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Silica-Immobilized NHC–Cu^{I} Complex: An Efficient and Reusable Catalyst for A^3-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 (A^3-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 SiO_2–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.

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 (A^3-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 A^3-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 A^3-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] Hg_2Cl_2[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–$AuCl_4$) reported by Likhar et al.,[15,16] and heteropolyacid-supported silver (Ag–HPA) obtained by Reddy et al.[17] were successfully used to catalyze A^3-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 A^3-coupling reactions. However, almost all of these A^3-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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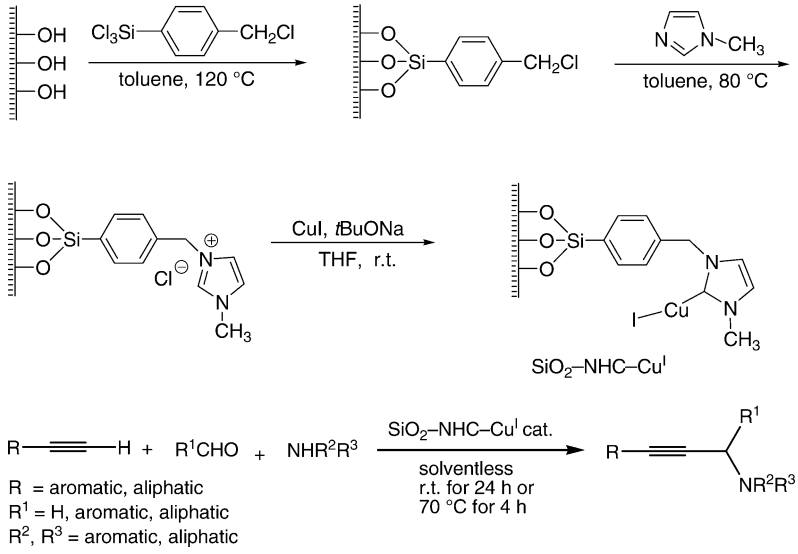


Scheme 1.

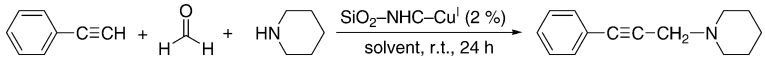
recently, as the potential advantages of these materials (simplified recovery and reusability, the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can have a major impact on the environmental performance of a synthesis.[25] As a part of our ongoing interest in the synthesis of propargylamines with A^3-coupling reactions, we herein report an efficient SiO_2–NHC–Cu^I heterogeneous catalyst without any additives for the three-component coupling of aldehydes, alkynes, and amines (A^3-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 A^3-coupling reactions (Scheme 1).

Results and Discussion

The SiO_2–NHC–Cu^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 NaO*t*Bu in dry THF at room temp. under an inert gas for 6 h. The SiO_2–NHC–Cu^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 A^3-coupling reactions. In general, A^3-coupling reac-

Table 1. Effect of solvent on the A^3-coupling reaction using SiO_2–NHC–Cu^I as catalyst.[a]



Entry	Solvent	Yield [%][b]
1	toluene	82
2	CH_3CN	90
3	THF	84
4	H_2O	24
5	CH_3CH_2OH	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), SiO_2–NHC–Cu^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 SiO_2–NHC–Cu^I (2 mol-%) as catalyst.

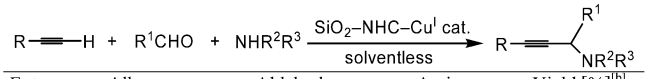
tions were carried out in toluene,[2,26] CH_3CN,[15,18a,27] THF,[16,18b] H_2O[6,7,9a,28] and other solvents. Here, different solvents were employed in the A^3-coupling of paraformaldehyde, phenylacetylene, and piperidine by using SiO_2–NHC–Cu^{I} as catalyst at room temp., and the results are summarized in Table 1. From Table 1, it is evident that acetone and CH_2Cl_2 are suitable reaction media for the A^3-coupling reaction (Table 1, Entries 6 and 9), whereas toluene, CH_3CN, 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 H_2O and CH_3CH_2OH (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 SiO_2–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.

