

Silica-Immobilized NHC–Cu^I Complex: An Efficient and Reusable Catalyst for A³-Coupling (Aldehyde–Alkyne–Amine) under Solventless Reaction Conditions

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A novel silica-immobilized NHC–Cu^I complex was developed and used as a highly efficient catalyst in the three-component coupling reactions of aldehydes, alkynes and amines (A³-coupling). The reactions were applicable to aromatic and aliphatic aldehydes, alkynes and amines, and generated the corresponding propargylamines in good yields only in the presence of SiO₂–NHC–Cu^I (2 mol-%) at room temp. under

solvent-free reaction conditions. Moreover, the catalyst was quantitatively recovered from the reaction mixture by a simple filtration and reused for ten cycles with almost consistent activity.

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Introduction

One of the most challenging tasks in organic synthesis is the efficient preparation of complex molecules starting from easily available raw materials. Especially attractive are one-pot multi-component coupling reactions (MCRs), which introduce several elements of diversity into a molecule in a single step.^[1] Three-component coupling of aldehydes, alkynes, and amines (A³-coupling) is one of the best examples of such a process and has received much more attention in recent years.^[2] The resultant propargylamines obtained from A³-coupling reactions are frequent skeletons^[3] and synthetically versatile key intermediates^[4] for the preparation of many nitrogen-containing biologically active compounds such as β -lactams, oxotremorine analogues, conformationally restricted peptides, isosteres, natural products, and therapeutic drug molecules.^[3b,5] There are several transition-metal catalysts, which are able to carry out these multi-component A³-coupling reactions. These include Ag^I salts,^[6] Au^I/Au^{III} salts,^[2,7] Au^{III}–salen complexes,^[8] Cu^I salts,^[9] Ir complexes,^[10] Hg₂Cl₂^[11] and Cu/Ru dimetallic systems^[12] under homogeneous reaction conditions. But all of these systems suffer from the loss of the precious or hazardous catalysts at the end of the reaction. In order to achieve the recyclability of the transition-metal catalysts, Au^I, Ag^I and Cu^I in ionic liquids developed by Li et al.^[13] and Park et al.,^[14] hydroxyapatite-supported copper (Cu–

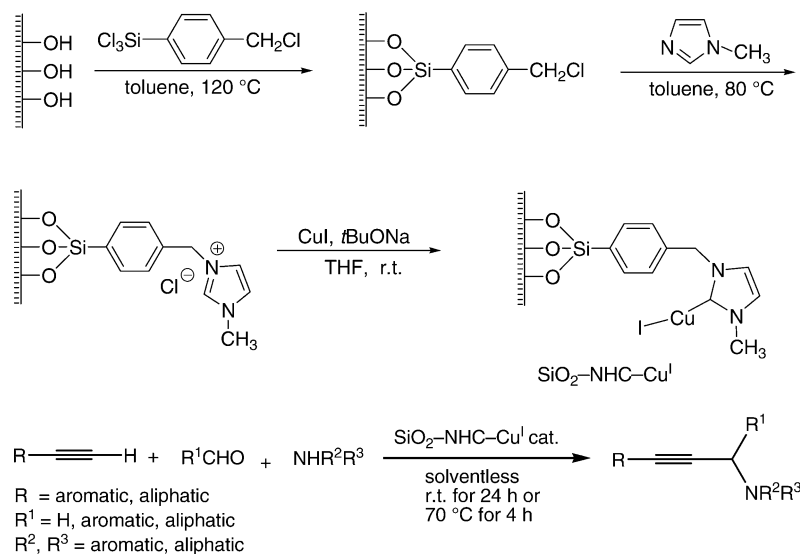
HAP) and layered double hydroxide supported gold (LDH–AuCl₄) reported by Likhar et al.,^[15,16] and heteropolyacid-supported silver (Ag–HPA) obtained by Reddy et al.^[17] were successfully used to catalyze A³-coupling reactions under heterogeneous reaction conditions with reusability of catalysts. Most recently, Kidwai et al.^[18] have reported gold and copper nanoparticles as reusable catalysts for the A³-coupling reactions. However, almost all of these A³-coupling reactions protocols were carried out under heating reaction conditions.

