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Palladium-Catalyzed Oxidative *N*-dealkylation/carbonylation of Tertiary Amines with Alkynes to α,β-Alkynylamides

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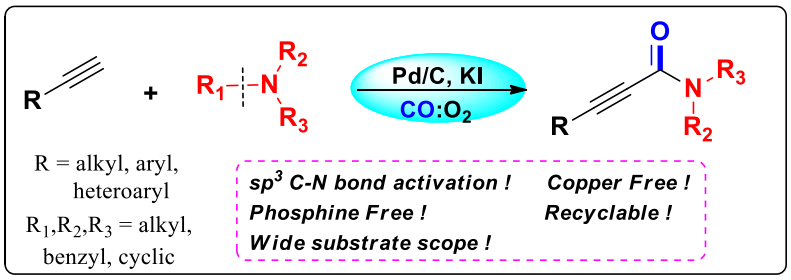
ABSTRACT:

The first highly effective Pd/C-catalyzed oxidative *N*-dealkylation/carbonylation of various aliphatic as well as cyclic tertiary amines with alkynes has been described. The selective sp^3 C-N bond activation of tertiary amines at the less steric side using O_2 as a sole oxidant and a plausible reaction pathway for the reaction are discussed. The general and operationally simple methodology provides an alternative for the synthesis of a wide range of alk-2-ynamide derivatives under mild conditions. The present protocol is an ecofriendly, practical and besides it shows significant recyclability.

TOC Graphic

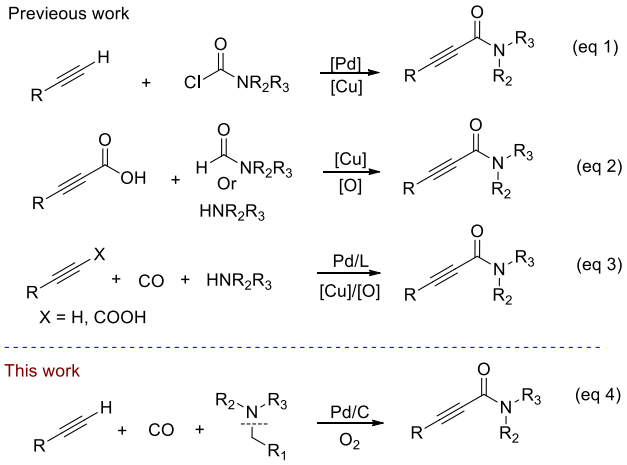


INTRODUCTION:

Alk-2-ynamide (α,β-alkynylamide) derivatives are important building blocks in organic synthesis and often fundamental scaffold of pharmaceutically relevant compounds.[1] These class of compounds play a crucial role in natural products as well as key intermediates in the synthesis of heterocycles.[2] Historically, tertiary amides were synthesized by Pd/Cu-catalyzed cross coupling reaction of alkynes with carbamoyl chlorides (Scheme 1, eq 1).[3] Moreover, Cu/TBHP mediated synthesis of tertiary amides can be achieved by using propiolic acids and its derivatives treated with secondary amines[4] or formamides[5] (Scheme 1, eq 2). Some drawbacks exist; nevertheless, these methodologies suffer from multistep synthesis, limited stability of carbamoyl chlorides, *i.e.,* moisture sensitive and lack of functional group tolerance with severe conditions.

Over the past decade, transition-metal catalyzed carbonylation reactions have gained great prominence in organic chemistry.[6] Carbon monoxide is a C1 building block in organic synthesis and is valued because of its simplicity and atom economy.[7] Palladium-catalyzed oxidative carbonylation reactions of alkynes with amines represents the most straightforward

Scheme 1. Synthetic Approach for the synthesis of Alkynylamides



approach to generate alkynylamides (Scheme1, eq 3). The oxidative carbonylation between two nucleophiles is a very challenging task.[8] A literature survey reveals that there are few reports known for the oxidative carbonylation of alkynes or propiolic acid using primary/secondary amines.[9] Hoberg *et al*. reported Ni(II)-catalyzed carbonylative synthesis of alkynylamides by treating with alkynes using secondary amines as amine source.[9a,b] Furthermore, Gabriele et al. reported first PdI_2/KI-catalyzed oxidative carbonylation for the synthesis of alkynylamides from alkynes and secondary amines in the presence of a CO/air mixture (20 atm) for 24 h.[9c] Yamamoto group employed $PdCl_2/PPh_3$ as a catalytic system for the direct oxidative aminocarbonylation using $CO/O_2$with 2 equiv of AcONa as base.[9d] Our group also disclosed Pd/C and TBAI as a catalytic system and the Xia group employed Pd-NHC/K_3PO_4 (2 equiv) for the synthesis of alkynylamides using secondary amines as an aminal source.[9e,f] Lee and Wu *et al.* also reported $Pd(OAc)_2$/AgO (1 equiv) and $Pd_2(dba)_3$/Xphos/$Co_2(CO)_8$ as a carbonyl source mediated synthesis of alkynylamides through the carbonylation of propiolic acids with primary/secondary amines.[9g,h] Although their catalytic activities are excellent, the development of a more efficient, selective and general method for the direct synthesis of alkynylamides is thus highly desirable. The development of heterogeneous, recyclable, cost-efficient and environmentally benign protocols to reduce the high production costs as well as the possible heavy-metal contamination is remaining essential. Nevertheless, these reported methodologies typically suffer from harsh conditions, requirement of stoichiometric copper as a co-catalyst or oxidant, excess base to inhibit the undesired homocoupling of alkynes and limited substrate scope with tedious workup. To circumvent these problems, we envisioned tertiary amines as an aminal source, which slowly release *in situ* secondary amines through the oxidative *N*-dealkylation/carbonylation of tertiary amines with alkynes which in turn could easily lead us to

direct synthesis of alkynylamides (Scheme 1, eq 4). However, the oxidative *N*-dealkylation/carbonylation of tertiary amines with alkynes using Pd/C with O_2 remains elusive, because of several fundamental challenges such as homocoupling of alkynes, tandem annulations and urea formation. Hence these challenges ought to be overcome.

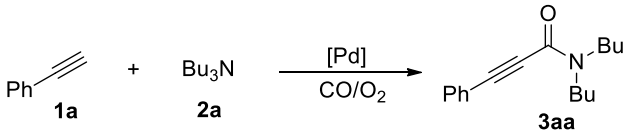
In recent years, the C-N bond activation of highly stable tertiary amines has emerged as an important approach in synthetic chemistry.[10,11] In this context, among the various known amine surrogates that could be used as nucleophile, tertiary amines stand out as particularly attractive substrates in terms of their availability. To the best of our knowledge, the use of stable tertiary amines as an aminal source for this transformation is unprecedented. Very recently, we demonstrated oxidative C-N bond activation of inert tertiary amines to tertiary amides *via* aminocarbonylation of aryl iodides.[12] Based on our research interest in oxidative carbonylation reactions,[13] herein, we report the first phosphine free Pd/C-catalyzed oxidative *N*-dealkylation/carbonylation of aliphatic as well as cyclic tertiary amines with terminal alkynes.

RESULTS AND DISCUSSIONS:

We began the alk-2-ynamides synthesis using phenylacetylene (**1a**) and Bu_3N (**2a**) as model substrates. When the reaction was performed in MeCN, using 5 mol % $PdCl_2(PPh_3)_2$ as a catalyst and 3 mmol K_3PO_4 as a base under the pressure of CO/O_2 at 100 °C for 24 h. The alkynylamide product **3aa** was only obtained in <5% yield. The iodide additive had a significant impact on the reaction efficiency. Surprisingly, when TBAI was used as an additive, overall yield of the desired product increased to 68% (Table 1, entry 2). Subsequently, the evaluation of additives revealed that KI was the best, and afforded 86% yield of **3aa** (Table 1, entry 4). Next, various palladium precursors including heterogeneous sources were screened as shown in Table

1. Interestingly, 10% Pd/C was found to be the most effective catalyst for this transformation and furnished an excellent yield of **3aa** in absence of base (Table 1, entry 11). The use of 3 mol % Pd/C was found to be adequate for this reaction. Next, we studied the effect of amount of KI and it was observed that 0.1 mmol of KI provides the highest yield of **3aa** (Table 1, entry 12).

Table 1. Effect of Additive, Catalyst, and Catalyst Loading[a]



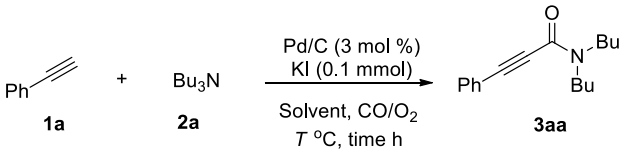
entry	catalyst	base	additive	yield (%)[b]
1[c]	$PdCl_2(PPh_3)_2$	K_3PO_4	-	<5
2	$PdCl_2(PPh_3)_2$	K_3PO_4	TBAI	68
3	$PdCl_2(PPh_3)_2$	K_3PO_4	TBAB	59
4	$PdCl_2(PPh_3)_2$	K_3PO_4	KI	86
5	$PdCl_2(PPh_3)_2$	K_3PO_4	NaI	79
6	$PdCl_2$	K_3PO_4	KI	91
7	$PdBr_2$	K_3PO_4	KI	63
8	$Pd(OAc)_2$	K_3PO_4	KI	81
9	10% Pd/C	K_3PO_4	KI	92
10	5% Pd/C	K_3PO_4	KI	84
11	10% Pd/C	-	KI	95
12[d]	10% Pd/C	-	KI	94
13[e]	10% Pd/C	-	KI	94
14[f]	10% Pd/C	-	KI	87

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), Pd (5 mol %), K_3PO_4 (3 mmol), additive (0.5 mmol), CO/O_2 = 9/1 in a 10 mL MeCN, 100 °C, 8 h. [b]Yields were determined by GC. [c]24 h.[d]0.1 mmol KI was used.[e]3 mol % and [f]2 mol % Pd/C were used.

In the next set of experiments, the effect of solvents such as acetonitrile, 1,4-dioxane, THF and toluene were examined. Among these, acetonitrile was the best solvent and provided a 94% yield of **3aa** (Table 2, entry 1). Remarkably, under CO/O_2 (5:1) pressure, the alkynylamide

product **3aa** was obtained with an yield of 94% (Table 2, entry 6).[9] Notably, while using air as oxidant instead of O_2, the yield of **3aa** decreased significantly and no formation of product was noted when the reaction was performed under inert atmosphere (Table 2, entries 8 and 9). This suggests that the additives are crucial in this transformation with molecular oxygen as sole oxidant. Decrease in the reaction temperature to 70 °C led to a decrease in the yield of **3aa**, while an increase had no significant effect on the yield (Table 2, entries 10-12).

Table 2. Optimization of Reaction Parameters[a]

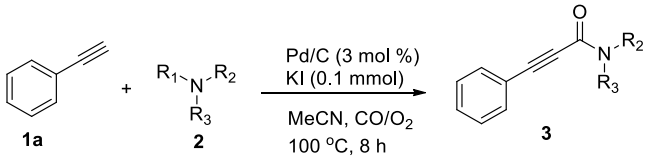


entry	solvent	CO/O_2 atm	*T* (°C)	time (h)	yield (%)[b]
1	MeCN	9:1	100	8	94
2	1,4-dioxane	9:1	100	8	52
3	THF	9:1	100	8	67
4	Toluene	9:1	100	8	74
5	MeCN	7:1	100	8	95
6	MeCN	5:1	100	8	94
7	MeCN	3:1	100	8	92
8[c]	MeCN	5:1	100	8	69
9	MeCN	5:0	100	8	NR
10	MeCN	5:1	120	8	89
11	MeCN	5:1	80	8	81
12	MeCN	5:1	70	8	53
13	MeCN	5:1	100	12	94
14	MeCN	5:1	100	5	86
15	MeCN	5:1	100	4	77

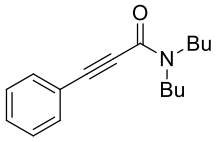
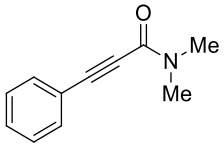
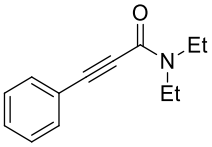
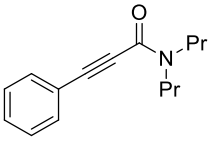
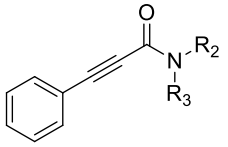
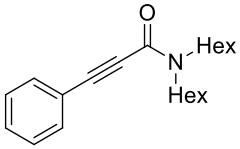
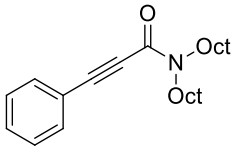
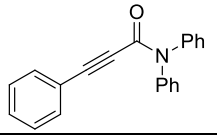
[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), 10% Pd/C (3 mol %), KI (0.1 mmol), CO/O_2 = 5/1 in a 10 mL MeCN, 100 °C, 8 h. [b]GC yield. [c]One atm of air. NR = No Reaction.

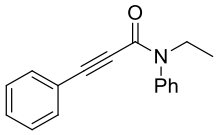
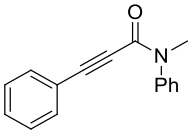
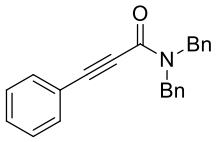
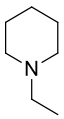
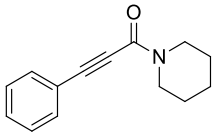
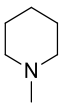
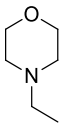
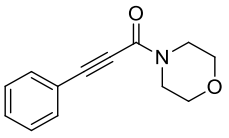
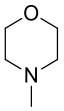
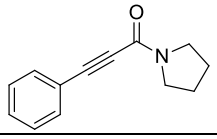
To demonstrate the general applicability of this new catalytic system, initially the *N*-dealkylation/carbonylation of various tertiary amines with **1a** was examined under the optimized

Table3. Scope of Carbonylation of 1a with Tertiary Amine as Amine Source[a]



1a + 2 → 3

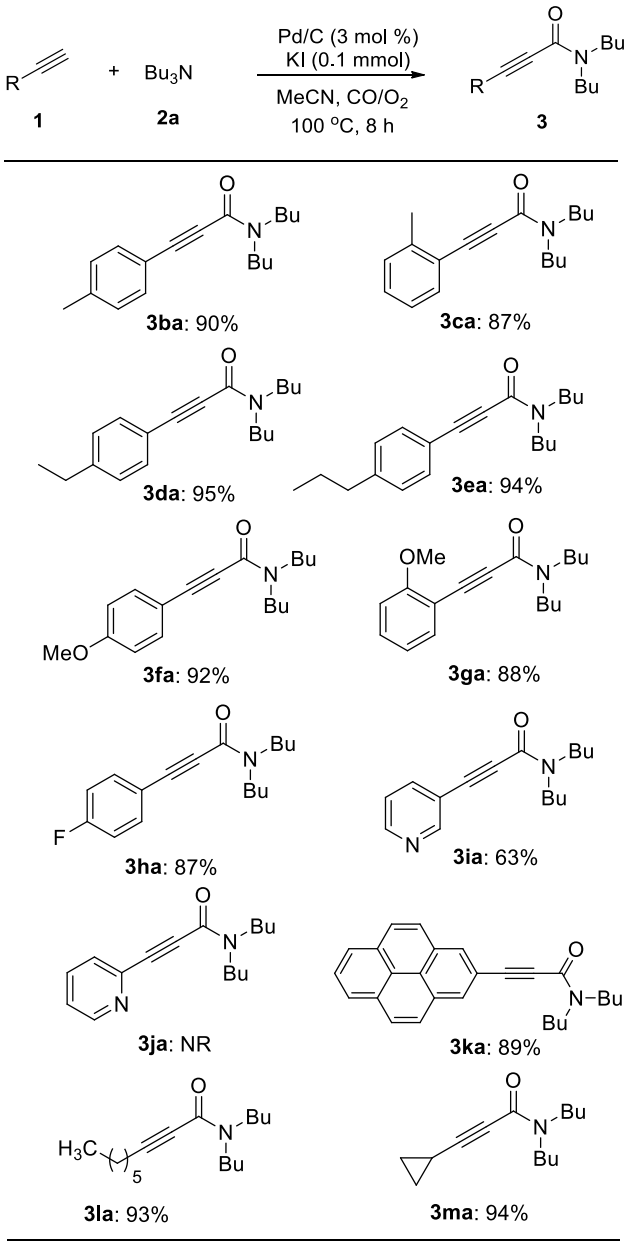
entry	amine	product		yield (%)[b]
1	Bu_3N		**3aa**	94, 82[c]
2	Me_3N		**3ab**	83
3	Me_2Noct		**3ab**	87
4	Et_3N		**3ac**	88
5	Pr_3N		**3ad**	92
6	*i*-Pr_2EtN		**3aea** R_2, R_3 = *i*-Pr **3aeb** R_2 = Et, R_3 = *i*-Pr	49 32
7	Hex_3N		**3af**	93
8	Oct_3N		**3ag**	85
9	Ph_3N		**3ah**	NR

10	$PhNEt_2$		**3ai**	NR
11	$PhNMe_2$		**3aj**	NR
12	Bn_3N		**3ak**	NR
13			**3al**	38
14			**3al**	32
15			**3am**	34
16			**3am**	29
17			**3an**	45

[a]Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol), 10% Pd/C (3 mol %), KI (0.1 mmol), CO/O_2 = 5/1 in 10 mL of MeCN, 100 °C, 8 h. [b]Isolated yield. [c]With 5.0 mmol of **1a**.

reaction conditions. As shown in Table3, this transformation proceeded quite smoothly and afforded desired alkynylamides in a good to excellent yields. Both, symmetrical as well as unsymmetrical tertiary amines could be well tolerated (**3aa-3an**). For symmetrical tertiary amines, the selectivity of the *N*-dealkylation was found to be independent of the alkyl chain lengths and oxidative *N*-dealkylation/carbonylation of different aliphatic amines with **1a** afforded the corresponding amides in high yields. When *N*,*N*-diisopropylethyl amine was employed,

Scheme 2. Scope of Carbonylation of Various Terminal Alkynes with 2a[a]



[a]Reaction conditions: **1** (1 mmol), **2a** (1.5 mmol), 10% Pd/C (3 mol %), KI (0.1 mmol), CO/O_2 = 5/1 in a 10 mL MeCN, 100 °C, 8 h. [b]Isolated yield.

potentially two kinds of *N*-dealkylation were observed. This resulted into formation of two types of products (**3aea** and **3aeb**). Gratifyingly, *N*,*N*-dimethyloctyl amine also efficiently utilized in this transformation and selectively cleavage of C-N bond at longest chain was observed (**3ab**).

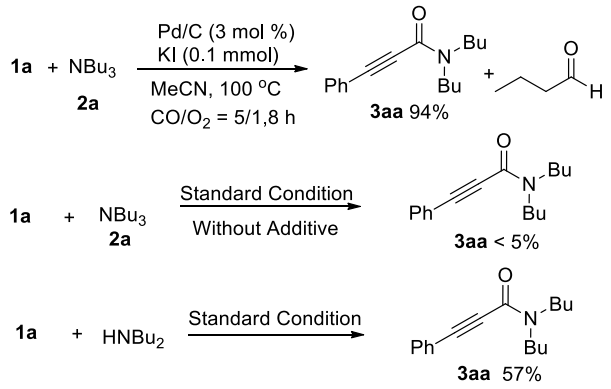
Surprisingly no products were observed with Ph_3N, $PhNEt_2$and $PhNMe_2$as a tertiary amine source, which could be because of the lacks of hydrogen atoms α to the nitrogen and the lone pair of nitrogen is conjugated with phenyl ring, thus suggesting that the sp^2 C−N bond does not cleave under these conditions (Table 3, entries 9-11). When Bn_3N was employed, reaction did not also proceed, which could be because of the steric hindrance of benzyl group (Table 3, entry 12). To our delight, cyclic tertiary amines *i.e.*, *N*-ethyl or *N*-methyl substituted afforded **3al**, **3am** and **3an**respectively. These results indicate that sterically less hindered alkyl group was much more facile for this transformation.

We next investigated the scope of aromatic alkynes **1** with *N*-dealkylation of Bu_3N **2a** under the optimal conditions and the results are shown in Scheme 2. Both, the electron donating and deficient substituent on the phenyl ring of alkynes were well tolerated and afforded excellent yields (**3ba-3ha**). Remarkably, the reaction with heteroaromatic alkyne **1i** (3-ethynylpyridine) furnished the corresponding product (**3ia**). However, alkyne **1j**(2-ethynylpyridine) did not undergo the transformation, possibly due to the formation of a chelate with the nitrogen atom of the pyridine ring and the alkyne. It is worth noting that aliphatic alkynes were also found to be compatible with this protocol, thus providing **3ja** and **3ka** in high yield. Interestingly, the reaction with highly conjugated 2-ethynylpyrene also gave an excellent yield of **3ka**. It is worth mentioning that, pyrene and its derivatives show fluorescence, having potential applications in OLEDs as efficient emitters.[14]

To gain insight into the role of additives in the reaction mechanism, several control experiments were carried out (Scheme 3). First, when Bu_3N **2a** as amine source was subjected to the optimized conditions, the alkynylamide product was obtained in an excellent yield (**3aa**, 96%

yield). While, in the absence of additive, the reaction failed to generate carbonylated product **3aa**, indicating that additives are crucial in this transformation. To our delight, when we used

Scheme 3. Some control experiments

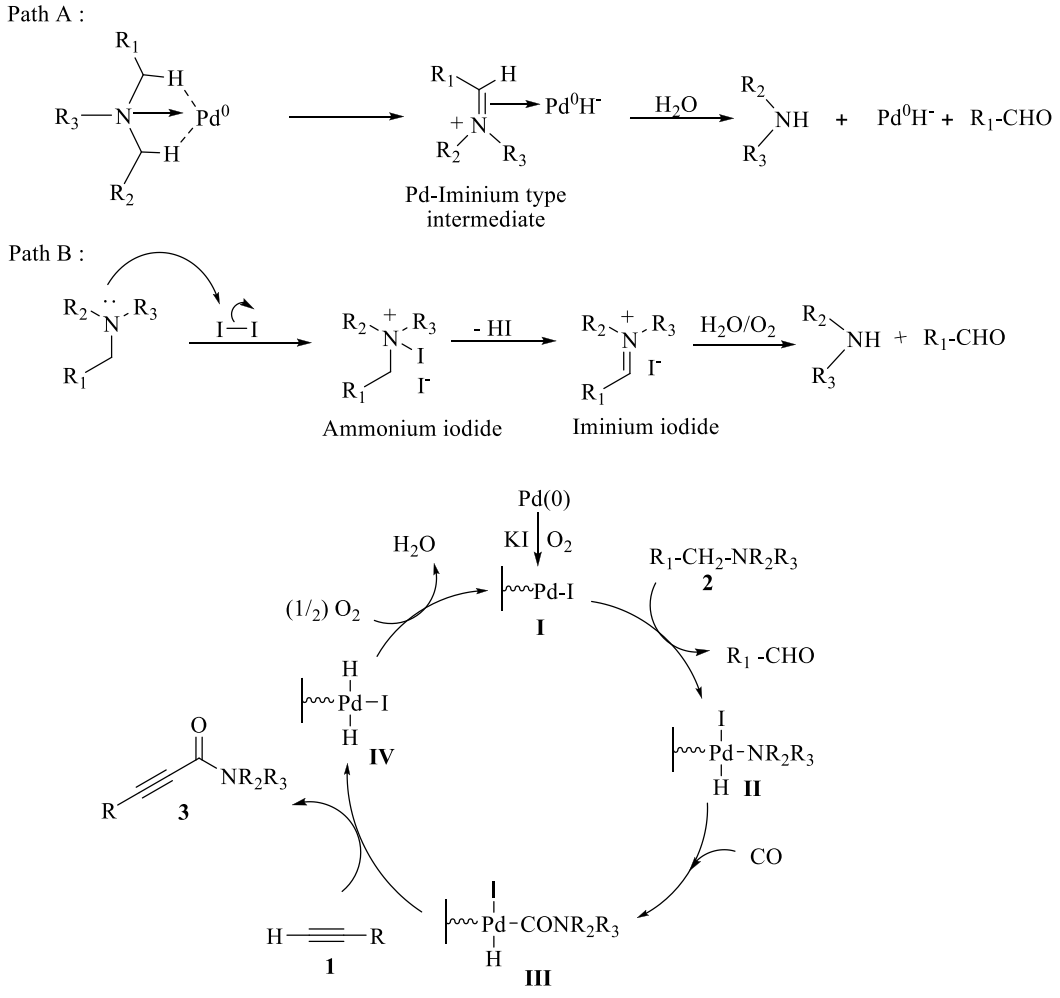


Bu_2NH as amine source, only 57% of **3aa** was obtained with tetrabutylurea as by product. These results indicate that the tertiary amine slowly releases *in situ* secondary amine under the optimized reaction conditions which in turn could led to provide highest yield of **3aa**.

From the green and sustainable chemistry point of view, the recyclability of Pd/C-catalyst was investigated. After the first reaction cycle, the catalyst was recovered from the reaction mixture and washed with excess of solvent, then finally with methanol to remove trace amounts of product. After washing and drying, recovered catalyst could be reused up to six times with a slight decrease in catalytic activity (95% to 89%). In order to check the leaching of palladium metal, 1st and 6th recycled samples were subjected to the inductively coupled plasma atomic emission spectrometry (ICP-AES) technique. No detectable amounts of palladium (below 0.1 ppm) were found, indicating a negligible catalyst leaching.

On the basis of the results obtained and previous reports, we propose two plausible reaction pathways for the *N*-dealkylation of tertiary amine to secondary amine as shown in Scheme 4.[10,11] In path A, the nitrogen of tertiary amine coordinates with Pd^0 to give Pd-iminium type intermediate.[15b,d] Then, the iminium intermediate gets hydrolyzed to provide secondary amine and aldehyde.[10g,h,12] At this stage another possible pathway cannot be ruled out (path B).

Scheme 4. Plausible Reaction Mechanism



In path B, the tertiary amine reacts with iodine to give an ammonium iodide.[16a,c,d] Subsequently, iminium iodide can be generated through the elimination of HI. Further, iminium iodide

hydrolyzes to provide secondary amine and aldehyde. The mechanism for the oxidative carbonylation of alkynes with amines using Pd/C-KI is not clear at the moment, on the basis of the experimental results and previous reports a plausible reaction pathway is outlined. Initially, *in situ* Pd(0) to Pd-I as an active species **I** could be generated in the presence of iodide promoter (KI) with O_2 as an terminal oxidant.[8h,i,j] As shown in Scheme 4, *N*-palladated **II** can be generated from amine and Pd-I. Then, the insertion of CO to form intermediate **III,** which can further reacts with alkyne to produce desired amide **3** and I**V**. The intermediate IV is re-oxidized to Pd-I as an active catalytic species **I**, in the presence of O_2 which completes the catalytic cycle.

In summary, we have illustrated a highly efficient strategy for the oxidative *N*-dealkylation/carbonylation of inert tertiary amines with alkynes. This conversion has been accomplished by using O_2 as an ideal oxidant and is catalyzed by Pd/C. This is the first instance where an extensive synthesis of alkynylamides *via* sp^3 C-N bond activation of various tertiary amines as an aminal source has been achieved. It is striking that, substrates including heteroaryl as well as aliphatic alkynes were also compatible. Additionally, this approach has numerous advantageous such as being recyclable, phosphine free, co-catalyst free, base free and uses molecular oxygen as an ideal and greener oxidant.

EXPERIMENTAL SECTION

General.

The Pd/C was purchased from Sigma-Aldrich (10 wt% loading, matrix: activated carbon support, product number: 205699, brand: Aldrich). Solvents were purchased with high purity and used without purification. All the reactions were monitored by using TLC, GC, GC-MS techniques. Products were purified by column chromatography on silica (100-200 mesh). The ^1H NMR spectrum was recorded on 400 MHz and 500 MHz spectrometer in $CDCl_3$ using

tetramethylsilane (TMS) as internal standard. The ^{13}C NMR spectrum was recorded on 100 MHz and 125 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as internal standard. The *J* (coupling constant) values are described in Hz. Splitting patterns of proton are depicted as s (singlet), d (doublet), t (triplet) and m (multiplet). HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The products were confirmed by the comparison of their GC-MS, LC-MS, ^1H NMR, ^{13}C NMR and High Resolution Mass Spectra (HR-MS).

General Experimental Procedure for Oxidative *N*-dealkylation/carbonylation of Tertiary Amines with Alkynes:

To a 100 mL stainless steel reactor, alkyne (1 mmol), tertiary amine (1.5 mmol), 10% Pd/C (3 mol %), KI (0.1 mmol) in 10 mL of MeCN were added. Then autoclave was closed and pressurized with oxygen (1 atm) and CO (5 atm) without flushing. Reaction mixture stirred with mechanical stirred (550 rpm), heated at 100 °C for 8 hour. The reactor was then cooled to room temperature, degassed carefully and the reactor was opened. The reactor vessel was washed with ethyl acetate (3 × 5 mL) to remove traces of product and catalyst if present. The reaction mixture filtered and filtrates washed with saturated solution of sodium thiosulphate (3 × 5 mL), dried over Na_2SO_4, and the solvent was evaporated under vacuum. Products were purified using column chromatography (Silica gel 100-200 mesh, petroleum ether/ethyl acetate) to afford the corresponding products in good to excellent yield. The purity of compounds was confirmed by LCMS and GCMS analysis. The structure of products was confirmed by LCMS, GCMS, HRMS, ^1H NMR and ^{13}C NMR spectroscopic techniques. (*Caution! CO and O_2 may form an explosive mixture under certain conditions*).

Procedure for Recycling of Catalyst:

After completion of reaction, the recovered catalyst was washed with distilled water (3 × 5 mL) and finally with methanol (3 × 5 mL) to remove trace amount of organic material. The catalyst was then dried in oven at 80 °C for 5 h. After washing and drying, the recovered catalyst was found it to be effectively recycled up to six run without any loss of its catalytic activity and selectivity.

***N*,*N*-Dibutyl-3-phenylpropiolamide** (**3aa**). Yellowish oil; 244.5 mg, 94% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (dd, J = 8.1, 1.4 Hz, 2H), 7.41–7.16 (m, 3H), 3.74–3.46 (m, 2H), 3.43–3.23 (m, 2H), 1.70–1.46 (m, 2H), 1.44–1.14 (m, 2H), 0.99–0.72 (m, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.4, 132.2, 129.8, 128.4, 120.8, 89.2, 82.1, 48.9, 44.6, 31.0, 29.5, 20.2, 19.9, 13.8, 13.8.**GC-MS** (EI, 70 eV) *m/z* (%): 257 (2) $[M]^+$, 228 (3), 214(13), 173(4), 129 (100), 101(5), 75(6).**HRMS** (ESI) calcd for $[(C_{17}H_{23}NO)H]$ $[M+H]^+$: 258.1858; found: 258.1856.

