Three-Component Coupling of Aldehydes, Amines, and Alkynes Catalyzed by Oxidized Copper Nanoparticles on Titania

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Dedicated to the memory of Professor Balbino Mancheño

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Copper nanoparticles (mainly as Cu₂O) on titania have been shown to catalyze the multicomponent synthesis of propargylamines from aldehydes, amines, and alkynes (A³ coupling) effectively at 70 °C under solvent-free conditions. Both aromatic and aliphatic aldehydes and alkynes have been combined with secondary amines to provide a wide range of propargylamines in moderate to excellent yields. Two exam-

ples of ketone/amine/alkyne (KA²) coupling are also included. The catalyst is easy to prepare, reusable at a low copper loading (0.5 mol-%), and exhibits higher catalytic activity than some commercially available copper sources. Some mechanistic aspects of the reaction have also been examined, which have unveiled the participation of copper(I) acetylides in a heterogeneous process.

Introduction

Propargylamines are a versatile class of compounds extensively applied as precursors in the synthesis of heterocyclic compounds such as quinolines,^[1a] phenanthrolines,^[1b] pyrroles,^[1c] pyrrolidines,^[1d] indolizines,^[1e] or oxazolidinones,^[1f] among others.^[2] They have also been utilized as intermediates in the total synthesis of some natural and pharmaceutical products.^[3] Moreover, some propargylamine derivatives have been confirmed to be potent anti-apoptotic agents that protect neurons against cell death in cellular and animal models of neurodegenerative disorders. Indeed, they have been shown to delay the need for symptomatic therapy in untreated Parkinson's disease patients, results consistent with a neuroprotection role for compounds of this type.^[4]

Conventional methods for the formation of the propargylamine moiety include direct amination of propargyl halides,^[5a] triflates,^[5b] phosphates, or acetates,^[5c] or the more widely practiced addition of alkynylmetal reagents to imines.^[6] The latter approach, normally involving stoichiometric amounts of lithium or magnesium acetylides, requires strict control of the reaction conditions and lacks atom economy, and its application is precluded in the presence of the more reactive functional groups. In recent years, metal-catalyzed coupling of aldehydes, amines, and alkynes

(A³ coupling) has emerged as a powerful tool that enables the direct addition of alkynes to imines (generated in situ) in a multicomponent and more efficient manner.^[7]

The catalytic activation of the C–H bond of terminal alkynes has been primarily achieved with complexes or salts of the late transition metals (e.g., Ir, Zn, Fe, Co, Ni, Ag, Au, Ir, Ru, but also In), but by far the most studied metal has been copper, especially with secondary amines.^[7] However, the majority of the catalytic systems are homogeneous, making the recovery and recycling of the catalyst troublesome. Nowadays, nanocatalysis is considered a sustainable and competitive alternative to conventional catalysis, because the metal nanoparticles possess a high surface-to-volume ratio, which enhances their activity and selectivity, at the same time maintaining the intrinsic features of a heterogeneous catalyst.^[8] In particular, the immobilization of metal nanoparticles on high-surface-area inorganic supports allows better stability and dispersity of the particles as well as a further exploitation of the special activity and recycling properties of the catalyst.^[9]

To the best of our knowledge there are two reports that describe the use of copper nanoparticles (CuNPs) in A³ coupling: a) Cu⁰NPs (18 ± 2 nm), prepared in the aqueous core of reverse micellar droplets, were applied at 15 mol-% in MeCN at 100–110 °C under nitrogen and were reutilized five times (94–61 %),^[10a] and b) nanocrystalline CuO was used at 10 mol-% in toluene at 90 °C and reutilized four times (82–76 %).^[10b] Although the heterogeneous catalysts studied in A³ coupling generally exhibit good reuse capability, there are still some drawbacks that limit their acceptance, such as the high prices of the catalysts (especially

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those derived from noble metals) and their tedious preparation. In addition, some protocols involve environmentally unfriendly solvents, harsh conditions, long reaction times, and the need for inert atmospheres. The quest for new and more efficient catalysts for the synthesis of propargylamines based on A^3 coupling is therefore still a subject of interest in synthetic organic chemistry.

As a part of our investigations into the reactivity of active metals and nanoparticles,^[11] a form of active copper was obtained from $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, lithium metal, and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) in THF at room temperature and applied in reductions of a range of organic functionalities.^[12] We discovered that copper nanoparticles (CuNPs) were formed either from $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ or from anhydrous CuCl_2 under these conditions. Unsupported CuNPs, generated from anhydrous CuCl_2 , were found to catalyze 1,3-dipolar cycloadditions of organic azides and terminal alkynes in remarkably short reaction times.^[13] A second generation of catalysts was introduced through the immobilization of the CuNPs on different inorganic supports. In particular, we developed a highly versa-

tile and reusable catalyst, consisting of oxidized copper nanoparticles on activated carbon (0.5 mol-% CuNPs/C), for the multicomponent synthesis of 1,2,3-triazoles from organic halides, aryldiazonium salts, anilines, and epoxides in water.^[14] A catalyst based on oxidized copper nanoparticles on titania (1 mol-% CuNPs/ TiO_2) for the homocoupling of terminal alkynes in THF or under solventless conditions at 65 °C in the presence of piperidine (30 mol-%) as a base has recently been reported.^[15] As part of our research into organic reactions promoted by CuNPs, here we wish to present our results on the performance and scope of supported CuNPs in the three-component coupling of aldehydes, amines, and alkynes under solvent-free conditions (Scheme 1).

