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Oxidative Aminocarbonylation of Terminal Alkynes for the Synthesis of Alk-2-ynamides by Using Palladium-on-Carbon as Efficient, Heterogeneous, Phosphine-Free, and Reusable Catalyst

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Abstract: Palladium-on-carbon (Pd/C)-catalyzed oxidative aminocarbonylations of alk-1-ynes with secondary amines provide the corresponding alk-2-ynamides in a good to excellent yields. This new methodology is applicable for the synthesis of a wide range of biologically active alk-2-ynamide derivatives. The developed protocol avoids the use of phosphine ligands, with an additional advantage of palladium catalyst recovery and reuse for up to four consecutive cycles.

Keywords: alk-2-ynamides; heterogeneous catalysis; oxidative aminocarbonylation; palladium-on-carbon (Pd/C); phosphine-free conditions

The alk-2-ynamides (α,β-alkynylamides) are important building blocks in the synthesis of various heterocyclic compounds[1] and biologically active molecules.[2] They exhibit excellent affinity for the mGluR5 receptor and antifilarial activity (Figure 1).[3] Moreover α,β-alkynylamides also play an crucial role in drug discovery and manufacturing processes.

The common route for the synthesis of α,β-alkynylamide involves a Pd/Cu-catalyzed reaction between alk-1-ynes and carbamoyl chlorides.[2b,d,f,4a] Hoberg and co-workers reported a non-catalytic synthesis of α,β-alkynylamides by reacting alk-1-ynes, secondary amines, carbon monoxide (CO) in the preesence of a Ni(II) complex.[4b] The synthesis of α,β-alkynylamides using oxidative aminocarbonylation, conceptually constitutes an alternative methodology, which has been scarcely studied.[5] In such reactions two nucleophiles get coupled together by a carbonylation reaction in the presence of a suitable oxidant.[6]

In 2001, Gabriele et al. first reported a direct oxidative aminocarbonylation for the synthesis of α,β-alkynylamides from alk-1-ynes and secondary amines by using PdI_2 and KI as a catalytic system in the presence of a CO/air mixture (20 atm) at 100 °C for 24 h.[5b] This seminal work was then followed by a report from Yamamoto et al. on using homogeneous $PdCl_2/PPh_3$ as a catalytic system for the direct oxidative aminocarbonylation using carbon monoxide/oxygen (CO/O_2) in basic conditions with NaOAc as base.[5c] All these above reported protocols made use of homogeneous catalysts; however the major drawback of homogeneous catalysis is the difficulty in separating the catalyst from the reaction mixture and its subsequent reuse for consecutive reactions. The high costs and toxicity of the transition metal catalysts has led to an increased interest in immobilizing catalysts on to a suitable solid support. In this context heterogeneous catalysis was found to be best alternative. In

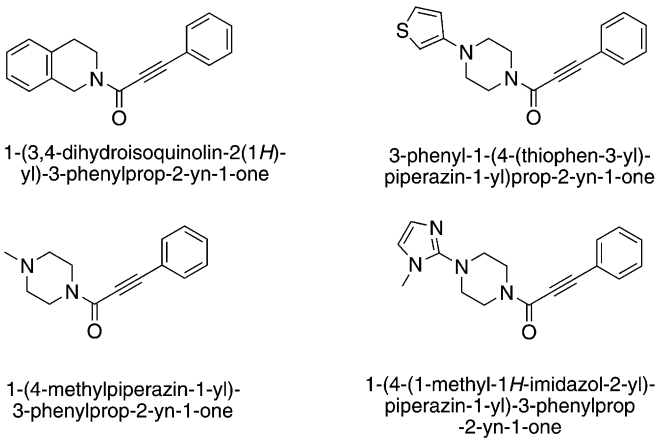
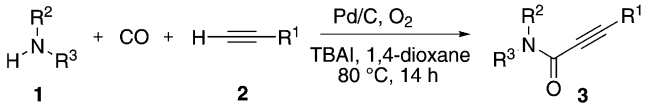


Figure 1. Structures of some biologically active α,β-alkynylamide derivatives.

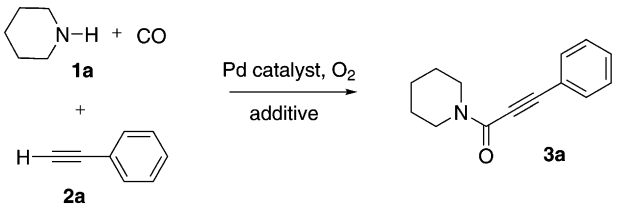
spite of this, all the above reported methods for direct oxidative aminocarbonylation suffer from one or more drawbacks such as use of expensive, air/moisture sensitive phosphine ligands, use of bases, longer reaction time, high temperature, low yield of products, use of high pressure of CO/O_2, that limit their applications. Therefore, the search for a heterogeneous and reusable catalyst which could efficiently catalyze the oxidative aminocarbonylation reaction under milder reaction conditions without the aid of phosphine ligands is subject of the present work. In search for new catalytic systems which can overcome the above drawbacks, Pd/C was found to be the best alternative. Pd/C is an economical and commercially available catalyst, also it is easy to handle and could be recovered from the reaction mixture by simple filtration and further reused. Application of Pd/C as a ligand-free catalyst has been well explored for various coupling reaction.[7]

In continuation of our interest in the aminocarbonylation reaction[8] and phosphine-free carbonylation reactions,[9] herein we report the first heterogeneous, phosphine-free and efficiently recyclable protocol for the synthesis of α,β-alkynylamides (**3**) by direct oxidative aminocarbonylation of terminal alkynes with a range of secondary amines using Pd/C as a catalyst under aa low pressure of CO/O_2 (5/1 atm) (Scheme 1).