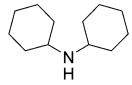
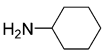
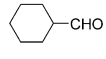
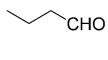
During the course of our further optimization of the conditions, when using 2 mol-% of SiO_2–NHC–Cu^{I}, the reactions were generally completed in 4 h when performed at 70 °C (Table 1, Entry 11). The reaction time, as expected, was inversely proportional to the temperature. Room temperature was found to be optimal. Thus, the optimized reaction conditions for this A^3-coupling reaction are SiO_2–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. A^3 (aldehyde/amine/alkyne) coupling reaction catalyzed by SiO_2–NHC–Cu^{I}.[a]



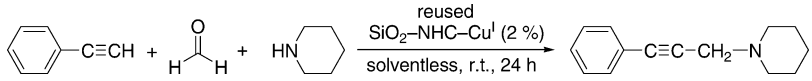
Entry	Alkyne	Aldehyde	Amine	Yield [%][b]
1	$C_6H_5C{\equiv}CH$	CH_2O		95
2	$C_6H_5C{\equiv}CH$	CH_2O		94
3	$C_6H_5C{\equiv}CH$	CH_2O		94
4	$C_6H_5C{\equiv}CH$	CH_2O		95
5	$C_6H_5C{\equiv}CH$	CH_2O		96
6	$C_6H_5C{\equiv}CH$	CH_2O		43
7	$C_6H_5C{\equiv}CH$	C_6H_5CHO		71 88[c]
8	$C_6H_5C{\equiv}CH$			87
9	$C_6H_5C{\equiv}CH$			89
10	$C_6H_5C{\equiv}CH$			86
11	$C_6H_5C{\equiv}CH$	C_6H_5CHO		79 91[c]
12	$C_6H_5C{\equiv}CH$	*p*-ClC_6H_4CHO		93[c]
13	$C_6H_5C{\equiv}CH$	*m*-ClC_6H_4CHO		90[c]
14	$C_6H_5C{\equiv}CH$	*o*-ClC_6H_4CHO		87[c]
15	$C_6H_5C{\equiv}CH$	*p*-$CH_3C_6H_4CHO$		96[c]
16	$C_6H_5C{\equiv}CH$	*p*-$CH_3OC_6H_4CHO$		92[c]
17	*p*-$CH_3C_6H_4C{\equiv}CH$	CH_2O		96
18	*n*-$C_8H_{17}C{\equiv}CH$	CH_2O		78 92[c]
19	*n*-$C_6H_{13}C{\equiv}CH$	CH_2O		86[c]
20	$EtOOCC{\equiv}CH$	CH_2O		75[c]

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol), SiO_2–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 A^3-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 higherr 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 SiO_2–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), SiO_2–NHC–Cu^I catalyst (2 mol-%), nitrogen, room temp., 24 h. [b] Isolated yield.

ability of the SiO_2–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 SiO_2–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 SiO_2–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 ^{13}C 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. ^{29}Si 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 elementar. 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 $m^2 g^{-1}$ and 0.53 $cm^3 g^{-1}$, 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 $m^2 g^{-1}$ and 0.43 $cm^3 g^{-1}$, respectively. ^{29}Si NMR (solid): δ = –79.4 (br., SiC), –111.5 (br., SiO_2) ppm.

Preparation of SiO_2–NHC–Cu^I Catalyst: In an oven-dried Schlenk flask, freshly prepared CuI (0.190 g, 1.0 mmol), NaO*t*Bu (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 × 2), and dried under vacuum at 60 °C for 12 h. The SiO_2–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 SiO_2–NHC–Cu^I were found to be 275 $m^2 g^{-1}$ and 0.38 $cm^3 g^{-1}$, respectively. ^{29}Si NMR (solid): δ = –78.7 (br., SiC), –111.5 (br., SiO_2) ppm.

Typical Procedure for A^3-Coupling Catalyzed by SiO_2–NHC–Cu^I: Under nitrogen, SiO_2–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 Na_2SO_4, 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 A^3-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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 2 H, Ar*H*), 7.27–7.24 (m, 3 H, Ar*H*), 3.45 (s, 2 H, C≡CCH_2), 2.54 (br. s, 2 × 2 H, NCH_2), 1.65–1.58 (m, 2 × 2 H, NCH$_2$CH_2), 1.45–1.42 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 2 H, Ar*H*), 7.29–7.27 (m, 3 H, Ar*H*), 3.76–3.73 (t, *J* = 4.8 Hz, 2 × 2 H, OCH_2),3.48 (s, 2 H, C≡CCH_2), 2.63–2.60 (t, *J* = 4.8 Hz, 2 × 2 H, NCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2 H, Ar*H*), 7.42–7.40 (m, 4 H, Ar*H*), 7.31–7.17 (m, 9 H, Ar*H*), 3.73 (s, 2 × 2 H, PhCH_2), 3.44 (s, 2 H, C≡CCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 2 H, Ar*H*), 7.27–7.25 (m, 3 H, Ar*H*), 3.69 (s, 2 H, C≡CCH_2), 2.85–2.78 (m, 2 × 1 H, NC*H*), 1.92–1.88 (m, 2 × 2 H, NCHCH_2), 1.80–1.76 (m, 2 × 2 H, NCHCH_2), 1.43–1.06 (m, 2 × 6 H, NCHCH$_2$CH_2CH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2 H, Ar*H*), 7.28–7.26 (m, 3 H, Ar*H*), 3.66 (s, 2 H, C≡CCH_2), 3.27 (sept, *J* = 7.2 Hz, 2 × 1 H, NC*H*), 1.16 (d, *J* = 6.6 Hz, 4 × 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 2 H, Ar*H*), 7.28–7.25 (m, 3 H, Ar*H*), 3.46 (s, 2 H, C≡CCH_2), 2.82–2.79 (m, 1 H, NC*H*), 2.56–2.52 (m, 2 × 2 H, NCH_2), 1.65–1.62 (m, 2 × 2 H, NCH$_2$CH_2), 1.45–1.43 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.6, 128.1, 127.8, 123.2, 85.0, 84.9, 53.3, 48.4, 25.8, 23.8 ppm. $C_{15}H_{19}N$ (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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 2 H, Ar*H*), 7.45–7.20 (m, 10 H, Ar*H*), 6.85–6.79 (m, 3 H, Ar*H*), 5.50 (s, 1 H, C≡CC*H*), 4.32 (s, 1 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 2 H, Ar*H*), 7.32–7.27 (m, 3 H, Ar*H*), 2.99 (d, *J* = 9.9 Hz, 1 H, C≡CC*H*), 2.68–2.64 (m, 2 H, NCH_2), 2.44–2.40 (m, 2 H, NCH_2), 1.96–1.88 (m, 1 H, CH$_3$C*H*CH$_3$), 1.64–1.43 (m, 6 H, NCH$_2$CH_2CH_2CH_2), 1.12 (d, *J* = 6.6 Hz, 3 H, CH$_3$C*H*CH$_3$), 1.03 (d, *J* = 6.6 Hz, 3 H, CH$_3$C*H*CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 2 H, Ar*H*), 7.30–7.25 (m, 3 H, Ar*H*), 3.12 (d, *J* = 9.9 Hz, 1 H, C≡CC*H*), 2.66–2.58 (m, 2 H, NCH_2), 2.44–2.34 (m, 2 H, NCH_2), 2.14–1.98 (m, 2 H, CH_2), 1.80–1.70 (m, 2 H, CH_2), 1.70–1.36 (m, 8 H, CH_2), 1.34–0.89 (m, 5 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 2 H, Ar*H*), 7.28–7.26 (m, 3 H, Ar*H*), 3.51–3.47 (m, 1 H, C≡CC*H*), 2.72–2.65 (m, 2 H, NCH_2), 2.50–2.48 (m, 2 H, NCH_2), 1.72–1.53 (m, 6 H, NCH$_2$CH_2), 1.46–1.41 (m, 4 H, CH$_3$CH_2), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 2 H, Ar*H*), 7.53–7.50 (m, 2 H, Ar*H*), 7.38–7.28 (m, 6 H, Ar*H*), 4.82 (s, 1 H, C≡CC*H*), 2.61–2.56 (m, 2 × 2 H, NCH_2), 1.63–1.56 (m, 4 H, NCH$_2$CH_2), 1.48–1.42 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 4 H, Ar*H*), 7.32–7.27 (m, 3 H, Ar*H*), 7.10 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 4.75 (s, 1 H, C≡CC*H*), 2.57–2.53 (m, 2 × 2 H, NCH_2), 2.33 (s, 3 H), 1.62–1.51 (m, 2 × 2 H, NCH$_2$CH_2), 1.45–1.40 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.48 (m, 4 H, Ar*H*), 7.30–7.26 (m, 3 H, Ar*H*), 6.90–6.85 (m, 2 H, Ar*H*), 4.73 (s, 1 H, C≡CC*H*), 3.74 (s, 3 H, OCH_3), 2.56–2.53 (m, 2 × 2 H, NCH_2), 1.62–1.53 (m, 2 × 2 H, NCH$_2$CH_2), 1.45–1.39 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.50–7.47 (m, 2 H, Ar*H*), 7.32–7.27 (m, 5 H, Ar*H*), 4.73 (s, 1 H, C≡CC*H*), 2.54–2.50 (m, 2 × 2 H, NCH_2), 1.59–1.53 (m, 2 × 2 H, NCH$_2$CH_2), 1.43–1.39 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 1 H, Ar*H*), 7.61–7.55 (m, 3 H, Ar*H*), 7.40–7.34 (m, 3 H, Ar*H*), 7.32–7.29 (m, 2 H, Ar*H*), 4.73 (s, 1 H, C≡CC*H*), 2.68–2.58 (m, 2 × 2 H, NCH_2), 1.72–1.59 (m, 2 × 2 H, NCH$_2$CH_2), 1.57–1.48 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 7.59–7.56 (m, 2 H, Ar*H*), 7.47–7.26 (m, 6 H, Ar*H*), 5.19 (s, 1 H, C≡CC*H*), 2.71–2.68 (m, 2 × 2 H, NCH_2), 1.70–1.62 (m, 2 × 2 H, NCH$_2$CH_2), 1.51–1.48 (m, 2 H, NCH$_2$CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.18 (m, 12 H, Ar*H*), 7.10 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 3.72 (s, 2 × 2 H, PhCH_2), 3.46 (s, 2 H, C≡CCH_2), 2.30 (s, 3

H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 10 H, Ar*H*), 3.66 (s, 2×2 H, PhCH_2), 3.24 (s, 2 H, C≡CC*H*), 2.24 (t, *J* = 6.6 Hz, 2 H, CH_2C≡CCH_2N), 1.55–1.30 (m, 12 H, CH_2CH_2CH_2CH_2CH_2CH_2), 0.90 (t, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.17 (m, 10 H, Ar*H*), 3.64 (s, 2×2 H, PhCH_2), 3.26 (s, 2 H, C≡CCH_2), 2.21 (t, *J* = 6.6 Hz, 2 H, CH_2C≡CCH_2N), 1.61–1.34 (m, 8 H, CH_2CH_2CH_2CH_2), 0.92 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 12.9 Hz, 1 H, C≡CC*H*), 7.38–7.30 (m, 6 H, Ar*H*), 7.20–7.18 (m, 4 H, Ar*H*), 4.84 (d, *J* = 13.2 Hz, 1 H, C≡CC*H*), 4.30 (s, 2×2 H, PhCH_2), 4.17 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2O), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 152.6, 135.9, 128.7, 127.7, 127.4, 85.8, 58.9, 26.7, 14.6 ppm. $C_{20}H_{21}NO_2$ (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 $C_{20}H_{21}NO_2$ 307.1572; found 307.1567.

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