Results and Discussion

Preparation and Screening of the Catalysts

The copper catalysts were prepared by addition of a variety of inorganic supports to a suspension of the recently prepared CuNPs, readily generated in turn from anhydrous copper(II) chloride, lithium metal, and a catalytic amount of DTBB (10 mol-%) in THF at room temperature. The supported catalysts were not subjected to any treatment prior to use. Firstly, a screening was carried out in order to optimize the catalyst support, solvent, and conditions, with the coupling of benzaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**) as a model reaction (Table 1). A control experiment at 70 °C in the absence of catalyst did not give the expected product, irrespective of the solvent used (Table 1, Entry 1). In general, all the catalysts were quite effective in CH_2Cl_2 , with the exception of CuNPs/ TiO_2 (Table 1, Entry 5/ CH_2Cl_2). The best results were achieved with CuNPs/C (Table 1, Entry 2/ CH_2Cl_2), either at 70

Scheme 1. Homocoupling of phenylacetylene and A^3 coupling catalyzed by CuNPs/ TiO_2 .

Table 1. Optimization of the support, solvent, and reaction conditions.^[a]

Entry	Catalyst ^[b]								
		THF	H_2O	EtOH	PhMe	CH_2Cl_2	MeCN	Acetone	Neat
1	none	—	—	—	—	—	—	—	3
2	CuNPs/C	70	7	23	—	98 [90] ^[c]	—	—	82
3	CuNPs/G	25	6	8	4	96 [47] ^[c]	5	—	51
4	CuNPs/ZY	25	2	—	2	92 [89] ^[c]	3	—	60
5	CuNPs/ TiO_2	22	7	24	32	27	—	—	98 [35] ^[d]
6	CuNPs/ ZnO	14	11	—	8	94 [75] ^[c]	—	—	72
7	CuNPs/MK	—	—	8	21	85	18	—	48
8	CuNPs/ SiO_2	32	6	31	21	92 [47] ^[c]	4	—	57
9	CuNPs/MS	38	4	44	13	86	42	—	—
10	CuNPs/MgO	3	3	12	7	87 [47] ^[c]	6	—	75

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), CuNPs/support (20 mg), solvent (2 mL), 70 °C; numbers in each solvent column refer to conversion into **4aaa** after 24 h, determined by GC. [b] C = activated carbon, G = graphite, ZY = sodium zeolite Y, MK = montmorillonite K-10, MS = molecular sieves (4 Å). [c] Reaction at 40 °C in brackets. [d] Reaction at room temperature in brackets.

(98%) or at 40 °C (90%), although the level of conversion with CuNPs on zeolite Y at 40 °C (89%) is also worthy of mention (Table 1, Entry 4/CH₂Cl₂). Acetone, THF, H₂O, EtOH, PhMe, or MeCN were shown to be inappropriate solvents, with only THF providing a moderate degree of conversion into **4aaa** in the presence of CuNPs/C (Table 1, Entry 2/THF). All the catalysts were tested in the absence of solvent, with the observation of no conversion for CuNPs/MS, modest levels of conversion for CuNPs/G, CuNPs/ZY, CuNPs/MK, and CuNPs/SiO₂, moderate to good levels of conversion for CuNPs/C, CuNPs/ZnO, and CuNPs/MgO, and excellent levels of conversion for CuNPs/TiO₂ (Table 1, neat). Unfortunately, low levels of conversion were observed in the latter case when the reaction was carried out at room temperature (Table 1, Entry 5/neat). Because solvent-free organic synthesis is one of the most promising steps for waste prevention and environmental protection,^[16] we selected CuNPs/TiO₂ at 70 °C under solvent-free conditions as the catalyst of choice, to the detriment of the potentially good performance of CuNPs/C in CH₂Cl₂ at 40 °C.

Characterization of the Catalyst^[15]

The CuNPs/TiO₂ catalyst had previously been characterized by different means including TEM, X-ray photoelectron spectroscopy (XPS), and powder XRD, among others. Analysis by TEM revealed the presence of well-defined and dispersed spherical nanoparticles with diameters of ca. 1.0 ± 0.4 nm on the titania. Auger analysis complemented the data obtained from XPS, denoting primarily the presence of Cu₂O. A copper content of 3.0 wt.-% in the catalyst was determined by inductively coupled plasma mass spectrometry (ICP-MS). This content corresponds to 1 mol.-% