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Palladium-Catalyzed Decarboxylative Aminocarbonylation with Alkynoic Acid and Tertiary Amine for the Synthesis of Alkynyl Amide

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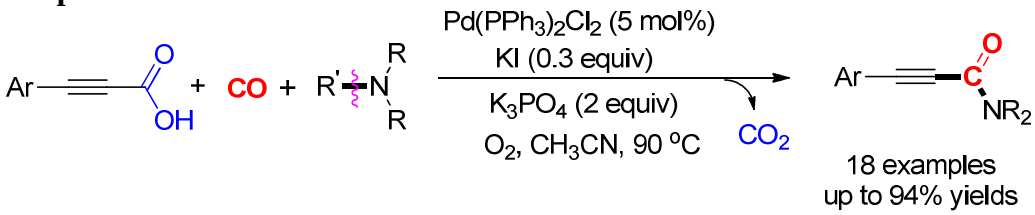
Keywords : alkynyl amide, carbonylation, tertiaryamine, decarboxylative coupling, propiolic acids

Graphic Abstract



Abstract

We developed a method for the synthesis of alkynyl amides via the carbonylation of alkynoic acids and C-N activation of tertiary amines. The reaction of alkynoic acid and tertiary amine with carbon monoxide using a palladium catalyst in the presence of oxygen, KI, and K_3PO_4, gave the desired alkynyl amides in good yields.

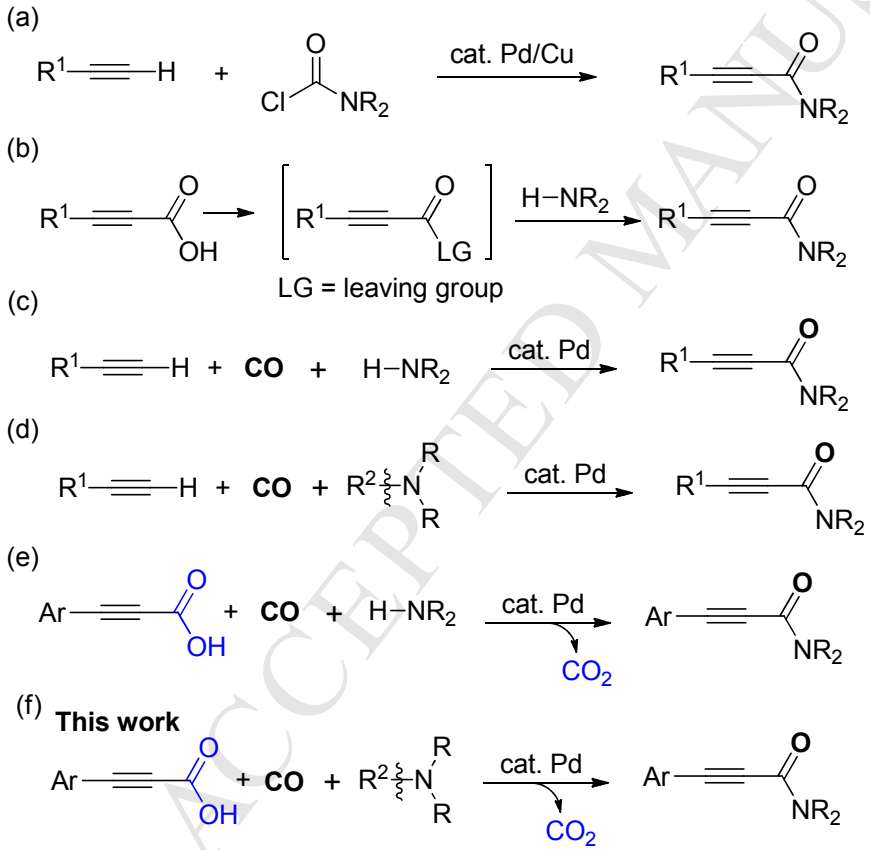
1. Introduction

The amide functionality is an important scaffold in many biologically active compounds and is the key structure of peptides and proteins [1]. In particular, the alkynyl amide functionality has attracted much attention in organic synthesis because it can be readily transformed into several useful building blocks for pharmaceutical and materials chemistry [2].

A number of methods have been reported for the preparation of alkynyl amides. A classical method in this regard is the Pd/Cu-catalyzed coupling reaction with a terminal alkyne and carbamoyl chloride (Scheme 1a) [3]. However, the use of carbamoyl chloride is problematic because it is moisture sensitive and not many commercially available. It has been reported that alkynoic acid can be converted to a carbonyl compound possessing a leaving group and that it further reacts with an amine to give the corresponding alkynyl amide, but this method requires multiple steps and has a narrow substrate scope (Scheme 1b) [4]. Another reported strategy involves the transition metal-catalyzed oxidative carbonylation of terminal alkynes with amines in the presence of carbon monoxide (Scheme 1c) [5]. Although this method is straightforward, the preparation of terminal alkynes has disadvantages in terms of high environmental load and poor cost effectiveness. Alkynoic acid has been widely used as a terminal alkyne surrogate since our first report on the decarboxylative coupling reactions of alkynoic acid in 2008 [6]. Specifically, aryl alkynoic acids could be readily prepared via a direct coupling reaction with aryl halides and propiolic acid and purified in a simple and convenient step [7]. Many decarboxylative coupling reactions with aryl alkynoic acids have been developed by our group [8] as well as other research groups [9].