***N*,*N*-Dimethyl-3-phenylpropiolamide** (**3ab**).[5b] White Solid, mp 97–99 °C; 143.6 and 150.5 mg, 83 and 87% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.52–7.49 (m, 2H), 7.35 (dd, J = 14.9, 7.3 Hz, 3H), 3.25 (s, 3H), 2.99 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ154.6, 132.3, 129.9, 128.4, 120.6, 90.1, 81.5, 77.3, 77.0, 76.7, 38.3, 34.1.**GC-MS** (EI, 70 eV) *m/z* (%): 173 (55) $[M]^+$, 172 (4), 144 (9), 130 (12), 129 (100), 101 (11), 75 (17), 51 (7).

***N*,*N*-Diethyl-3-phenylpropiolamide** (**3ac**).[5b,9f]Colorless oil; 176.9 mg, 88% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.52–7.49 (m, 2H), 7.38–7.24 (m, 3H), 3.64 (q, J = 7.1 Hz, 2H), 3.45 (q, J = 7.2 Hz, 2H), 1.27–1.23 (m, 3H), 1.17–1.13 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.9, 132.3, 129.8, 129.6, 128.9, 128.4, 120.7, 89.0, 81.9, 77.3, 77.0, 76.7, 43.6, 39.3, 14.4, 14.0, 12.8.**GC-MS** (EI, 70 eV) *m/z* (%): 201 (17.5) $[M]^+$, 200 (44), 186 (25), 130 (11.4), 129 (100), 101 (11), 75 (14.5), 51 (5).

***N*,*N*-Dipropyl-3-phenylpropiolamide** (**3ad**).[9f,9g] Colorless oil; 210.8 mg, 92% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.50 (t, J = 8.7 Hz, 2H), 7.44–7.34 (m, 3H), 3.57–3.54 (t, 2H), 3.37–3.34 (t, 2H), 1.71–1.57 (m, 4H), 0.93 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.5, 133.6, 132.2, 130.1, 128.4, 128.4, 120.8, 89.3, 82.1, 77.3, 76.9, 76.6, 50.8, 46.5, 22.2, 20.7, 11.3, 11.2.**GC-MS** (EI, 70 eV) *m/z* (%): 229 (4) $[M]^+$, 214 (6), 200 (23), 130 (11.5), 129 (100), 101 (6), 75 (6).

***N*,*N*-Diisopropyl-3-phenylpropiolamide (3aea).**[5b]Yellowish oil; 112.2 mg, 49% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.0, 1.4 Hz, 2H), 7.38–7.28 (m, 3H), 4.64–4.52 (m, 1H), 3.75–3.62 (m, 1H), 1.34 (m, 12H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.6, 132.1, 129.6, 128.4, 121.0, 88.5, 83.1, 50.3, 45.7, 29.6, 22.4, 21.0, 20.1. **GC-MS** (EI, 70 eV) *m/z* (%): 229 (5) $[M]^+$, 214 (8), 186 (11), 129 (100), 79 (15), 43 (5). **HRMS** (ESI) calcd for $[(C_{15}H_{19}NO)H]$ $[M+H]^+$: `

***N*-Ethyl-*N*-isopropyl-3-phenylpropiolamide (3aeb).** Colorless oil; 68.5 mg, 32% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.58–7.43 (m, 2H), 7.36 (dd, J = 6.8 Hz, 3H), 4.82–4.55 (m, 1H), 3.55 (q, J = 7.1 Hz, 1H), 3.34 (q, J = 7.1 Hz, 1H), 1.35–1.16 (m, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.9, 132.3, 132.2, 129.8, 128.4, 128.4, 120.8, 89.5, 81.9, 50.6, 39.3, 21.8, 20.4, 14.5. **GC-MS** (EI, 70 eV) *m/z* (%): 214 (18) $[M]^+$, 200 (11), 172 (3), 129 (100), 101 (6.5), 75 (3), 42 (4). **HRMS** (ESI) calcd for $[(C_{14}H_{17}NO)H]$ $[M+H]^+$: 216.1388; found: 216.1383.

***N*,*N*-Dihexyl-3-phenylpropiolamide (3af).** Yellowish oil; 291.1 mg, 93% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.56–7.45 (m, 2H), 7.32 (m, 3H), 3.61–3.52 (m, 2H), 3.41–3.32 (m, 2H), 1.57 (m, 4H), 1.27 (m, 12H), 0.85–0.79 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.4, 132.2, 129.8, 128.4, 120.7, 89.4, 82.0, 49.2, 44.9, 34.0, 31.5, 31.4, 31.2, 28.8, 27.4, 26.6, 26.4, 24.4, 22.5, 22.3, 14.0, 13.9. **GC-MS** (EI, 70 eV) *m/z* (%): 313 (2) $[M]^+$, 312 (4), 284 (2), 256 (4), 242 (10), 200

(3.5), 172(6), 162 (10), 129 (100), 119 (10), 92 (7), 75 (3), 43(5). **HRMS** (ESI) calcd for $[(C_{21}H_{31}NO)H]$ $[M+H]^+$: 314.2484; found: 314.2479.

***N,N*-Dioctyl-3-phenylpropiolamide (3ag).** Colorless oil; 312.5 mg, 85% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.1, 1.4 Hz, 2H), 7.41–7.29 (m, 3H), 3.75–3.54 (m, 4H), 3.43–3.20 (m, 4H), 1.61 (s, 4H), 1.32–1.21 (m, 20H), 0.87–0.81 (m, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.4, 132.2, 129.8, 128.4, 120.8, 89.2, 82.1, 49.1, 44.8, 31.7, 31.7, 29.3, 29.2, 29.2, 29.1, 28.9, 27.5, 27.0, 26.7, 22.6, 22.5, 14.0. **GC-MS** (EI, 70 eV) *m/z* (%): 368 (2) $[M]^+$, 355 (4), 326 (2.6), 298 (3.4), 270 (10), 172 (5), 129 (100), 115 (4), 77 (8), 57 (9), 44 (20), 32 (92). **HRMS** (ESI) calcd for $[(C_{25}H_{39}NO)H]$ $[M+H]^+$: 370.3110; found: 370.3104.

3-Phenyl-1-(piperidin-1-yl)prop-2-yn-1-one (3al).[5b,9g]White solid, mp 79–81 °C; 80.9 and 68.1 mg, 38 and 32% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.53–7.51 (m, 2H), 7.39–7.32 (m, 3H), 3.77–3.74 (m, 2H), 3.62–3.59 (m, 2H), 1.67–1.54 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.9, 132.3, 129.8, 128.4, 120.7, 90.2, 81.4, 48.2, 42.3, 26.4, 25.3, 24.5. **GC-MS** (EI, 70 eV) *m/z* (%): 213 (43.23) $[M]^+$, 212 (45), 196 (8), 184 (20.5), 136 (14), 130 (12), 129 (100), 101 (12), 75 (14), 55 (7), 42 (6).

1-Morpholino-3-phenylprop-2-yn-1-one (3am).[5b,9g]White solid, mp 56–58 °C; 73.5 and 62.3 mg, 34 and 29% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.50–7.48 (m, 2H), 7.39–7.28 (m, 3H), 3.78 (dd, J = 5.4, 3.8 Hz, 2H), 3.70–3.68 (m, 2H), 3.64 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.1, 132.3, 130.1, 128.5, 120.2, 91.1, 80.7, 66.8, 66.4, 47.2, 41.9. **GC-MS** (EI, 70 eV) *m/z* (%): 215 (26.5) $[M]^+$, 186 (10.9), 130 (12.6), 129 (100), 116 (10), 101 (11.6), 75 (16.35), 56 (29.58).

3-Phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-one (3an).[9g,9f]Yellowish oil; 89.5 mg,45% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.1, 1.4 Hz, 2H), 7.34 (dd, J = 7.2, 2.1 Hz, 3H), 3.70 (t, J = 6.4 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 1.97–1.88 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ152.7, 132.3, 129.9, 128.4, 120.6, 88.7, 82.6, 77.3, 77.0, 76.7, 48.1, 45.3, 25.3, 24.7. **GC-MS** (EI, 70 eV) *m/z* (%): 199 (39.5) $[M]^+$, 198 (15), 170 (18), 143 (10), 130 (11.1), 129 (100), 116 (12.39), 102 (19.81), 101 (12.5), 75 (16.3), 51 (6).

***N*,*N*-Dibutyl-3-(*p*-tolyl)propiolamide (3ba).** Yellowish oil; 243.9 mg, 90% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 3.60–3.54 (m, 2H), 3.40–3.34 (m, 2H), 2.35 (s, 3H), 1.62–1.50 (m, 4H), 1.40–1.29 (m, 4H), 0.93 (m, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.5, 140.3, 132.2, 129.2, 117.7, 89.6, 81.7, 48.9, 44.5, 30.9, 29.5, 21.6, 20.2, 20.0, 13.9, 13.8.**GC-MS** (EI, 70 eV) *m/z* (%): 271 (2) $[M]^+$, 242 (3), 228 (11), 187 (4), 143 (100), 115 (8), 89 (4.5), 65 (2), 43 (2). **HRMS** (ESI) calcd for $[(C_{18}H_{25}NO)H]$ $[M+H]^+$: 272.2014; found: 272.2009.

***N*,*N*-Dibutyl-3-(*o*-tolyl)propiolamide (3ca).** Yellowish oil; 235.8 mg, 87% yield.**^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 1H), 7.25 (m, 3H), 3.65–3.56 (m, 2H), 3.44–3.36 (m, 2H), 2.47 (s, 3H), 1.67–1.54 (m, 4H), 1.35 (m, 4H), 0.95 (m, 6H).**^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.5, 141.1, 132.9, 129.8, 129.6, 125.7, 120.6, 88.3, 85.9, 49.0, 44.6, 31.1, 29.6, 20.7, 20.2, 20.0, 13.8. **GC-MS** (EI, 70 eV) *m/z* (%): 271 (5) $[M]^+$, 256 (12.5), 242 (10.5), 228 (14.5), 214 (10), 186 (6), 143 (100), 144 (15), 115 (43.7), 89 (8), 65 (3), 41 (6).**HRMS** (ESI) calcd for $[(C_{18}H_{25}NO)H]$ $[M+H]^+$: 272.2014; found: 272.2009.

***N*,*N*-Dibutyl-3-(4-ethylphenyl)propiolamide (3da).** Yellowish oil; 270.6 mg, 95% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ7.42 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 3.59–3.55 (m,

2H), 3.39–3.35 (m, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.64–1.51 (m, 4H), 1.37–1.29 (m, 4H), 1.21 (t, *J* = 7.6 Hz, 3H), 0.96–0.89 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ154.5, 146.5, 132.3, 128.0, 117.9, 89.6, 81.7, 77.3, 77.0, 76.7, 48.9, 44.5, 31.0, 29.6, 28.9, 20.2, 20.0, 15.1, 13.8, 13.8.**GC-MS** (EI, 70 eV) *m/z* (%): 285 (6) $[M]^+$, 242 (23.2), 201 (8), 200 (4), 157 (100), 142 (18), 114 (7), 77 (2), 44 (2).**HRMS** (ESI) calcd for $[(C_{19}H_{28}NO)H]$ $[M+H]^+$: 286.2171; found: 286.2165.

***N*,*N*-Dibutyl-3-(4-propylphenyl)propiolamide (3ea).** Yellowish oil; 281 mg, 94% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 3.59–3.50 (m, 2H), 3.41–3.34 (m, 2H), 2.62–2.54 (m, 2H), 1.62–1.21 (m, 10H), 0.99–0.87 (m, 9H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.5, 145.0, 132.2, 128.6, 117.9, 89.6, 81.7, 77.3, 48.9, 44.5, 38.0, 31.0, 29.6, 24.2, 20.2, 20.0, 13.8, 13.8, 13.7. **GC-MS** (EI, 70 eV) *m/z* (%): 299 (4) $[M]^+$, 270 (5), 256 (19), 214 (8), 200 (2.5), 171 (100), 157 (4), 142 (25), 114 (9.5), 84 (2), 57 (3), 41 (5).**HRMS** (ESI) calcd for $[(C_{20}H_{29}NO)H]$ $[M+H]^+$: 300.2327; found: 300.2321.

***N*,*N*-Dibutyl-3-(4-methoxyphenyl)propiolamide (3fa).** Yellowish oil; 264 mg, 92% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 3.57–3.54 (m, 2H), 3.38–3.34 (m, 2H), 1.52–1.45 (m, 4H), 1.30 (m, 4H), 0.94–0.88 (m, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ160.8, 154.7, 134.0, 114.1, 112.7, 89.8, 81.3, 77.3, 77.0, 76.7, 55.3, 48.9, 44.5, 30.9, 29.6, 20.1, 20.0, 13.8, 13.8.**GC-MS** (EI, 70 eV) *m/z* (%): 287 (6) $[M]^+$, 258 (8), 245 (10), 244 (15), 202 (13), 160 (13), 159 (100), 144 (10), 116 (6), 88 (2), 77 (2), 41 (4). **HRMS** (ESI) calcd for $[(C_{18}H_{25}NO)H]$ $[M+H]^+$: 288.1964; found: 288.1958.