Scheme 1. Pd/C catalyzed oxidative aminocarbonylation of alk-1-ynes (**2**).

Table 1. Effect of catalyst screening and loading on the oxidative aminocarbonylation of alk-1-ynes.[a]



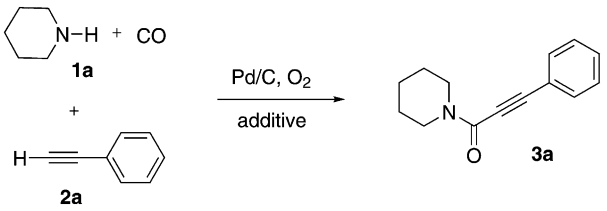
Entry	Catalyst	Catalyst loading [mol%]	Yield [%][b]
Catalyst screening			
1	PS-Pd-NHC	8	75
2	Pd/C (10%)	8	95
3	Pd/C (5%)	8	82
Catalyst loading			
4	Pd/C (10%)	6	52
5	Pd/C (10%)	10	96

[a] *Reaction conditions:* phenylacetylene (1 mmol), piperidine (1.5 mmol), CO/O_2 pressure (5/1 atm), TBAI (0.90 mmol), 1,4-dioxane (10 mL), temperature 80 °C, time 14 h.
[b] GC yield.

The reaction of phenylacetylene with piperidine in the presence of CO/O_2 and tetrabutylammonium iodide (TBAI) as an additive using 10% Pd/C as a catalyst was chosen as a model reaction. A series of experiments was performed to optimize various reaction parameters such as nature of the catalyst, effect of catalyst loading, solvent, additive, reaction temperature, time and CO pressure. The results obtained are summarized in Table 1 and Table 2.

Initially we screened various heterogeneous palladium catalysts such PS-Pd-NHC (polymer-supported palladium-N-heterocyclic carbene), 10% Pd/C and 5% Pd/C (Table 1, entries 1–3) on the model reaction system, in which 10% Pd/C was found to be the best

Table 2. Optimization of the Pd/C-catalyzed oxidative aminocarbonylation reaction of alk-1-yne.[a]



Entry	Solvent	Additive	Temp. [°C]	Time [h]	Yield [%][b]
Effect of solvent					
1	toluene	TBAI	80	14	25
2	cyclohexane	TBAI	80	14	32
3	THF	TBAI	80	14	66
4	1,4-dioxane	TBAI	80	14	95
Effect of additive					
5	1,4-dioxane	KI	80	14	80
6	1,4-dioxane	NaI	80	14	88
7	1,4-dioxane	TBAB	80	14	84
8	1,4-dioxane	KBr	80	14	82
9	1,4-dioxane	–	80	14	–
Effect of temperature					
10	1,4-dioxane	TBAI	40	14	49
11	1,4-dioxane	TBAI	60	14	61
12	1,4-dioxane	TBAI	70	14	70
13	1,4-dioxane	TBAI	120	14	88
Effect of time					
14	1,4-dioxane	TBAI	80	10	70
15	1,4-dioxane	TBAI	80	12	80
16[c]	1,4-dioxane	TBAI	80	14	65
17[d]	1,4-dioxane	TBAI	80	14	63

[a] *Reaction conditions:* phenylacetylene (1 mmol), piperidine (1.5 mmol), 10% Pd/C (8 mol%), CO/O_2 pressure (5/1 atm), TBAI (0.90 mmol), 1, 4-dioxane (10 mL), temperature 80 °C, time 14 h.
[b] GC yield.
[c] CO pressure: 2 atm.
[d] CO/air pressure: 5/1 atm.

catalyst providing an excellent yield of the desired product (Table 1, entry 2). We further studied catalyst loadings ranging from 6 to 10 mol% wherein the increase in catalyst concentration from 6 to 8 mol% showed an increase in the yield of desired product (Table 1, entries 4 and 2); while on further increases in catalyst concentration no profound effect on the yield of desired product was observed (Table 1, entry 5). Next by using 10% Pd/C as a catalyst, we studied the effect of the solvent on the oxidative aminocarbonylation reaction. The solvents like toluene and cyclohexane provided lower yields of the expected product (Table 2, entries 1 and 2), while THF provided a moderate yield of the desired product (Table 2, entry 3). Using 1,4-dioxane as a solvent a 95% yield of the α,β-alkynylamide was observed, hence it was used for further study (Table 2, entry 4). It is well known that an iodide-containing additive along with molecular oxygen as an oxidant plays a vital role in the oxidative aminocarbonylation reaction.[5a,b,10]

Therefore we screened various iodide-containing additives such as TBAI, KI and NaI (Table 2, entries 4–6), the maximum yield of the expected product was observed using TBAI. We also screened bromide-containing additives like TBAB (tetrabutylammonium bromide) and KBr which provided moderate yields of the respective product (Table 2, entries 7 and 8). To confirm the role of an additive in our system, the reaction was performed without additive, but no formation of the desired product was observed which indicates the essential role of an additive in the reaction (Table 2, entry 9). While studying effect of temperature, the yield of the desired product increased with increasing the reaction temperature from 40 to 80 °C, whereby 80 °C proves to be the optimum temperature for the reaction (Table 2, entries 4, 10–12). Thereafter no profound increase in the yield of the desired product was observed upon increasing reaction temperature up to 120 °C (Table 2, entry 13). Then the reaction time was also optimized (Table 2, entries 14 and 15) and maximum yield of the desired product was obtained after 14 hours (Table 2, entry 4). When the reaction was run at a lower CO pressure (2 atm) a reduced yield of the expected product was observed (Table 2, entry 16), hence all reactions were carried out at 5 atm CO pressure, as it provides the maximum yield of desired product. When air was used as an oxidant a poor yield of the desired product was observed (Table 2, entry 17). With these optimized reaction conditions in hand, we screened different aliphatic linear/cyclic amines, asymmetric amines and aromatic substituted amines. The results obtained are summarized in Table 3.

The model reaction of phenylacetylene with piperidine under the optimized reaction condition provides

Table 3. Oxidative aminocarbonylation of alk-1-ynes with various secondary amines.[a]

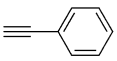
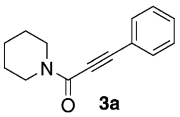
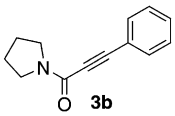
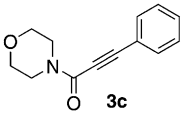
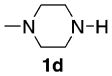
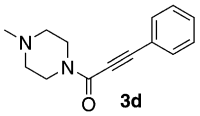
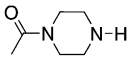
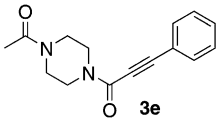
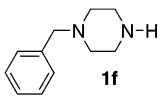
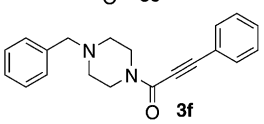
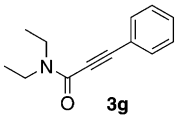
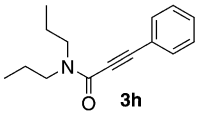
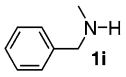
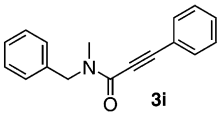
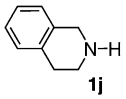
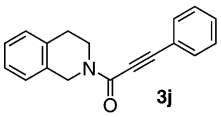
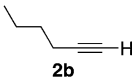
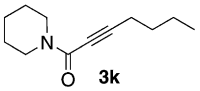
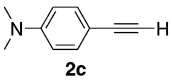
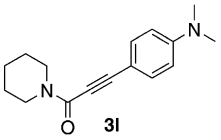
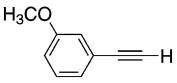
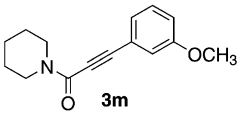
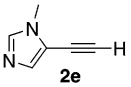
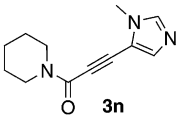
Entry	Secondary amine	Alk-1-yne	Product	Yield [%][b]
1	 **1a**	 **2a**	 **3a**	93
2	**1a**	**2a**	**3a**	89[c]
3	 **1b**	**2a**	 **3b**	92
4	 **1c**	**2a**	 **3c**	91
5	 **1d**	**2a**	 **3d**	85
6	 **1e**	**2a**	 **3e**	90
7	 **1f**	**2a**	 **3f**	86

Table 3. (Continued)

Entry	Secondary amine	Alk-1-yne	Product	Yield [%][b]
8	 **1g**	**2a**	 **3g**	88
9	 **1h**	**2a**	 **3h**	89
10	 **1i**	**2a**	 **3i**	92
11	 **1j**	**2a**	 **3j**	87
12	**1a**	 **2b**	 **3k**	55
13	**1a**	 **2c**	 **3l**	94
14	**1a**	 **2d**	 **3m**	88
15	**1a**	 **2e**	 **3n**	94

[a] *Reaction conditions:* alk-1-yne (1 mmol), secondary amine (1.5 mmol), 10% Pd/C (8 mol%), CO/O_2 pressure (5/1 atm), TBAI (0.90 mmol), 1,4-dioxane (10 mL), temperature 80 °C, time 14 h.
[b] Isolated yield.
[c] The reaction was scaled up to 4 mmol of alk-1-yne.

a 93% yield of corresponding amide (Table 3, entry 1). Cyclic secondary amines like pyrollidine and morpholine provide excellent yield of desired product (Table 3, entries 3 and 4). Furthermore, we could synthesize the piperazylamides of 3-phenylpropynoic acid in excellent yields starting from *N*-methyl-, *N*-acyl- and *N*-benzylpiperazines (Table 3 entries 5–7). Secondary aliphatic amines such as diethylamine and dibutylamine also showed excellent activity in this transformation (Table 3, entries 8 and 9). To our delight, unsymmetrical amines such as *N*-methyl-1-phenylmethanamine and 1,2,3,4-tetrahydroisoquinoline gave the corresponding products in high yield (Table 3, entries 10 and 11). The ^{1}H and ^{13}C NMR spectra showed that the amides **3i** and **3j** were obtained mostly as a 1/1 mixture of *E*/*Z* rotamers around the amide bond. While screening primary amines, we observed the formation of side products along with trace amounts of the desired product. However, hindered amines like diisopropyl amine and low nucleophilic amines like *N*-methylaniline were found to be unreactive.

Next we examined the reaction between various aliphatic, aromatic and heteroaromatic substituted alkynes with piperidine in the presence of CO. 1-Hexyne was found to react smoothly with piperidine furnishing a moderate yield of the corresponding product (Table 3, entry 12). Aromatic alkynes such as 4-ethynyl-*N,N*-dimethylaniline and 3-ethynylanisole provided the carbonylated products in good to excellent yield (Table 3, entries 13 and 14). Heteroaromatic alkynes such as 5-ethynylimidazole also reacted efficiently giving a 94% yield of desired product (Table 3, entry 15). In this way, the present methodology was

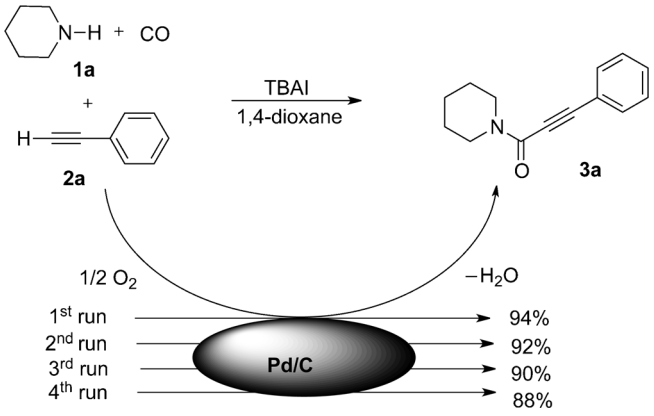


Figure 2. Recycle study of the oxidative aminocarbonylation of alk-1-yne.

successfully applied to aryl- and heteroarylacetylenes which are consistently more reactive than alkylacetylenes and gave excellent yields of the desired product.

To make the synthetic protocol more economical, we have also demonstrated the recyclability of Pd/C under the optimized reaction conditions; it was found that the catalyst could effectively be recycled for four consecutive cycles without loss in activity and selectivity (Figure 2). The leaching of palladium metal was investigated after the 1st and 4th recycle runs by ICP-AES analysis revealing Pd to be below the detectable level (0.01 ppm) in solution after completion of the reaction. Thus we estimate no significant leaching of this palladium metal catalyst. To check palladium metal leaching on a larger scale of reagents, we performed ICP-AES of a reaction mixture on a larger scale (4 mmol of alk-1-yne) but the palladium content was still below the detectable level indicating no significant leaching of the palladium.

In summary, we have reported a first heterogeneous, phosphine-free and reusable catalytic system for the direct oxidative aminocarbonylation of alk-1-ynes for the synthesis of α,β-alkynylamides. The developed protocol uses simple starting materials such as alk-1-ynes, secondary amines, the stable heterogeneous recyclable Pd/C as a catalyst, carbon monoxide gas and oxygen as oxidant. The protocol furnishes good to excellent yields of α,β-alkynylamides starting from a variety of nucleophilic secondary amines and alk-1-ynes, demonstrating a good functional group tolerance. Furthermore, the recyclability of the developed catalytic system for up to four consecutive cycles without loss in activity makes it most attractive. We believe that the developed methodology will find wide use by allowing a practical access to a variety of α,β-alkynylamide.