Although reactions with primary and secondary amines have a wide substrate scope, undesired side reactions are often encountered. As an alternative method, the reaction with

tertiary amines has recently gained considerable attention because of the high stability and ready availability of the amines and the absence of side reactions. C-N activation of tertiary amines has been developed via oxidative addition [10], as well as imine, iminium [11], ammonium [12], and alkyl migration [13], or β-amino elimination [14] to provide the corresponding secondary amine source. Recently, palladium-catalyzed carbonylation of tertiary amines via N-dealkylation has been reported for the synthesis of indolin-2-ones [15] and arylamides [16]. Bhanage and co-workers reported a similar method based on the carbonylation of tertiary amines for the synthesis of alkynylamides (Scheme 1d)[17].



Scheme 1. Synthesis of alkynyl amides

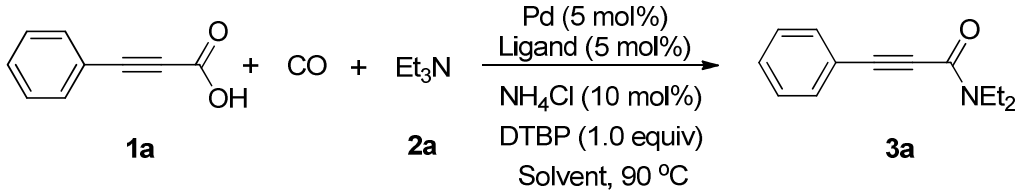
We reported the palladium-catalyzed oxidative decarboxylative aminocarbonylation for the synthesis of alkynylamides via the reaction of alkynoic acid and secondary amine (Scheme

1e) [18]. Thus, we envisioned that the reaction involving the use of a tertiaryamine could be selectively controlled at the C-N activation stage to afford the desired alkynylamide by tuning the reaction parameters (Scheme 1f). With this idea in mind, we carried out several trials to accomplish our goal.

2. Results and discussion

To obtain the optimal conditions for the synthesis of alkynylamides, we chose phenyl propiolic acid and trimethylamine as the standard substrates. First, we employed di-*tert*-butyl peroxide as an oxidant and carried out this carbonylation under various conditions, as shown in Table 1. When $PdCl_2$ was used in the absence of a ligand, the desired product was not formed (entry 1). A number of ligands were tested (entries 2–5), among which dppf (1,1′-bis(diphenylphosphino)ferrocene) gave the best yield, though not more than 50% (entry 5). Attempts to carry out the reaction using different palladium sources (entries 6–9) and solvents (entries 10–12) were unsuccessful and did not give satisfactory results. From these results, we determined that DTBP is not a suitable oxidant for this transformation and hence turned our attention to oxygen gas as an alternative choice.

Table 1. Decarboxylative carbonylation with **1a** and **2a** in the presence of DTBP. [a]



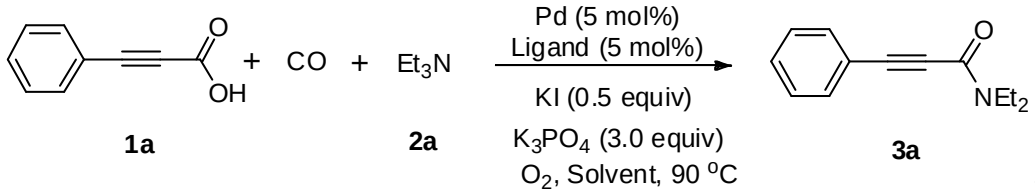
1a **2a** **3a**

Entry	Cat.	Ligand[b]	Solvent	**3a** Yield (%)[c]
1	$PdCl_2$	-	Anisole	0
2	$PdCl_2$	dppm	Anisole	34
3	$PdCl_2$	Dppp	Anisole	3
4	$PdCl_2$	dppb	Anisole	5
5	$PdCl_2$	dppf	Anisole	45
6	$Pd(OAc)_2$	dppf	Anisole	3
7	$Pd(TFA)_2$	dppf	Anisole	22
8	$Pd(acac)_2$	dppf	Anisole	38
9	$Pd(PPh_3)_2Cl_2$	dppf	Anisole	22
10	$PdCl_2$	dppf	Toluene	0
11	$PdCl_2$	dppf	*o*-Xylene	11
12	$PdCl_2$	dppf	CH_3CN	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Pd (0.015 mmol), ligand (0.015 mmol), NH_4Cl (0.03 mmol), and DTBP (0.3 mmol) were reacted under CO (7 atm) atmosphere in a solvent (1.0 mL) at 90 °C for 12 h. [b]dppm = bis(diphenylphosphino)methane, dppp = bis(diphenylphosphino)propane, dppb = bis(diphenylphosphino)butane, dppf = bis(diphenylphosphino)ferrocene. [c]Determined by gas chromatography using an internal standard (naphthalene).

We next investigated the parameters for the reaction of phenyl propiolic acid and trimethylamine under oxygen atmosphere (Table 2). When the reaction was conducted with $PdCl_2$ as the palladium source in the absence of a ligand, the product was obtained in 14% yield in anisole solvent (entry 1), while the yield increased to 55% in CH_3CN solvent (entry 2). Among the palladium sources we tested (entries 3–7), $Pd(PPh_3)Cl_2$ showed the best result and the product was obtained in 74% yield (entry 7). The reactions performed with ligands such as dppf and dppb did not improve the yield of the product (entries 8 and 9). Changing the solvent to 1,4-dioxane, THF, and toluene led to very low yields of the product or no product (entries 10–12).