N-Heterocyclic carbenes (NHCs) are widely used as ligands in inorganic and organometallic chemistry since Arduengo and co-workers isolated the first stable N-heterocyclic carbene in 1991.^[19] NHCs were first considered as simple phosphane mimics in organometallic chemistry.^[20] However, increasing experimental data clearly show that NHC–metal catalysts can surpass their phosphane-based counterparts in both activity and scope.^[21] NHCs are stronger σ -donors and weaker π -acceptors, causing the properties of NHC–metal complexes to be notably different than those of a corresponding phosphane complex. Because of their specific coordination chemistry, NHCs both stabilize and activate metal centers in quite different key catalytic steps of organic syntheses, for example, C–C, C–H, C–O, and C–N bond formation.^[22] To avoid catalyst leaching, polymer-, PEG- or silica-supported NHC–metal complexes were synthesized and applied successfully in organic reactions.^[23] However, there has been no report on supported NHC–Cu^I complexes.

The increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses.^[24] The development of heterogeneous catalysts for the synthesis of fine chemicals has become a major area of research

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Scheme 1.

recently, as the potential advantages of these materials (simplified recovery and reusability, the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can have a major impact on the environmental performance of a synthesis.^[25] As a part of our ongoing interest in the synthesis of propargylamines with $\text{A}^3\text{-coupling}$ reactions, we herein report an efficient $\text{SiO}_2\text{-NHC-Cu}^{\text{I}}$ heterogeneous catalyst without any additives for the three-component coupling of aldehydes, alkynes, and amines ($\text{A}^3\text{-reactions}$) to synthesize propargylamines at room temp. under solvent-free conditions. This method provides a wide range of substrate applicability and can be applied to aromatic and aliphatic aldehydes, amines and alkynes. In most cases, nearly quantitative yields were obtained. To the best of our knowledge, this is the first catalyst example with N-heterocyclic carbene as ligand for $\text{A}^3\text{-coupling}$ reactions (Scheme 1).

Results and Discussion

The $\text{SiO}_2\text{-NHC-Cu}^{\text{I}}$ catalyst was readily prepared in a three-step procedure (Scheme 1). Activated silica was treated with trichloro[4-(chloromethyl)phenyl]silane in dry toluene at 120°C under an inert gas for 24 h to afford the benzyl chloride functionalized silica. The obtained functionalized silica material was then treated with *N*-methylimidazole in toluene at 80°C for 24 h to generate the corresponding silica-supported ionic liquid. The silica-supported ionic liquid was then treated with freshly prepared CuI in the presence of NaOtBu in dry THF at room temp. under an inert gas for 6 h. The $\text{SiO}_2\text{-NHC-Cu}^{\text{I}}$ catalyst was obtained as a gray-green powder, and the copper content of the catalyst was found to be 0.86 mmol g^{-1} .

Our initial investigation focused on the effect of solvents on the $\text{A}^3\text{-coupling}$ reactions. In general, $\text{A}^3\text{-coupling}$ reac-

Table 1. Effect of solvent on the $\text{A}^3\text{-coupling}$ reaction using $\text{SiO}_2\text{-NHC-Cu}^{\text{I}}$ as catalyst.^[a]

Entry	Solvent	Yield [%] ^[b]
1	toluene	82
2	CH_3CN	90
3	THF	84
4	H_2O	24
5	$\text{CH}_3\text{CH}_2\text{OH}$	30
6	CH_2Cl_2	94
7	DMSO	62
8	DMF	52
9	acetone	95
10	neat	95
11	neat	95 ^[c]
12	neat	93 ^[d]

[a] Reaction conditions: paraformaldehyde (1.0 mmol), piperidine (1.1 mmol), phenylacetylene (1.2 mmol), $\text{SiO}_2\text{-NHC-Cu}^{\text{I}}$ (2 mol-%), solvent (0.5 mL), nitrogen, room temp., 24 h. [b] Isolated yields. [c] 70°C for 4 h. [d] Using NHC-Cu^{I} (2 mol-%) instead of $\text{SiO}_2\text{-NHC-Cu}^{\text{I}}$ (2 mol-%) as catalyst.

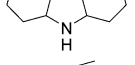
tions were carried out in toluene,^[2,26] CH₃CN,^[15,18a,27] THF,^[16,18b] H₂O^[6,7,9a,28] and other solvents. Here, different solvents were employed in the A³-coupling of paraformaldehyde, phenylacetylene, and piperidine by using SiO₂–NHC–Cu^I as catalyst at room temp., and the results are summarized in Table 1. From Table 1, it is evident that acetone and CH₂Cl₂ are suitable reaction media for the A³-coupling reaction (Table 1, Entries 6 and 9), whereas toluene, CH₃CN, and THF afforded lower yields (Table 1, Entries 1, 2, and 3). Moderate yields were obtained when the reactions were performed in DMSO and DMF (Table 1, Entries 7 and 8). Poor results were observed when the reactions were carried out in H₂O and CH₃CH₂OH (Table 1, Entries 4 and 5). Surprisingly, 95% of the desired product was isolated under solvent-free reaction conditions at room temp. for 24 h (Table 1, Entry 10). We also investigated the reaction by using NHC–Cu^I (2 mol-%) instead of SiO₂–NHC–Cu^I (2 mol-%) as catalyst, and the result indicated that both of them are effective in the reaction (Table 1, Entry 12). To avoid the use of volatile solvents and to reduce the environmental pollution, all the three-component coupling reactions were performed under solvent-free reaction conditions.