***N*,*N*-Dibutyl-3-(2-methoxyphenyl)propiolamide (3ga).** Yellowish oil; 252.5 mg, 88% yield.**^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.36 (dd, *J* = 8.5 Hz, 1H), 6.95–6.86 (m, 2H), 3.86 (s, 3H), 3.67–3.63 (m, 2H), 3.42–3.37 (m, 2H), 1.64–1.55 (m, 4H), 1.42–1.31 (m,

4H), 0.97–0.92 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.0, 154.6, 134.3, 131.4, 120.5, 110.6, 110.1, 86.2, 85.9, 55.6, 48.9, 44.5, 31.0, 29.6, 20.2, 20.0, 13.8, 13.8. **GC-MS** (EI, 70 eV) *m/z* (%): 287 (2.5) $[M]^+$, 256 (29.5), 244 (12.3), 214 (10), 200 (9), 159 (100), 160 (12.7), 131 (21.5), 115 (34), 103 (10), 77 (17), 41 (5). **HRMS** (ESI) calcd for $[(C_{18}H_{25}NO)H]$ $[M+H]^+$: 288.1964; found: 288.1958.

***N*,*N*-Dibutyl-3-(4-fluorophenyl)propiolamide (3ha).** Yellowish oil; 239.2 mg, 87% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.63–7.41 (m, 2H), 7.10–6.92 (m, 2H), 3.65–3.47 (m, 2H), 3.41–3.26 (m, 2H), 1.66–1.49 (m, 4H), 1.39–1.26 (m, 4H), 1.00–0.87 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): *δ*163.35 (d, $^1J_{C-F}$ = 251 Hz),154.3, 134.3 (d, $^3J_{C-F}$ = 10 Hz), 115.9 (d, $^2J_{C-F}$ = 22 Hz), 88.2, 81.9, 48.9, 44.6, 30.9, 29.5, 20.8, 19.9, 13.8, 13.8. **GC-MS** (EI, 70 eV) *m/z* (%): 275 (2) $[M]^+$, 232 (14), 218 (2), 191 (4), 147 (100), 119 (5), 99 (6), 41 (2.5). **HRMS** (ESI) calcd for $[(C_{17}H_{22}FNO)H]$ $[M+H]^+$: 276.1764; found: 276.1761.

***N*,*N*-Dibutyl-3-(pyridin-3-yl)propiolamide (3ia).** Yellowish brown oil; 162.5 mg, 63% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.65 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 7.1 Hz, 1H), 3.63–3.50 (t, 2H), 3.39–3.35 (t, 2H), 1.66–1.48 (m, 4H), 1.44–1.23 (m, 4H), 0.97–0.74 (m, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 153.7, 152.5, 149.9, 139.2, 123.2, 85.6, 85.1, 48.9, 44.6, 30.9, 29.5, 20.1, 19.9, 13.8, 13.7. **GC-MS** (EI, 70 eV) *m/z* (%): 258 (2) $[M]^+$, 215 (17), 201 (3), 173 (5), 160 (2.5), 130 (100), 102 (10), 75 (5), 43 (3). **HRMS** (ESI) calcd for $[(C_{16}H_{22}N_2O)H]$ $[M+H]^+$: 259.1810; found: 259.1805.

***N*,*N*-Dibutyl-3-(pyren-2-yl)propiolamide (3ka).** Yellow oil; 339.9 mg, 89% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.53 (d, *J* = 9.1 Hz, 1H), 8.26–8.01 (m, 8H), 3.78–3.73 (t, 2H), 3.50–3.46 (t, 2H), 1.81–1.73 (m, 2H), 1.66–1.62 (m, 2H), 1.51–1.35 (m, 4H), 1.02–0.95 (m, 6H). **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 154.6, 130.3, 129.0, 128.9, 127.1, 126.4, 126.1, 126.0, 125.0, 124.45, 114.8, 88.7, 87.5, 49.2, 44.7, 31.2, 29.7, 20.2, 20.1, 13.9, 13.9. **HRMS** (ESI) calcd for $[(C_{27}H_{27}NO)H]$ $[M+H]^+$: 382.2171; found: 382.2165.

***N*,*N*-Dibutylnon-2-ynamide (3la).** Colorless oil; 246.4 mg, 93% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ3.57–3.41 (m, 2H), 3.34–3.23 (m, 2H), 2.32 (t, J = 7.1 Hz, 2H), 1.64–1.21 (m, 18H), 0.99–0.81 (m, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.6, 92.1, 74.5, 48.8, 44.4, 31.2, 30.9, 29.5, 28.5, 27.8, 22.4, 20.1, 19.9, 18.9, 14.0, 13.8, 13.7. **GC-MS** (EI, 70 eV) *m/z* (%): 265 (2.5) $[M]^+$, 266 (4), 250 (11), 236 (26.5), 222 (50), 208 (17), 166 (17), 137 (100), 86 (10), 67 (63.5), 55 (32), 43 (23), 41 (32.7). **HRMS** (ESI) calcd for $[(C_{17}H_{31}NO)H]$ $[M+H]^+$: 266.2484; found: 266.2479.

***N*,*N*-Dibutyl-3-cyclopropylpropiolamide (3ma).** Colorless oil; 207.7 mg, 94% yield.**^{1}H NMR** (400 MHz, $CDCl_3$): δ3.50 – 3.39 (m, 2H), 3.37–3.25 (m, 2H), 1.54–1.21 (m, 10H), 0.9 –0.83 (m, 8H), 0.81–0.79 (m, 2H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.5, 95.4, 69.7, 48.6, 44.3, 30.8, 29.5, 20.1, 19.9, 13.8, 13.8, 13.7, 8.8,-0.4.**GC-MS** (EI, 70 eV) *m/z* (%): 221 (1) $[M]^+$, 206 (4.3), 192 (5.3), 136 (8), 122 (5), 93 (100), 65 (17.6), 41 (6.4).**HRMS** (ESI) calcd for $[(C_{14}H_{23}NO)H]$ $[M+H]^+$: 222.1858; found: 222.1854.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra analysis, this material is available free of charge via the Internet athttp://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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