Table 2. Decarboxylative carbonylation with **1a** and **2a** in the presence of oxygen.[a]



1a **2a** **3a**

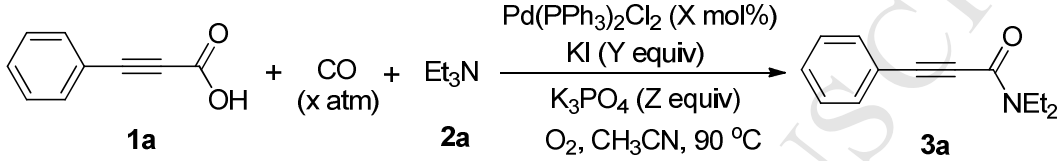
Entry	Pd	Ligand	Solvent	**3a** Yield (%)[b]
1	$PdCl_2$	-	Anisole	14
2	$PdCl_2$	-	CH_3CN	55
3	PdI_2	-	CH_3CN	34
4	$Pd(TFA)_2$	-	CH_3CN	59
5	Pd/C 10%	-	CH_3CN	50
6	$Pd(MeCN)_2Cl_2$	-	CH_3CN	41
7	$Pd(PPh_3)_2Cl_2$	-	CH_3CN	74
8	$Pd(PPh_3)_2Cl_2$	dppf	CH_3CN	35
9	$Pd(PPh_3)_2Cl_2$	dppb	CH_3CN	40
10	$Pd(PPh_3)_2Cl_2$		dioxane	5
11	$Pd(PPh_3)_2Cl_2$		THF	4
12	$Pd(PPh_3)_2Cl_2$		Toluene	trace

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Pd (0.015 mmol), ligand (0.015 mmol), KI (0.15 mmol), and K_3PO_4 (0.9 mmol) were reacted under CO (7 atm) and O_2 (1 atm) atmosphere in solvent (1.0 mL) at 90 ^oC for 12 h. [b]Determined by gas chromatography with an internal standard (naphthalene)..

With these conditions, we further investigated the effect of the mole ratio of all reagents. The results are summarized in Table 3. When the pressure of carbon monoxide was decreased to 3 atm or increased to 9 atm, **3a** was formed in 6% and 72% yields, respectively (entries 1 and 2). With a decrease in the amount of KI to 0.3 equiv or an increase in the amount of K_3PO_4 to 2.0 equiv, the product **3a** was obtained in 94% yield (entries 3 and 4). However, when the reaction was performed with 1.0 equiv of K_3PO_4, the yield of **3a** decreased to 74% (entry 5). It was noteworthy that **3a** was formed even in the absence of K_3PO_4, although the yield was not satisfactory (entry 6). Moreover, no product was formed in the absence of KI (entry 7). Decreasing the amount of $Pd(PPh_3)_2Cl_2$ to 3 mol% provided the product in 65% yield (entry

8). No amide product was formed when the reaction conducted in the absence of CO gas. (entry 9). This result support that the source of "CO" in the amide product might come from CO gas. No product was formed in the absence of oxygen (entry 10). Finally, we established the optimal conditions as follows: reaction of **1a** (1.0 equiv), tertiary amine (1.5 equiv), CO (7 atm), O_2 (1 atm), $Pd(PPh_3)_2Cl_2$ (5 mol%), KI (0.3 equiv), and K_3PO_4 (2.0 equiv) in CH_3CN at 90 ^oC for 12 h.

Table 3. Optimal conditions for the synthesis of **3a** from **1a**, **2a**, and carbon monoxide. [a]



1a **2a** **3a**

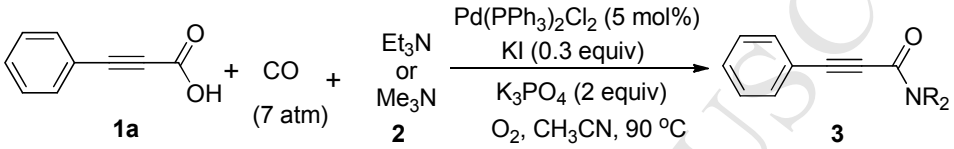
Entry	$Pd(PPh_3)_2Cl_2$ (mol%)	K_3PO_4 (equiv)	KI (equiv)	CO (atm)	**3a** Yield[c](%)
1	5	3	0.5	3	6
2	5	3	0.5	9	72
3	5	3	0.3	7	94
4	5	2	0.3	7	94
5	5	1	0.3	7	74
6	5	0	0.3	7	60
7	5	3	0	7	0
8	3	2	0.3	7	65
9	5	2	0.3	0	0
10[b]	5	2	0.3	7	0

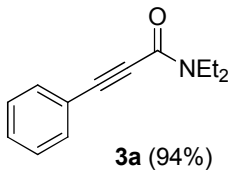
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $Pd(PPh_3)_2Cl_2$ (X mol%), KI (Y equiv), and K_3PO_4 (Z equiv) were reacted under CO (x atm) and O_2 (1 atm) atmosphere in CH_3CN (1.0 mL) at 90 ^oC for 12 h. [b]No oxygen was used. [c]Determined by gas chromatography with an internal standard(naphthalene)..