Experimental Section

Materials and Methods

All the chemicals were purchased from Sigma Aldrich, S.D., Fine chemical, Lancaster (Alfa-Aesar) and other commercial suppliers. The progress of the reaction was monitored by gas chromatography on a Perkin–Elmer Clarus 400 GC equipped with flame ionization detector (FID) and capillary column (30 m × 0.25 mm × 0.25 μm) or thin layer chromatography using Merck silica gel 60 F254 plates. The product was visualized with a 254 nm UV lamp. Products were purified by column chromatography on silica gel (100–200) mesh. All yields reported in Table 1, Table 2 and Figure 2 are GC yields, while yields reported in Table 3 refer to isolated yields and pure compounds as determined by ^{1}H NMR and ^{13}C NMR. All new compounds were confirmed by LC-MS, GC-MS, FT-IR, ^{1}H NMR, ^{13}C NMR and HR-MS techniques. However known compounds were confirmed by comparison with authentic samples on GC and GC-MS. Mass spectra were obtained on a Shimadzu LCMS-2010EV instrument (column length 50 mm, internal diameter 4.6 mm, particle size 3 μ, nebulizing gap 1.5 L min^{-1}, vacuum 10^{-3} Pa) (column flow 1.2 mL min^{-1}, serial temperature 260 °C and heat block temperature- 200 °C), GC-MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, film thickness 0.25 μm df) (column flow 2 mL min^{-1}, 80 °C to 240 °C at 10°/min rise.).The HR-MS were recorded on a quadrapole time-of-flight (Q-STAR XL) mass spectrometer (Applied Biosystem, USA). The IR spectra were recorded with an FT-IR (Perkin–Elmer) spectrometer. The GC analysis was carried out on a Perkin–Elmer (Clarus-400) gas chromatograph equipped with flame ionization detector with a capillary column (Elite-1, 30 m × 0.32 mm × 0.25 μm). The ^{1}H NMR spectra were recorded with Varian-400 MHz FT-NMR spectrometer in $CDCl_3$. The ^{13}C NMR spectra were recorded with JEOL FT-NMR, Model-AL300 (75 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as internal standard. *J* (coupling constant) values are reported in Hz, splitting patterns of proton are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

General Procedure for Oxidative Aminocarbonylation of Alk-1-ynes

To a 100-mL stainless steel autoclave, the 1-alkyne (1 mmol), secondary amine (1.5 mmol), 10% Pd/C (8 mol%), TBAI (0.90 mmol), 1,4-dioxane (10 mL, solvent purged by oxygen – balloon pressure – for one hour at room temperature) were added. The autoclave was closed, pressurized with oxygen (1 atm) and CO (5 atm) without flushing. The reaction mixture stirred with a mechanical stirre (625 rpm) and heated at 80 °C for 14 hour. The reactor was then cooled to room temperature, degassed carefully and opened. The reactor vessel was washed with ethyl acetate (3 × 5 mL) to remove traces of product and catalyst if present. The reaction mixture was 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. Purification of residue was carried out by 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 LC-MS and GC-MS analysis. However known compounds were confirmed by comparison with their authentic samples on GC and GC-MS. The structures of new compounds were confirmed by LC-MS, GC-MS, FT-IR, ^{1}H NMR, ^{13}C NMR, and HR-MS techniques.

Procedure for Catalyst Recycling

The filtered catalyst was washed with distilled water (3× 5 mL), methanol (3×5 mL) to remove trace amounts of organic material. The catalyst was then dried in an oven at 80 °C for 6 h and used for the next run.

Spectroscopic Data of the Products

3-Phenyl-1-(piperidin-1-yl)prop-2-yn-1-one **(3a):**[11a] Yellowish solid; yield: 93%; IR (KBr): ν = 2923, 2855, 2216 (C≡C), 1610, 1456, 1284, 1140, 854, 761, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.54 (m, 2H, C*H*, Ar), 7.38–7.36 (m, 3H, C*H*, Ar), 3.78 (t, *J* = 5.68 Hz, 2H, NCH_2CH$_2$), 3.63 (t, *J* = 5.64 Hz, 2H, NCH_2CH$_2$), 1.69–1.65 (m, 4H, NCH$_2$CH_2CH$_2$), 1.61–1.59 (m, 2H, NCH$_2$CH$_2$CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.93 (*C*q, C=O), 132.31 (2*C*H, Ar), 129.87 (*C*H, Ar), 128.47 (2*C*H, Ar), 120.72 (*C*q, Ar), 90.25 (*C*q, C≡C), 81.46 (*C*q, C≡C), 48.22 (N*C*H$_2$CH$_2$), 42.37 (NCH$_2$CH$_2$), 26.45 (NCH$_2$*C*H$_2$), 25.39 (NCH$_2$*C*H$_2$), 24.53 (NCH$_2$CH$_2$*C*H$_2$); GC-MS (EI, 70 eV): *m/z* (% relative intensity) = 213 (35, M$^+$), 212 (35), 184 (18), 171 (3), 157 (6), 143 (4), 136 (13), 130 (12), 129 (100), 116 (6), 102 (10), 101 (13), 75 (18).

