)_2$, 25.4 (CH), 26.0 (CH), 50.4 (NCH_2), 54.9 (NCH_2), 113.6 ($=CH_2$), 125.0 (C4′), 127.6 (C3′, C5′), 127.8 (C2′, C6′), 135.5 (C1′), 145.4 ($\underline{C}=CH_2$), 170.4 (C=O); GC-MS m/z 259 (M^+); analysis calculated for $C_{17}H_{25}NO$ (259.38): C, 78.72; H, 9.71; N, 5.40. Found: C, 78.69; H, 9.83; N, 5.54.

*N-hexyl-2-phenylpropenamide (**3ab$_2$**)*

Oil, IR ($CHCl_3$) ν (cm^{-1}) 1657 (CO), 3299 (NH); ^{1}H NMR δ ($CDCl_3$): 0.83 (t, 3 H, CH_3CH_2, J = 7.7 Hz), 1.21–1.48 [m, 6 H, -$(CH_2)_3$-], 2.31 (m, 2H, $NCH_2\underline{CH_2}$), 3.28 (t, 2 H, NCH_2, J = 6.4 Hz), 5.56 (s, 1 H, $=CH_2$), 5.98 (s, 1 H, $=CH_2$), 6.30 (s, 1 H, NH), 7.11–7.72 (m, 5 H arom.); ^{13} C NMR δ ($CDCl_3$): 14.0 (CH_3), 22.5 ($CH_3\underline{CH_2}$), 26.5 ($CH_3CH_2CH_2\underline{CH_2}$), 29.3 ($CH_3CH_2\underline{CH_2}CH_2$), 31.4 ($NCH_2\underline{CH_2}$), 39.9 ($NCH_2$), 120.8 ($=CH_2$), 125.9 (C4′), 127.9 (C3′, C5′), 128.6 (C2′, C6′), 137.0 (C1′), 145.1 ($\underline{C}=CH_2$), 167.8 (C=O); GC-MS m/z 231 (M^+); analysis calculated for $C_{15}H_{21}NO$ (231.33): C, 77.88; H, 9.15; N, 6.05. Found: C, 78.02; H, 9.04; N, 6.17.

*N-cyclohexyl-2-phenylpropenamide (**3ab$_3$**)*

Oil, IR ($CHCl_3$) ν (cm^{-1}) 1641 (CO), 3279 (NH); ^{1}H NMR δ ($CDCl_3$): 0.83–2.33 [m, 10 H, -$(CH_2)_5$-], 3.88 (m, 1 H, NCH), 5.58 (d, 1 H, $=CH_2$, J = 1.6 Hz), 5.79 (s, 1 H, NH), 6.03 (d, 1 H, $=CH_2$, J = 1.6 Hz), 6.98–7.48 (m, 5 H arom.); ^{13}C NMR δ ($CDCl_3$): 24.7 ($2CH_2$), 25.7 (CH_2), 32.8 ($2CH_2$), 48.5 (NCH), 121.2 ($=CH_2$), 125.9 (C4′), 127.9 (C3′, C5′), 128.6 (C2′, C6′), 137.0 (C1′), 145.1 ($\underline{C}=CH_2$), 166.6 (C=O); GC-MS m/z 229 (M^+); analysis calculated for $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.69; H, 8.41; N, 5.97.

*N-benzyl-2-phenylpropenamide (**3ab$_4$**)*

Oil, IR ($CHCl_3$) ν (cm^{-1}) 1652 (CO), 3403 (NH); ^{1}H NMR δ ($CDCl_3$): 4.14 (s, 1 H, NH), 4.37 (s, 2 H, NCH_2), 5.50 (s, 1 H, $=CH_2$), 5.90 (s, 1 H, $=CH_2$), 6.79–7.62 (m, 10 H arom.); ^{13}C NMR δ ($CDCl_3$): 43.1 (NCH_2), 120.7 (C4′), 125.4 (C4 benzyl), 126.5 (C3′, C5′), 126.8 (C3, C5 benzyl), 127.4 (C2′, C6′), 127.8 (C2, C6 benzyl), 136.2 (C1′), 137.8 (C1 benzyl), 144.3 ($\underline{C}=CH_2$), 167.6 (C=O); GC-MS m/z 237 (M^+); analysis calculated for $C_{16}H_{15}NO$ (237.29): C, 80.98; H, 6.37; N, 5.90. Found: C, 80.86; H, 6.45; N, 5.98.

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