With the optimal conditions in hand, we evaluated a variety of aryl propiolic acids for the reactions with triethyl amines and trimethyl amines, as shown in Scheme 1. As expected, the reaction with phenyl propiolic acid and triethylamine provided the desired product **3a** in 94% isolated yield. Methyl-substituted aryl propiolic acids such as *o*-, *m*-, and *p*-tolyl propiolic acids gave the corresponding products **3b**, **3c**, and **3d** in good yields. Methoxy-substituted aryl propiolic acids also led to the formation of **3e**, **3f**, **3g**, and **3h** in good yields. Chloro- and

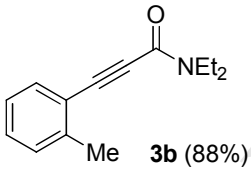
fluoro-substituted aryl propiolic acids provided **3i** and **3j** in 91% and 89% yields, respectively. Cyano-substituted aryl propiolic acid furnished the product in good yield. 2-Thiophenyl propiolic acid afforded **3l** in 72% yield. The use of trimethyl amine in the reactions with phenyl propiolic acid and tolyl propiolic acids also resulted in good product yields. These results indicated that there was no notable difference between the yields obtained with aryl propiolic acids having electron-withdrawing or electron-donating groups.

Table 4. Synthesis of alkynyl amides from the reaction of substituted-aryl propiolic acids[a]

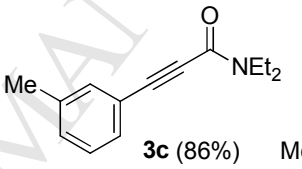




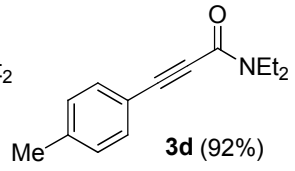
3a (94%)



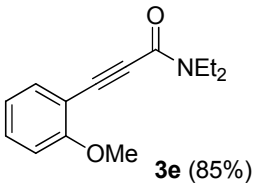
3b (88%)



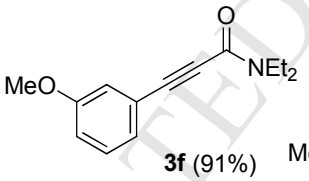
3c (86%)



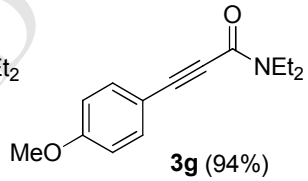
3d (92%)



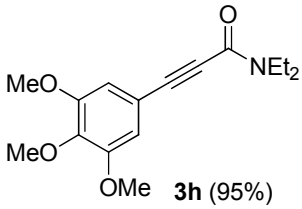
3e (85%)



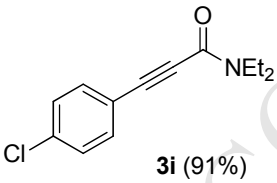
3f (91%)



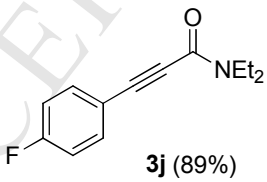
3g (94%)



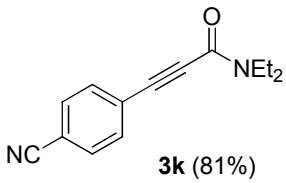
3h (95%)



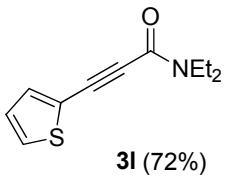
3i (91%)



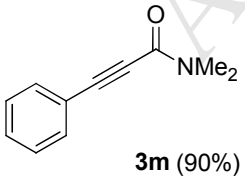
3j (89%)



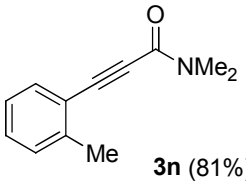
3k (81%)



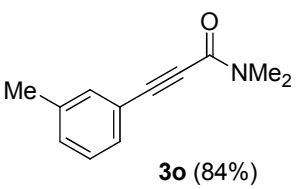
3l (72%)



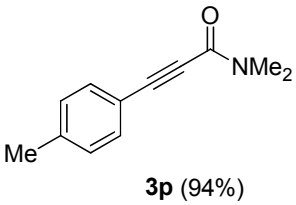
3m (90%)



3n (81%)



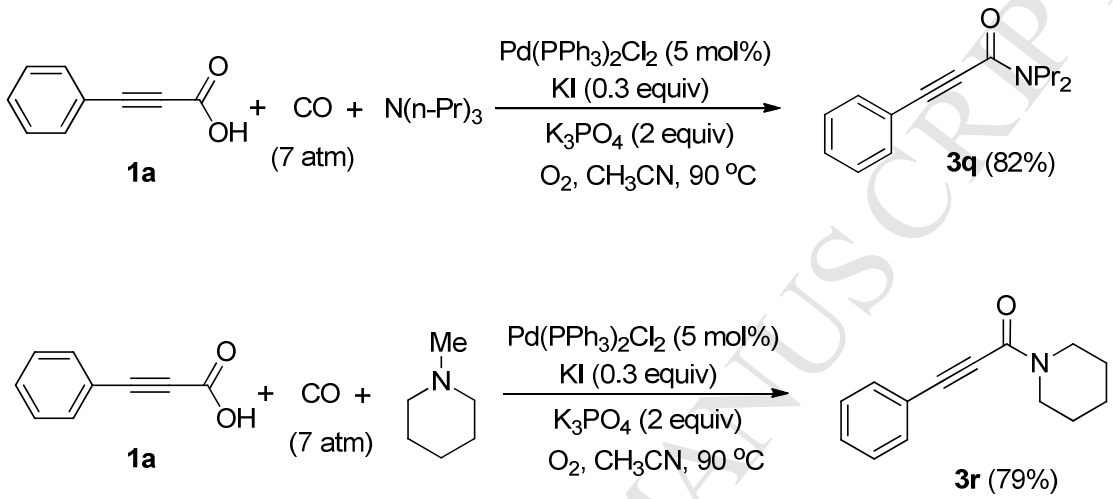
3o (84%)



3p (94%)

[a]Reaction conditions: **1** (1.0 equiv), tertiary amine (1.5 equiv), CO (7 atm), O_2 (1 atm), $Pd(PPh_3)_2Cl_2$ (5 mol%), KI (0.3 equiv), and K_3PO_4 (2.0 equiv) in CH_3CN at 90 ^oC for 12 h.

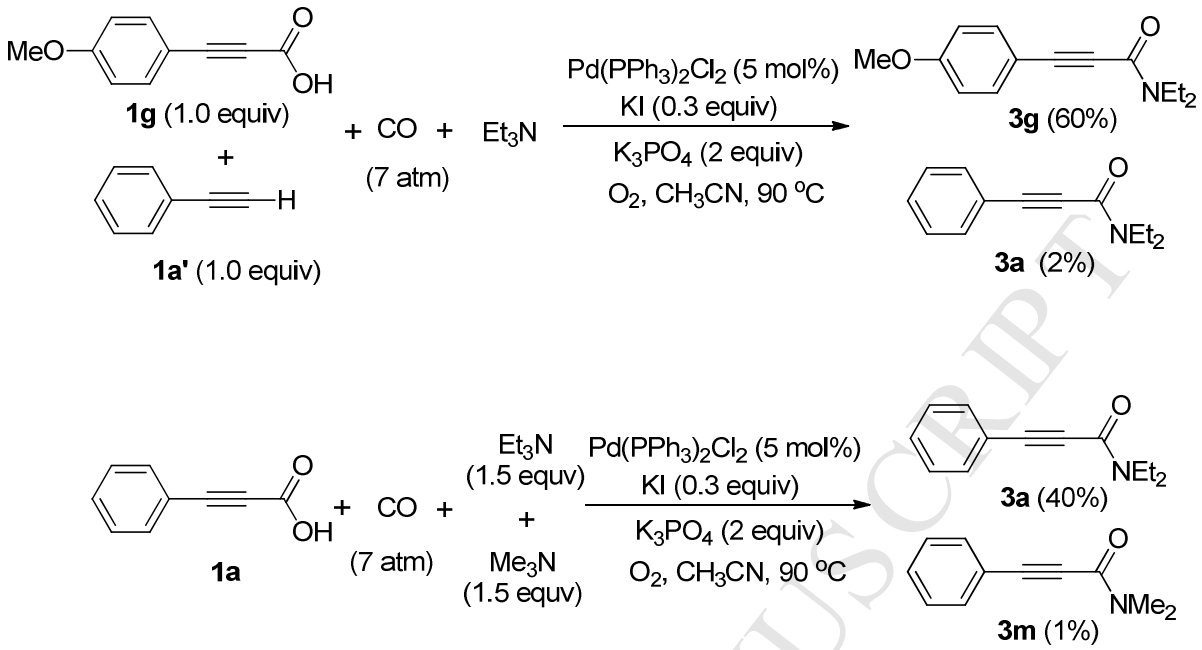
In addition, tripropylamine and N-methylpiperidine were used as a tertiaryamine in this transformation. As shown in Scheme 2, the corresponding amides **3q** and **3r** were formed in good yields.



Scheme 2. Reactions with tripropylamine and N-methylpiperidine.

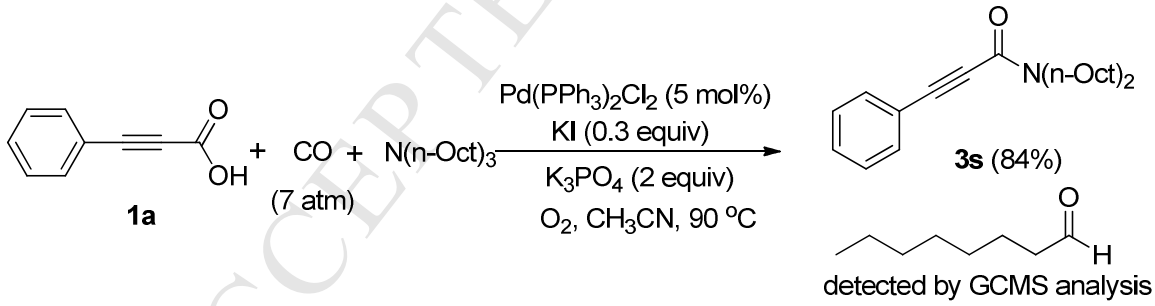
We next carried out control experiments for understanding the reactivity of the starting materials in this transformation (Scheme 3). When equal amounts of 3-(4-methoxyphenyl)propiolic acid and phenyl acetylene were allowed to react with trimethylamine under the optimal standard conditions, **3g** and **3a** were formed in 60% and 2% yields, respectively, implying that the reactivity of the alkynoic acid is higher than that of the terminal alkyne in this transformation. In order to understand the steric effect of the substituent in tertiary amine, a similar control experiment using trimethylamine and trimethylamine was carried out. When two tertiary amines were allowed to react with phenyl propiolic acid under the optimal standard conditions, **3a** was formed as the major product and **3m** was formed in very low yield. This result supports that the size of alkyl group in tertiary

amine is not a major factor in the C-N bond cleavage.