During the course of our further optimization of the conditions, when using 2 mol-% of SiO₂–NHC–Cu^I, the reactions were generally completed in 4 h when performed at 70 °C (Table 1, Entry 11). The reaction time, as expected, was inversely proportional to the temperature. Room temperature was found to be optimal. Thus, the optimized reaction conditions for this A³-coupling reaction are SiO₂–NHC–Cu^I (2 mol-%) in the absence of a solvent at room temp. for 24 h.

To examine the scope of this three-component coupling reaction, we extended our studies to different combinations of aldehydes, amines, and alkynes. The results are listed in Table 2. At the beginning of the determination of the amine substrate scope, phenylacetylene was used as a model substrate, and various amines with different aldehydes were examined (Table 2, Entries 1–7). The results indicated that cyclic, heterocyclic and acyclic secondary aliphatic amines gave excellent yields of products at room temp. in the combination of phenylacetylene/paraformaldehyde/amines under standard reaction conditions (Table 2, Entries 1–5), whereas primary aliphatic amines generated the corresponding secondary propargylamines in moderate yield (Table 2, Entry 6). Aromatic primary amines, such as aniline, also reacted with benzaldehyde and phenylacetylene to give the corresponding products in good yields (Table 2, Entry 7).

In order to expand the scope of aldehyde substrates, a combination of phenylacetylene/piperidine/aldehydes was chosen, and various aldehydes were examined. Aliphatic aldehydes, cyclic or acyclic, displayed high reactivity under the reaction conditions (Table 2, Entries 8–10). Aromatic aldehydes with both electron-donating and electron-withdrawing functionalities afforded the corresponding propargylamines in good to excellent yields, and the reaction of arenecarbaldehydes was also tolerant of *ortho* substitution (Table 2, Entries 11–16).

Table 2. A³ (aldehyde/amine/alkyne) coupling reaction catalyzed by SiO₂–NHC–Cu^I.^[a]

$\text{R}-\text{C}\equiv\text{CH} + \text{R}^1\text{CHO} + \text{NHR}^2\text{R}^3 \xrightarrow[\text{solventless}]{\text{SiO}_2\text{-NHC-Cu}^{\text{I}} \text{ cat.}} \text{R}-\text{C}\equiv\text{C}(\text{R}^1)(\text{NR}^2\text{R}^3)$				
Entry	Alkyne	Aldehyde	Amine	Yield [%] ^[b]
1	C ₆ H ₅ C≡CH	CH ₂ O		95
2	C ₆ H ₅ C≡CH	CH ₂ O		94
3	C ₆ H ₅ C≡CH	CH ₂ O		94
4	C ₆ H ₅ C≡CH	CH ₂ O		95
5	C ₆ H ₅ C≡CH	CH ₂ O		96
6	C ₆ H ₅ C≡CH	CH ₂ O		43
7	C ₆ H ₅ C≡CH	C ₆ H ₅ CHO		71 88 ^[c]
8	C ₆ H ₅ C≡CH			87
9	C ₆ H ₅ C≡CH			89
10	C ₆ H ₅ C≡CH			86
11	C ₆ H ₅ C≡CH	C ₆ H ₅ CHO		79 91 ^[c]
12	C ₆ H ₅ C≡CH	<i>p</i> -ClC ₆ H ₄ CHO		93 ^[c]
13	C ₆ H ₅ C≡CH	<i>m</i> -ClC ₆ H ₄ CHO		90 ^[c]
14	C ₆ H ₅ C≡CH	<i>o</i> -ClC ₆ H ₄ CHO		87 ^[c]
15	C ₆ H ₅ C≡CH	<i>p</i> -CH ₃ C ₆ H ₄ CHO		96 ^[c]
16	C ₆ H ₅ C≡CH	<i>p</i> -CH ₃ OC ₆ H ₄ CHO		92 ^[c]
17	<i>p</i> -CH ₃ C ₆ H ₄ C≡CH	CH ₂ O		96
18	<i>n</i> -C ₈ H ₁₇ C≡CH	CH ₂ O		78 92 ^[c]
19	<i>n</i> -C ₆ H ₁₃ C≡CH	CH ₂ O		86 ^[c]
20	EtOOC≡CH	CH ₂ O		75 ^[c]

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol), SiO₂–NHC–Cu^I (2 mol-%), nitrogen, room temp., 24 h. [b] Isolated yield. [c] 70 °C for 4 h.

Subsequently, a variety of alkynes were also examined for the A³-coupling by using paraformaldehyde/*N,N*-dibenzylamine/alkynes (Table 2, Entries 17–20). As can be seen from Table 2, reactivity of both aliphatic and aromatic alkynes was observed, in which the aromatic alkynes were often much more reactive than the aliphatic alkynes. Aromatic alkynes, such as phenylacetylene and (*p*-methylphenyl)acetylene, were able to undergo the three-component-coupling smoothly and generated the corresponding products in excellent yields (Table 2, Entries 3 and 17). Fortunately, the reactions involving aliphatic alkynes also gave both higher conversions and isolated yields, leading to the corresponding propargylamines in high yields (Table 2, Entries 18–20).

For any heterogeneous catalyst, it is important to know its ease of separation and possible reusability. The recycl-

Table 3. Successive runs by using recovered SiO₂-NHC-Cu^I catalyst.^[a]

Cycle	Yield [%] ^[b]	Cycle	Yield [%] ^[b]
1	95	6	93
2	94	7	92
3	93	8	90
4	92	9	89
5	91	10	88

[a] Reaction conditions: paraformaldehyde (1.0 mmol), piperidine (1.1 mmol), phenylacetylene (1.2 mmol), SiO₂-NHC-Cu^I catalyst (2 mol-%), nitrogen, room temp., 24 h. [b] Isolated yield.

ability of the SiO₂-NHC-Cu^I catalyst was also investigated. After carrying out the reaction, the catalyst was separated by simple filtration and washed with acetone (2 mL). After being air-dried, it can be reused directly without further purification. The recovered catalyst was used in the next run, and almost consistent activity was observed for ten consecutive cycles (Table 3, Entries 1–10). Possible copper leaching in SiO₂-NHC-Cu^I was also determined. Inductively coupled plasma (ICP) analyses of the clear filtrates obtained by filtration after the reaction indicated that the Cu content was <0.1 ppm.

Conclusions

We have successfully developed a novel, practical and environmentally friendly method for the synthesis of propargylamines through a three-component coupling of aldehydes, amines and alkynes by using SiO₂-NHC-Cu^I as catalyst (2 mol-%) at room temp. under solventless reaction conditions. The reactions generated the corresponding propargylamines in high yields and were applicable to aromatic and aliphatic aldehydes, alkynes, and amines. In addition, this methodology offers the competitiveness of recyclability of the catalyst without significant loss of catalytic activity, and the catalyst could be readily recovered and reused for ten cycles, thus making this procedure environmentally more acceptable, whilst no catalyst leaching was observed.

Further investigation on the application of this kind of supported catalysts in asymmetric catalysis is still underway in our laboratory.

Experimental Section

General: All ¹H and ¹³C NMR spectra were recorded with a Bruker 300 MHz FT-NMR spectrometer. Chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as the internal standard. ²⁹Si NMR (solid) spectra were obtained with a Bruker 400 MHz FT-NMR spectrometer. The C, H, and N analyses were performed with a Vario El III elemental. The Cu content was determined with a Jarrell-Ash 1100 ICP analysis. Specific surface areas and pore volumes of the samples were determined in a Micromeritics ASAP-2000 automated nitrogen physisorption apparatus and calculated according to the BET method. Products were purified by flash column chromatography on 230–400 mesh silica gel.

The chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China) and were used without purification prior to use.

Preparation of Benzyl Chloride Functionalized Silica: Into a 100-mL round-bottom flask were introduced successively anhydrous toluene (30 mL), activated silica (5.0 g), and trichloro[4-(chloromethyl)phenyl]silane (2.0 g). The solution was refluxed at 120 °C under an inert gas for 24 h. The solution was filtered, and the solid was washed subsequently with toluene, dichloromethane, and methanol, and dried under reduced pressure at 80 °C for 10 h to yield 5.81 g of product. The loading of the modified silica was readily quantified by CHN microanalysis and found to be 1.12 mmol g⁻¹ based on the C content. The surface area and pore volume of the modified silica were found to be 433 m² g⁻¹ and 0.53 cm³ g⁻¹, respectively.