3-Phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-one **(3b):**[11b] Yellowish solid; yield: 92%: IR (KBr): ν = 2926, 2212 (C≡C), 1622, 1422, 1342, 1176, 762, 729, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 2H, C*H*, Ar), 7.41–7.34 (m, 3H, C*H*, Ar), 3.74 (t, *J* = 6.64 Hz, 2H, NCH_2CH$_2$), 3.54 (t, *J* = 6.28 Hz, 2H, NCH_2CH$_2$), 2.00–1.94 (m, 4H, NCH$_2$CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.70 (*C*q, C=O), 132.35 (2*C*H, Ar), 129.92 (*C*H, Ar), 128.46 (2*C*H, Ar), 120.56 (*C*q, Ar), 88.72 (*C*q, C≡C), 82.60 (*C*q, C≡C), 48.14 (N*C*H$_2$CH$_2$), 45.35 (N*C*H$_2$CH$_2$), 25.34 (NCH$_2$*C*H$_2$), 24.69 (NCH$_2$*C*H$_2$); GC-MS (EI, 70 eV): *m/z* (% relative intensity) = 199 (36, M$^+$), 170 (17), 143 (10), 129 (100), 116 (14), 103 (10), 102 (26), 101 (17), 89 (27), 87 (19), 75 (24), 73 (24), 45 (92).

1-(4-Methylpiperazin-1-yl)-3-phenylprop-2-yn-1-one **(3d):**[3a] Yellowish liquid; yield: 85%; IR (neat): ν = 2944, 2215 (C≡C), 1623, 1437, 1296, 1144, 1042, 756, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.54 (m, 2H, C*H*, Ar), 7.43–7.35 (m, 3H, C*H*, Ar), 3.89 (t, *J* = 5.2 Hz 2H, CONCH_2CH$_2$), 3.75 (t, *J* = 5.08 Hz, 2H, CONCH_2CH$_2$), 2.52 (t, *J* = 5.04 Hz, 2H, CH$_3$NCH_2CH$_2$), 2.46 (t, *J* = 5.04 Hz, 2H, CH$_3$NCH_2CH$_2$), 2.36 (s, 3H, NCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.90 (*C*q, C=O), 132.24 (2*C*H, Ar), 130.03 (*C*H, Ar), 128.44 (2*C*H, Ar), 120.19 (*C*q, Ar), 90.76 (*C*q, C≡C), 80.84 (*C*q, C≡C), 54.77 (CON*C*H$_2$CH$_2$), 54.03 (CON*C*H$_2$CH$_2$), 46.50 (CH$_3$N*C*H$_2$CH$_2$), 45.61 (CH$_3$N*C*H$_2$CH$_2$), 40.95 (NCH$_3$); LC-MS: *m/z* = 229 (M$^+$+1); HR-MS (ESI): *m/z* = 229.1350, calcd. for [(C$_{14}$H$_{16}$N$_2$O)H]$^+$: 229.1340.

1-(4-Acetylpiperazin-1-yl)-3-phenylprop-2-yn-1-one **(3e):** yellowish solid; yield: 90%; IR (KBr): ν = 2928, 2224 (C≡C), 1620, 1440, 1285, 1260, 1031,998, 756, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.54 (m, 2H, C*H*, Ar), 7.47–7.36 (m, 3H, C*H*, Ar), 3.81 (m, 2H, C≡CCONCH_2CH$_2$), 3.73–3.67(m, 4H, C≡CCONCH_2CH$_2$, CH$_3$CONCH_2CH$_2$), 3.58–3.48 (m, 2H, CH$_3$CONCH_2CH$_2$), 2.15(s, 3H, CH$_3$CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.26 (CH$_3$*C*O), 153.30 (C≡C*C*O), 132.42 (2*C*H, Ar), 130.33 (*C*H, Ar), 128.60 (2H, Ar), 120.04 (*C*q, Ar), 91.56 (*C*q, C≡C), 80.57 (*C*q, C≡C), 46.94 (C≡CCONCH_2CH$_2$), 46.44 (C≡CCONCH_2CH$_2$), 41.30 (CH$_3$CONCH_2CH$_2$), 40.87 (CH$_3$CONCH_2CH$_2$), 21.39 (*C*H$_3$CO); LC-MS: *m/z* = 257 (M$^+$+1); HR-MS (ESI): *m/z* = 257.1299, calcd. for [(C$_{15}$H$_{16}$N$_2$O$_2$)H]$^+$: 257.1290.

1-(4-Benzylpiperazin-1-yl)-3-phenylprop-2-yn-1-one **(3f):** yellowish oil; yield: 86%; IR (neat): ν = 2921, 2810, 2212 (C≡C), 1618, 1491, 1459, 1296, 1043, 998, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.51 (m, 2H, 2C*H*, Ar), 7.41–7.27 (m, 8H, 8C*H*, Ar), 3.84 (t, *J* = 5 Hz, 2H, C≡CCONCH_2CH$_2$), 3.70 (t, 2H, C≡CCONCH_2CH$_2$), 3.55 (s, 2H, PhCH$_2$), 2.51 (t, *J* = 5.08 Hz, 2H, PhCH$_2$NCH_2CH$_2$), 2.47 (t, *J* = 5.2 Hz, 2H, PhCH$_2$NCH_2CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.98 (*C*q, C=O), 137.43 (*C*q, Ar), 132.34 (2*C*H, Ar), 130.03 (*C*H, Ar), 129.14 (2*C*H, Ar), 128.51 (2*C*H, Ar), 128.36 (2*C*H, Ar), 127.34 (*C*H, Ar), 120.45 (*C*q, Ar), 90.66 (*C*q, C≡C), 81.13 (*C*q, C≡C), 62.78 (C≡CCON*C*H$_2$CH$_2$), 53.08 (C≡CCONCH_2CH$_2$), 52.37 (PhCH$_2$), 47.05 (PhCH$_2$N*C*H$_2$CH$_2$), 41.50 (PhCH$_2$NCH_2CH$_2$); LC-MS: *m/z* = 305 (M$^+$+1); HR-MS (ESI): *m/z* = 305.1663, calcd. for [(C$_{20}$H$_{20}$N$_2$O)H]$^+$: 305.1653.

N,N-Diethyl-3-phenylpropiolamide **(3g):**[4b] yellowish liquid; yield: 88%; IR (neat): ν = 2982, 2221 (C≡C), 1622, 1431, 1280, 1139, 755, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.53 (m, 2H, C*H*, Ar), 7.41–7.34 (m, 3H, C*H*, Ar), 3.66 (q, *J* = 8 Hz 2H, NCH_2CH$_3$), 3.48 (q, *J* = 7.16 Hz, 2H, NCH_2CH$_3$), 1.28 (t, *J* = 7.16 Hz, 3H, CH$_2$CH_3), 1.18 (t, *J* = 7.16 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.94 (*C*q, C=O), 132.27 (2*C*H, Ar), 129.85 (*C*H, Ar), 128.46 (2*C*H, Ar), 120.68 (*C*q, Ar), 88.98 (*C*q, C≡), 81.89 (*C*q, C≡C), 43.59 (N*C*H$_2$CH$_3$), 39.30 (N*C*H$_2$CH$_3$), 14.37 (*C*H$_3$CH$_2$), 12.83(*C*H$_3$CH$_2$); GC-MS (EI, 70 eV): *m/z* (% relative intensity) = 201 (11, M$^+$), 200 (27), 186 (9), 129 (100), 101 (9), 75 (13).

N-benzyl-N-methyl-3-phenylpropiolamide **(3i):** yellowish solid; yield: 92%; IR (KBr): ν = 2857, 2216 (C≡C), 1621, 1443, 1199, 922, 692 cm^{-1}; ^{1}H and ^{13}C NMR spectra are described for both rotamers about the amide bond; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.50 (m, 2H, C*H*, Ar), 7.48–7.30 (m, 8H, C*H*, Ar), 4.88 (s, 2H, NCH$_2$), 4.68 (s, 2H, NCH$_2$), 3.20 (s, 3H, NCH$_3$), 2.92 (s, 3H, NCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.75, 154.67, 136.18, 136.07, 132.34, 132.28, 129.99, 128.81, 128.63, 128.45, 128.43, 128.12, 127.89, 127.57, 127.40, 120.44, 120.32, 90.68, 90.18, 81.53, 54.89, 49.78, 35.77, 31.87; GC-MS (EI, 70 eV): *m/z* (% relative intensity) = 249 (29, M$^+$), 248 (50), 220 (27), 192 (14), 191 (20), 144 (17), 129 (100), 118 (33), 102 (21), 91 (25), 75 (20), 65 (11), 42 (20); HR-MS (ESI): *m/z* = 250.1241, calcd. for [(C$_{17}$H$_{15}$NO)H]$^+$: 250.1231.

1-(3,4-Dihydroisoquinolin-2(1H)-yl)-3-phenylprop-2-yn-1-one **(3j):** yellowish solid; yield: 87%; IR (KBr): ν = 2921, 2219 (C≡C), 1622, 1444, 1272, 1195, 924, 754 cm^{-1}; ^{1}H and ^{13}C NMR spectra are described for both rotamers about the amide bond; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.55

(m, 2H, C*H*, Ar), 7.47–7.35 (m, 3H, C*H*, Ar), 7.25–7.14 (m, 4H, C*H*, Ar), 5.00 (s, 2H, NCH_2Ph), 4.82 (s, 2H, NCH_2Ph), 4.08 (t, $J=5.96$ Hz, 2H, NCH_2CH_2Ph), 3.92 (t, $J=6.08$ Hz, 2H, NCH_2CH_2Ph), 2.99 (t, $J=5.84$ Hz, 2H, NCH_2CH_2Ph), 2.92 (t, $J=6.04$ Hz, 2H, NCH_2CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=153.63$, 153.31, 134.50, 133.79, 132.35, 132.28, 132.19, 130.03, 128.91, 128.57, 128.48, 126.96, 126.66, 126.63, 126.55, 126.46, 126.06, 120.39, 91.02, 90.28, 81.38, 81.28, 48.57, 44.61, 43.97, 39.59, 29.45, 28.25; LC-MS: $m/z=262$ ($M^+ + 1$); HR-MS (ESI): $m/z=262.1242$, calcd. for $[(C_{18}H_{15}NO)H]^+$: 262.1231.