Scheme 3. Control experiments

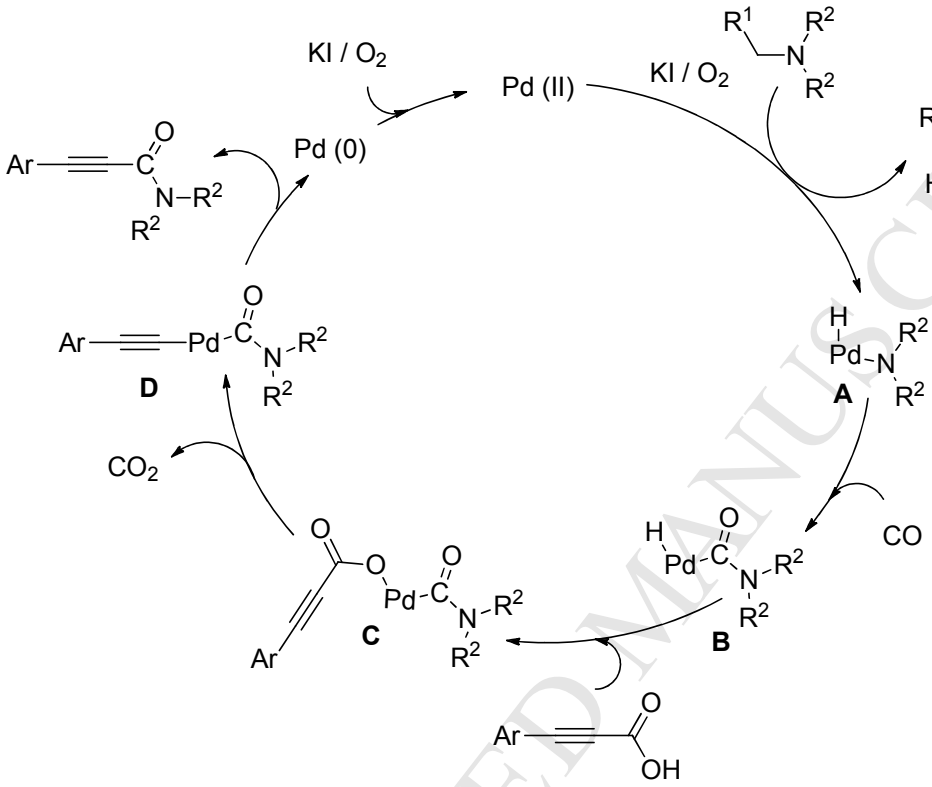
To understand the reaction mechanism, trioctylamine was allowed to react with phenyl propiolic acid under optimal condition. As shown in Scheme 4, the desired product **3s** was formed with 84 % yield, and the octanal was found in the reaction mixture.



Scheme 4. Reaction with trioctylamine.

Based on our experiment result and previous report of the C-N bond cleavage of tertiary amine [17], we proposed the reaction mechanism as shown in Scheme 5. Tertiary amine reacts with palladium in the presence of oxygen to afford *N*-palladated complex **A** and follow

by CO insertion to give intermediate **B**. Alkynoic acid reacts with intermediate **B** to give **C** and intermediate **D** is formed through decarboxylation. Finally, the reductive elimination provides the desired product and palladium (0). Palladium (II) active species is regenerated through oxidation.



Scheme 5. Proposed mechanism

3. Conclusion

Alkynoic acids and tertiary amines were allowed to react with carbon monoxide in the presence of a palladium catalyst to provide the corresponding alkynyl amides via decarboxylation, carbonylation, and C-N activation of the tertiary amine. We found that the optimal conditions are as follows: reaction of aryl propiolic acid (1.0 equiv), tertiary amine (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), KI (0.3 equiv), and K_3PO_4 (2.0 equiv) with CO (7 atm)

in the presence of oxygen (1 atm) in CH_3CN at 90 °C for 12 h. A number of substituted aryl propiolic acids provided the corresponding alkynyl amides in good yields. It was found that the alkynoic acid showed higher reactivity than the terminal alkyne under these optimal conditions. In addition, triethyl amine was much more reactive than trimethylamine. However, the reaction mechanism is not clear at present, and further investigations to elucidate the mechanism this regard are underway in our lab.

4. Experimental

Aryl propiolic acid (1.0 mmol), tertiary amine (1.5 mmol), $Pd(PPh_3)_2Cl_2$ (25 mg, 0.05 mmol), KI (25 mg, 0.3 mmol), and K_3PO_4 (100 mg, 2.0 mmol) were added to CH_3CN (5.0 mL) in a 20-mL sealed tube reactor, which was purged with carbon monoxide and oxygen. The solution was stirred at 90 °C for 12 h. The resulting mixture was placed in a separating funnel, followed by the addition of water and NH_4Cl, and the mixture was extracted with EtOAc. The separated organic layer was washed with water and dried over anhydrous $MgSO_4$. After removal of the organic layer under vacuum, the crude product was purified by silica gel column chromatography with *n*-hexane/ethyl acetate as the eluent to obtain the desired product.

4.1. N,N-Diethyl-3-phenylpropiolamide (**3a**) [5h]

Phenyl propiolic acid (146 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3a** (189 mg, 0.94 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.41 – 7.33 (m, 3H), 3.66 (q, *J* = 7.2 Hz, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 132.3, 129.9, 128.5, 120.8, 89.0, 82.0, 43.6, 39.3, 14.4, 12.9.

4.2. N,N-Diethyl-3-(o-tolyl)propiolamide (**3b**) [3d]

3-(*o*-Tolyl)propiolic acid (160 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3b** (189 mg, 0.88 mmol, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.24 – 7.15 (m, 2H), 3.68 (q, *J* = 7.1 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 141.2, 133.0, 129.9, 129.7, 125.8, 120.6, 88.0, 85.8, 43.6, 39.4, 20.7, 14.5, 12.9.

4.3. N,N-Diethyl-3-(m-tolyl)propiolamide (**3c**)

3-(*m*-Tolyl)propiolic acid (160 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3c** (185 mg, 0.86 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 6.1, 1.6, 0.6 Hz, 2H), 7.29 – 7.19 (m, 2H), 3.66 (q, *J* = 7.1 Hz, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 138.3, 132.8, 130.8, 129.4, 128.4, 120.6, 89.3, 81.7, 43.6, 39.3, 21.2, 14.4, 12.9. ; HRMS (ESI, TOF) calcd. for $C_{14}H_{18}NO$ $[M+H]^+$ 216.1388, found 216.1386.

4.4. N,N-Diethyl-3-(p-tolyl)propiolamide (**3d**) [3d]

3-(*p*-Tolyl)propiolic acid (160 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3d** (198 mg, 0.92 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.16 (dd, *J* = 8.5, 0.6 Hz, 2H), 3.66 (q, *J* = 7.1 Hz, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 140.3, 132.3, 129.3, 117.7, 89.4, 81.6, 43.6, 39.3, 21.6, 14.4, 12.9.

4.5. N,N-Diethyl-3-(2-methoxyphenyl)propiolamide (**3e**) [3d]

3-(2-Methoxyphenyl)propiolic acid (176 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3e** (197 mg, 0.85 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H), 6.93 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.73 (q, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 153.3, 133.3, 130.5, 119.5, 109.6, 109.1, 85.0, 84.8, 54.7, 42.6, 38.3, 13.3, 11.9.

4.6. N,N-Diethyl-3-(3-methoxyphenyl)propiolamide (**3f**) [3d]

3-(3-Methoxyphenyl)propiolic acid (176 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3f** (210 mg, 0.91 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.13 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.06 (m, 1H), 6.96 (ddd, *J* = 8.4, 2.6, 0.9 Hz, 1H), 3.81 (s 3H), 3.66 (q, *J* = 7.2 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 1.28(t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 154.1, 129.6, 124.8, 121.6, 117.2, 116.6, 89.3, 81.5, 55.4, 43.7, 39.4, 14.4, 12.8.

4.7. N,N-Diethyl-3-(4-methoxyphenyl)propiolamide (**3g**) [3d]

3-(4-Methoxyphenyl)propiolic acid (176 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3g** (217 mg, 0.94 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H), 6.89 – 6.86 (m, 2H), 3.83 (s, 3H), 3.66 (m, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 154.4, 134.1, 114.2, 112.6, 89.8, 81.1, 55.4, 43.6, 39.3, 14.4, 12.9.

4.8. N,N-Diethyl-3-(3,4,5-trimethoxyphenyl)propiolamide (**3h**)

3-(3,4,5-Trimethoxyphenyl)propiolic acid (236 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3h** (277 mg, 0.95 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 2H), 3.87 (s, 3H), 3.86 (s, 6H), 3.67 (q, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 153.2, 140.3, 115.6, 109.7, 89.4, 81.2, 61.0, 56.3, 43.6, 39.3, 14.4, 12.9. HRMS (ESI, TOF) calcd. for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1549, found 292.1548.

4.9. 3-(4-Chlorophenyl)-N,N-diethylpropiolamide (**3i**) [5h]

3-(4-Chlorophenyl)propiolic acid (181 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3i** (214 mg, 0.91 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.461 (m, 2H), 7.34 (m, 2H), 3.65 (q, *J* = 7.2 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 136.2, 133.6, 129.0, 119.2, 88.0, 82.7, 43.7, 39.4, 14.4, 12.8.

4.10. N,N-Diethyl-3-(4-fluorophenyl)propiolamide (**3j**) [3d]

3-(4-Fluorophenyl)propiolic acid (164 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3j** (195 mg, 0.89 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.06 (m, 2H), 3.65 (q, *J* = 7.2 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, $J_{C\text{-}F}$ = 252.5 Hz), 153.9, 134.4 (d, $J_{C\text{-}F}$ = 8.1 Hz) 116.9 (d, $J_{C\text{-}F}$ = 3.1 Hz) 116.0 (d, $J_{C\text{-}F}$ = 23.2 Hz), 88.0, 81.8, 43.6, 39.3, 14.4, 12.8.

4.11. 3-(4-Cyanophenyl)-N,N-diethylpropiolamide (**3k**) [3d]

3-(4-Cyanophenyl)propiolic acid (171 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol)

afforded **3k** (183 mg, 0.81 mmol, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.63 (m, 2H), 3.65 (q, *J* = 7.2 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 132.7, 132.2, 125.6, 118.0, 113.3, 86.6, 85.3, 43.7, 39.5, 14.5, 12.8.

4.12. N,N-Diethyl-3-(thiophen-2-yl)propiolamide (**3l**) [5h]

3-(Thiophen-2-yl)propiolic acid (152 mg, 1.0 mmol) and triethylamine (152 mg, 1.5 mmol) afforded **3l** (149 mg, 0.72 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.03 (dd, *J* = 5.0, 3.9 Hz, 1H), 3.63 (q, *J* = 7.1 Hz, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 134.8, 129.7, 127.4, 120.6, 86.0, 82.8, 43.6, 39.3, 14.4, 12.9.

4.13. N,N-Dimethyl-3-phenylpropiolamide (**3m**) [17]

Phenyl propiolic acid (146 mg, 1.0 mmol) and trimethylamine (89 mg, 1.5 mmol) afforded **3m** (156 mg, 0.90 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.43 – 7.34 (m, 3H), 3.30 (s, 3H), 3.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 132.4, 130.0, 128.5, 120.6, 90.2, 81.6, 38.4, 34.2.

4.14. N,N-Dimethyl-3-(o-tolyl)propiolamide (**3n**)

3-(*o*-Tolyl)propiolic acid (160 mg, 1.0 mmol) and trimethylamine (89 mg, 1.5 mmol) afforded **3n** (152 mg, 0.81 mmol, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.6, 0.5 Hz, 1H), 7.30 (m, 1H), 7.23 – 7.15 (m, 2H), 3.30 (s, 3H), 3.04 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 141.2, 132.9, 130.0, 129.7, 125.8, 120.5, 89.2, 85.5, 38.4, 34.2, 20.8. HRMS (ESI, TOF) calcd. for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1075, found 188.1075.

4.15. N,N-Dimethyl-3-(m-tolyl)propiolamide (**3o**)

3-(*m*-Tolyl)propiolic acid (160 mg, 1.0 mmol) and trimethylamine (89 mg, 1.5 mmol) afforded **3o** (157 mg, 0.84 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.27 – 7.21 (m, 2H), 3.29 (s, 3H), 3.03 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 138.3, 132.9, 130.9, 129.5, 128.4, 120.5, 90.5, 81.3, 38.4, 34.2, 21.2. HRMS (ESI, TOF) calcd. for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1075, found 188.1075.

4.16. N,N-Dimethyl-3-(p-tolyl)propiolamide (**3p**)

3-(*p*-Tolyl)propiolic acid (160 mg, 1.0 mmol) and trimethylamine (89 mg, 1.5 mmol) afforded **3p** (176 mg, 0.94 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 3.28 (s, 3H), 3.02 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 140.5, 132.3, 129.3, 117.5, 90.6, 81.2, 38.4, 34.2, 21.6. HRMS (ESI, TOF) calcd. for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1075, found 188.1075.

4.17. 3-Phenyl-N,N-dipropylpropiolamide (**3q**) [18]

Phenyl propiolic acid (146 mg, 1.0 mmol) and tripropylamine (215 mg, 1.5 mmol) afforded **3q** (188 mg, 0.82 mmol, 82% yield)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.43 – 7.34 (m, 3H), 3.57 (m, 2H), 3.37 (m, 2H), 1.70 (m, 2H), 1.61 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 132.3, 129.9, 128.5, 120.8, 89.7, 81.96, 51.0, 46.6, 22.2, 20.7, 11.4, 11.3.

4.18. 3-Phenyl-1-(piperidin-1-yl)prop-2-yn-1-one (**3r**) [18]

Phenyl propiolic acid (146 mg, 1.0 mmol) and 1-methylpiperidine (149 mg, 1.5 mmol)

afforded **3r** (169 mg, 0.79 mmol, 79% yield)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.43 – 7.33 (m, 3H), 3.77 (m, 2H), 3.63 (m, 2H), 1.69 – 1.67 (m, 4H), 1.65 – 1.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 132.4, 129.9, 128.5, 120.8, 90.3, 81.5, 48.3, 42.4, 26.5, 25.4, 24.6.

4.19. N,N-dioctyl-3-phenylpropiolamide (**3s**) [16b]

Phenyl propiolic acid (146 mg, 1.0 mmol) and trioctylamine (531 mg, 1.5 mmol) afforded **3x** (310 mg, 0.84 mmol, 84% yield)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.37 – 7.25 (m, 3H), 3.55 – 3.49 (m, 2H), 3.36 – 3.29 (m, 2H), 1.62 – 1.47 (m, 4H), 1.27 – 1.17 (m, 20H), 0.82 – 0.76 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 131.3, 128.8, 127.5, 119.9, 88.2, 81.2, 48.2, 43.9, 30.78, 30.75, 28.4, 28.3, 28.2, 27.9, 26.5, 26.0, 25.6, 22.1, 21.62, 21.59, 13.07, 13.05.

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Supplementary data

Supplementary data to this article can be found online at..

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Highlights

The C-N bond activation of tertiary amines

The decarboxylative aminocarbonylation with alkynoic acids

Synthesis of alkynyl amides