Preparation of Silica-Supported Ionic Liquid: Under nitrogen, *N*-methylimidazole (0.41 g, 5.0 mmol) and benzyl chloride functionalized silica (2.0 g) were mixed in toluene (15 mL) in a round-bottom flask. The reaction was carried out at 80 °C for 24 h. Then the solution was filtered, and the solid was washed with chloroform, methanol and ethyl acetate, and dried under vacuum at 60 °C to yield 2.08 g of a pale powder. The loading of the silica-supported ionic liquid was quantified by CHN microanalysis and found to be 0.96 mmol g⁻¹ based on the N content. The surface area and pore volume of the silica-supported ionic liquid were found to be 308 m² g⁻¹ and 0.43 cm³ g⁻¹, respectively. ²⁹Si NMR (solid): δ = -79.4 (br., SiC), -111.5 (br., SiO₂) ppm.

Preparation of SiO₂-NHC-Cu^I Catalyst: In an oven-dried Schlenk flask, freshly prepared CuI (0.190 g, 1.0 mmol), NaOtBu (0.096 g, 1.0 mmol), silica-supported ionic liquid (1.0 g) and THF (5 mL) were added. The resulting suspension was stirred at room temp. under an inert gas for 6 h. Then the solution was filtered, and the solid was washed with water (3 mL), methanol (3 mL), acetone (3 mL $\times$ 2), and dried under vacuum at 60 °C for 12 h. The SiO₂-NHC-Cu^I catalyst was obtained as a gray-green powder (1.14 g). The copper content of the catalyst was found to be 0.86 mmol g⁻¹ based on ICP analysis. The surface area and pore volume of the SiO₂-NHC-Cu^I were found to be 275 m² g⁻¹ and 0.38 cm³ g⁻¹, respectively. ²⁹Si NMR (solid): δ = -78.7 (br., SiC), -111.5 (br., SiO₂) ppm.

Typical Procedure for A³-Coupling Catalyzed by SiO₂-NHC-Cu^I: Under nitrogen, SiO₂-NHC-Cu^I catalyst (23.3 mg, Cu^I content 0.02 mmol), phenylacetylene (120 mg, 1.2 mmol), paraformaldehyde (30 mg, 1.0 mmol) and piperidine (94 mg, 1.1 mmol) were added in a 10-mL of Schlenk flask. The mixture was stirred at room temp. for 24 h. After the reaction was completed, diethyl

ether (3 mL × 2) was added, and the slurry was stirred, then filtered using a sintered-glass funnel. The residue was washed with diethyl ether to ensure removal of the product from the surface of the catalyst. The combined organic phases were dried with Na₂SO₄, filtered, concentrated, and the residue was purified by flash chromatography on silica gel (eluant: hexane/ethyl acetate, 3:1, v/v) to give the corresponding A³-coupling product *N*-[1-(3-phenylprop-2-ynyl)]piperidine as a colorless oil (190 mg, 95% yield).

***N*-[1-(3-Phenylprop-2-ynyl)]piperidine:**^[29] ¹H NMR (300 MHz, CDCl₃): δ = 7.43–7.40 (m, 2 H, ArH), 7.27–7.24 (m, 3 H, ArH), 3.45 (s, 2 H, C≡CCH₂), 2.54 (br. s, 2 × 2 H, NCH₂), 1.65–1.58 (m, 2 × 2 H, NCH₂CH₂), 1.45–1.42 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.4, 127.9, 127.7, 123.1, 84.8, 84.7, 53.2, 48.2, 25.7, 23.7 ppm.

***N*-[1-(3-Phenylprop-2-ynyl)]morpholine:**^[30] ¹H NMR (300 MHz, CDCl₃): δ = 7.45–7.41 (m, 2 H, ArH), 7.29–7.27 (m, 3 H, ArH), 3.76–3.73 (t, *J* = 4.8 Hz, 2 × 2 H, OCH₂), 3.48 (s, 2 H, C≡CCH₂), 2.63–2.60 (t, *J* = 4.8 Hz, 2 × 2 H, NCH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.6, 128.2, 128.1, 123.0, 85.5, 84.1, 66.8, 52.4, 48.0 ppm.

***N,N*-Dibenzyl-3-phenylprop-2-ynylamine:**^[31] ¹H NMR (300 MHz, CDCl₃): δ = 7.49–7.46 (m, 2 H, ArH), 7.42–7.40 (m, 4 H, ArH), 7.31–7.17 (m, 9 H, ArH), 3.73 (s, 2 × 2 H, PhCH₂), 3.44 (s, 2 H, C≡CCH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 138.8, 131.7, 129.0, 128.2, 127.8, 127.0, 123.4, 85.8, 84.4, 57.7, 42.1 ppm.

***N,N*-Dicyclohexyl-3-phenylprop-2-ynylamine:**^[32] ¹H NMR (300 MHz, CDCl₃): δ = 7.39–7.37 (m, 2 H, ArH), 7.27–7.25 (m, 3 H, ArH), 3.69 (s, 2 H, C≡CCH₂), 2.85–2.78 (m, 2 × 1 H, NCH), 1.92–1.88 (m, 2 × 2 H, NCHCH₂), 1.80–1.76 (m, 2 × 2 H, NCHCH₂), 1.43–1.06 (m, 2 × 6 H, NCHCH₂CH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.5, 128.2, 127.6, 124.0, 89.7, 83.3, 57.6, 35.8, 31.4, 29.8, 27.0, 26.4 ppm.

***N,N*-Diisopropyl-3-phenylprop-2-ynylamine:**^[31] ¹H NMR (300 MHz, CDCl₃): δ = 7.41–7.38 (m, 2 H, ArH), 7.28–7.26 (m, 3 H, ArH), 3.66 (s, 2 H, C≡CCH₂), 3.27 (sept, *J* = 7.2 Hz, 2 × 1 H, NCH), 1.16 (d, *J* = 6.6 Hz, 4 × 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.2, 128.0, 127.4, 123.6, 88.9, 83.4, 48.6, 34.8, 20.6 ppm.

***N*-Cyclohexyl-3-phenylprop-2-ynylamine:** ¹H NMR (300 MHz, CDCl₃): δ = 7.44–7.41 (m, 2 H, ArH), 7.28–7.25 (m, 3 H, ArH), 3.46 (s, 2 H, C≡CCH₂), 2.82–2.79 (m, 1 H, NCH), 2.56–2.52 (m, 2 × 2 H, NCH₂), 1.65–1.62 (m, 2 × 2 H, NCH₂CH₂), 1.45–1.43 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.6, 128.1, 127.8, 123.2, 85.0, 84.9, 53.3, 48.4, 25.8, 23.8 ppm. C₁₅H₁₉N (213.32): calcd. C 84.46, H 8.98, N 6.57; found C 84.28, H 9.05, N 6.67.

***N*-(1,3-Diphenyl-2-propynyl)aniline:**^[9d] ¹H NMR (300 MHz, CDCl₃): δ = 7.70–7.65 (m, 2 H, ArH), 7.45–7.20 (m, 10 H, ArH), 6.85–6.79 (m, 3 H, ArH), 5.50 (s, 1 H, C≡CCH), 4.32 (s, 1 H, NH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 146.9, 139.9, 132.2, 129.5, 129.1, 128.6, 128.5, 128.2, 127.6, 123.1, 118.9, 114.5, 88.8, 85.4, 50.9 ppm.

***N*-[4-(1-Isopropyl-3-phenyl-2-propynyl)]piperidine:**^[33] ¹H NMR (300 MHz, CDCl₃): δ = 7.44–7.40 (m, 2 H, ArH), 7.32–7.27 (m, 3 H, ArH), 2.99 (d, *J* = 9.9 Hz, 1 H, C≡CCH), 2.68–2.64 (m, 2 H, NCH₂), 2.44–2.40 (m, 2 H, NCH₂), 1.96–1.88 (m, 1 H, CH₃CHCH₃), 1.64–1.43 (m, 6 H, NCH₂CH₂CH₂CH₂), 1.12 (d, *J* = 6.6 Hz, 3 H, CH₃CHCH₃), 1.03 (d, *J* = 6.6 Hz, 3 H, CH₃CHCH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.9, 128.4, 127.8, 123.9, 87.9, 85.7, 65.7, 50.6, 30.6, 26.2, 24.7, 20.7, 19.9 ppm.

***N*-[1-(1-Cyclohexyl-3-phenyl-2-propynyl)]piperidine:**^[34] ¹H NMR (300 MHz, CDCl₃): δ = 7.44–7.40 (m, 2 H, ArH), 7.30–7.25 (m, 3 H, ArH), 3.12 (d, *J* = 9.9 Hz, 1 H, C≡CCH), 2.66–2.58 (m, 2 H, NCH₂), 2.44–2.34 (m, 2 H, NCH₂), 2.14–1.98 (m, 2 H, CH₂), 1.80–1.70 (m, 2 H, CH₂), 1.70–1.36 (m, 8 H, CH₂), 1.34–0.89 (m, 5 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.9, 128.4, 127.7, 123.8, 87.9, 86.3, 64.7, 39.7, 31.4, 30.5, 27.0, 26.4, 26.1, 24.8 ppm.

***N*-[4-(3-Phenyl-1-propyl-2-propynyl)]piperidine:**^[35] ¹H NMR (300 MHz, CDCl₃): δ = 7.44–7.42 (m, 2 H, ArH), 7.28–7.26 (m, 3 H, ArH), 3.51–3.47 (m, 1 H, C≡CCH), 2.72–2.65 (m, 2 H, NCH₂), 2.50–2.48 (m, 2 H, NCH₂), 1.72–1.53 (m, 6 H, NCH₂CH₂), 1.46–1.41 (m, 4 H, CH₃CH₂), 0.96 (t, *J* = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.7, 128.2, 127.8, 123.7, 88.2, 85.7, 58.3, 35.7, 29.8, 26.9, 24.7, 20.2, 14.0 ppm.

***N*-(1,3-Diphenyl-2-propynyl)piperidine:**^[36] ¹H NMR (300 MHz, CDCl₃): δ = 7.65–7.63 (m, 2 H, ArH), 7.53–7.50 (m, 2 H, ArH), 7.38–7.28 (m, 6 H, ArH), 4.82 (s, 1 H, C≡CCH), 2.61–2.56 (m, 2 × 2 H, NCH₂), 1.63–1.56 (m, 4 H, NCH₂CH₂), 1.48–1.42 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 138.8, 132.0, 128.7, 128.4, 128.2, 127.6, 123.6, 87.9, 86.3, 62.6, 59.8, 26.4, 24.7 ppm.

***N*-[1-(4-Methylphenyl)-3-phenyl-2-propynyl]piperidine:**^[36] ¹H NMR (300 MHz, CDCl₃): δ = 7.52–7.48 (m, 4 H, ArH), 7.32–7.27 (m, 3 H, ArH), 7.10 (d, *J* = 8.1 Hz, 2 H, ArH), 4.75 (s, 1 H, C≡CCH), 2.57–2.53 (m, 2 × 2 H, NCH₂), 2.33 (s, 3 H), 1.62–1.51 (m, 2 × 2 H, NCH₂CH₂), 1.45–1.40 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 137.2, 135.8, 132.1, 129.0, 128.8, 128.5, 128.2, 123.7, 87.9, 86.7, 62.4, 51.0, 26.4, 24.8, 21.4 ppm.

***N*-[1-(4-Methoxyphenyl)-3-phenyl-2-propynyl]piperidine:**^[36] ¹H NMR (300 MHz, CDCl₃): δ = 7.55–7.48 (m, 4 H, ArH), 7.30–7.26 (m, 3 H, ArH), 6.90–6.85 (m, 2 H, ArH), 4.73 (s, 1 H, C≡CCH), 3.74 (s, 3 H, OCH₃), 2.56–2.53 (m, 2 × 2 H, NCH₂), 1.62–1.53 (m, 2 × 2 H, NCH₂CH₂), 1.45–1.39 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.0, 131.8, 130.0, 129.1, 128.0, 127.8, 123.1, 112.9, 87.9, 86.7, 61.8, 55.2, 50.4, 26.4, 24.5 ppm.

***N*-[1-(4-Chlorophenyl)-3-phenyl-2-propynyl]piperidine:**^[36] ¹H NMR (300 MHz, CDCl₃): δ = 7.56 (d, *J* = 8.7 Hz, 2 H, ArH), 7.50–7.47 (m, 2 H, ArH), 7.32–7.27 (m, 5 H, ArH), 4.73 (s, 1 H, C≡CCH), 2.54–2.50 (m, 2 × 2 H, NCH₂), 1.59–1.53 (m, 2 × 2 H, NCH₂CH₂), 1.43–1.39 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 137.4, 133.4, 132.0, 130.1, 128.5, 128.3, 123.3, 88.4, 85.6, 62.0, 61.8, 50.8, 26.4, 24.5 ppm.

***N*-[1-(3-Chlorophenyl)-3-phenyl-2-propynyl]piperidine:**^[36] ¹H NMR (300 MHz, CDCl₃): δ = 7.69–7.65 (m, 1 H, ArH), 7.61–7.55 (m, 3 H, ArH), 7.40–7.34 (m, 3 H, ArH), 7.32–7.29 (m, 2 H, ArH), 4.73 (s, 1 H, C≡CCH), 2.68–2.58 (m, 2 × 2 H, NCH₂), 1.72–1.59 (m, 2 × 2 H, NCH₂CH₂), 1.57–1.48 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 140.9, 134.7, 132.1, 129.6, 128.7, 128.5, 128.2, 127.7, 126.3, 123.4, 88.6, 85.5, 62.1, 50.9, 26.4, 24.7 ppm.

***N*-[1-(2-Chlorophenyl)-3-phenyl-2-propynyl]piperidine:**^[37] ¹H NMR (300 MHz, CDCl₃): δ = 7.84 (d, *J* = 7.5 Hz, 1 H, ArH), 7.59–7.56 (m, 2 H, ArH), 7.47–7.26 (m, 6 H, ArH), 5.19 (s, 1 H, C≡CCH), 2.71–2.68 (m, 2 × 2 H, NCH₂), 1.70–1.62 (m, 2 × 2 H, NCH₂CH₂), 1.51–1.48 (m, 2 H, NCH₂CH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 136.5, 134.8, 131.9, 130.7, 129.9, 128.9, 128.4, 128.2, 126.3, 123.3, 87.8, 85.9, 59.4, 50.9, 26.3, 24.6 ppm.

***N,N*-Dibenzyl[3-(*p*-tolyl)prop-2-ynyl]amine:**^[29] ¹H NMR (300 MHz, CDCl₃): δ = 7.43–7.18 (m, 12 H, ArH), 7.10 (d, *J* = 7.8 Hz, 2 H, ArH), 3.72 (s, 2 × 2 H, PhCH₂), 3.46 (s, 2 H, C≡CCH₂), 2.30 (s, 3

H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 139.0, 138.0, 131.7, 129.1, 128.2, 127.0, 120.3, 86.1, 83.6, 57.7, 42.0, 21.5 ppm.

***N,N*-Dibenzyl(undec-2-ynyl)amine**:^[29] ¹H NMR (300 MHz, CDCl₃): δ = 7.41–7.21 (m, 10 H, ArH), 3.66 (s, 2 × 2 H, PhCH₂), 3.24 (s, 2 H, C≡CCH₂), 2.24 (t, *J* = 6.6 Hz, 2 H, CH₂C≡CCH₂N), 1.55–1.30 (m, 12 H, CH₂CH₂CH₂CH₂CH₂), 0.90 (t, *J* = 6.9 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 139.0, 128.7, 128.0, 126.9, 85.6, 74.4, 57.5, 41.5, 31.8, 29.3, 29.1, 28.9, 22.7, 18.7, 14.0 ppm.

***N,N*-Dibenzyl(non-2-ynyl)amine**:^[29] ¹H NMR (300 MHz, CDCl₃): δ = 7.39–7.17 (m, 10 H, ArH), 3.64 (s, 2 × 2 H, PhCH₂), 3.26 (s, 2 H, C≡CCH₂), 2.21 (t, *J* = 6.6 Hz, 2 H, CH₂C≡CCH₂N), 1.61–1.34 (m, 8 H, CH₂CH₂CH₂CH₂), 0.92 (t, *J* = 6.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 139.0, 129.1, 128.4, 126.8, 85.7, 74.4, 57.6, 41.4, 31.4, 29.1, 28.6, 22.6, 18.7, 14.2 ppm.

Ethyl 4-(Dibenzylamino)but-2-ynoate: Oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.84 (d, *J* = 12.9 Hz, 1 H, C≡CCH), 7.38–7.30 (m, 6 H, ArH), 7.20–7.18 (m, 4 H, ArH), 4.84 (d, *J* = 13.2 Hz, 1 H, C≡CCH), 4.30 (s, 2 × 2 H, PhCH₂), 4.17 (q, *J* = 7.2 Hz, 2 H, CH₃CH₂O), 1.28 (t, *J* = 7.2 Hz, 3 H, CH₃CH₂O) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 169.7, 152.6, 135.9, 128.7, 127.7, 127.4, 85.8, 58.9, 26.7, 14.6 ppm. C₂₀H₂₁NO₂ (307.39): calcd. C 78.15, H 6.89, N 4.56; found C 78.28, H 6.75, N 4.79. HRMS: calcd. for C₂₀H₂₁NO₂ 307.1572; found 307.1567.

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