***3-[4-(Dimethylamino)phenyl]-1-(piperidin-1-yl)prop-2-yn-1-one* (3l):** yellowish solid; yield: 94%; IR (KBr): $\nu=$ 2926, 2195 (C≡C), 1610, 1435, 724, 529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.40$ (d, $J=8.84$ Hz, 2H, C*H*, Ar), 6.60 (d, $J=8.92$ Hz, 2H, C*H*, Ar), 3.76 (t, $J=5.76$ Hz, 2H, NCH_2CH_2), 3.60 (t, $J=5.6$ Hz, 2H, NCH_2CH_2), 2.99 [s, 6H, $N(CH_3)_2$], 1.66–1.62 (m, 6H, $CH_2CH_2CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=153.72$ (*C*q, C=O), 151.04 (*C*q, Ar), 133.85 (2*C*H, Ar), 111.48 (2*C*H, Ar), 106.65 (*C*q, Ar), 92.64 (*C*q, C≡C), 80.49 (*C*q, C≡C), 48.15 (NCH_2CH_2), 42.22 (NCH_2CH_2), 40.01 [$N(CH_3)_2$], 26.43 ($NCH_2CH_2CH_2$), 25.44 ($NCH_2CH_2CH_2$), 24.60 ($NCH_2CH_2CH_2$); LC-MS: $m/z=257$ ($M^+ + 1$); HR-MS (ESI): $m/z=257.1660$, calcd. for $[(C_{16}H_{20}N_2O)H]^+$: 257.1653.

***3-(3-Methoxyphenyl)-1-(piperidin-1-yl)prop-2-yn-1-one* (3m):** yellowish solid; yield: 88%; IR (KBr): $\nu=2939$, 2857, 2215 (C≡C), 1614,1476, 1294,1164,1044,853,789,636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.26$ (t, $J=7.92$ Hz, 1H, C*H*, Ar), 7.14–7.07 (m, 1H, C*H*, Ar), 7.06 (s, 1H, C*H*, Ar), 6.97–6.94 (m, 1H, C*H*, Ar), 3.75 (m, 5H, OCH_3, NCH_2CH_2), 3.61 (t, 2H, NCH_2CH_2), 1.65 (m, 4H, $NCH_2CH_2CH_2$), 1.62–1.56 (m, 2H, $NCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=159.30$ (*C*q, C=O), 152.86 (*C*q, Ar), 129.56 (*C*H, Ar), 124.74 (*C*H, Ar), 121.62 (*C*q, Ar), 117.00 (*C*H, Ar), 116.52 (*C*H, Ar), 90.17 (*C*q, C≡C), 81.15 (*C*q, C≡C), 55.33 (OCH_3), 48.21 (NCH_2CH_2), 42.35 (NCH_2CH_2), 26.43 ($NCH_2CH_2CH_2$), 25.37 ($NCH_2CH_2CH_2$), 24.50 ($NCH_2CH_2CH_2$); GC-MS (EI, 70 eV): m/z (% relative intensity) = 243 (61, M^+), 242 (45), 214 (27), 159 (100), 116 (26), 88 (23), 84 (14), 45 (44); HR-MS (ESI): $m/z=$ 244.1348, calcd. for $[(C_{15}H_{17}NO_2)H]^+$: 244.1337.

***3-(1-Methyl-1H-imidazol-5-yl)-1-(piperidin-1-yl)prop-2-yn-1-one* (3n):** yellowish solid; yield: 94%; IR (KBr): $\nu=$ 2923, 2855, 2216 (C≡C), 1610, 1456, 1223, 1140, 854, 761, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.52$ (s, 1H, C*H*, Ar), 7.44 (s, 1H, C*H*, Ar), 3.74–3.72 (m, 5H, NCH_3, NCH_2CH_2), 3.62 (t, $J=5.68$ Hz, 2H, NCH_2CH_2), 1.72–1.57 (m, 6H, $NCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 152.46 (*C*q, C=O), 139.62 (*C*H, Ar), 137.30 (*C*H, Ar), 114.13 (*C*q, Ar), 89.53 (*C*q, C≡C), 78.80 (*C*q, C≡C), 48.17 (NCH_3), 42.35 (NCH_2CH_2), 32.32 (NCH_2CH_2), 26.40 ($NCH_2CH_2CH_2$), 25.32 ($NCH_2CH_2CH_2$), 24.45 ($NCH_2CH_2CH_2$); GC-MS (EI, 70 eV): m/z (% relative intensity) = 217 (32, M^+), 188 (21), 161 (12), 106 (76) 133 (100), 84 (32), 78 (22), 42 (25); HR-MS (ESI): $m/z=$ 218.1295, calcd. for $[(C_{12}H_{15}N_3O)H]^+$: 218.1293.

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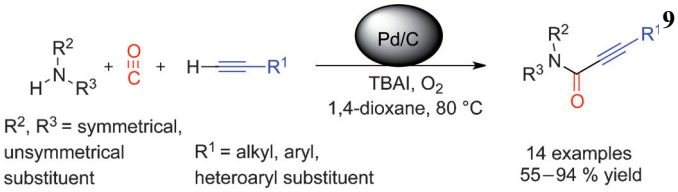

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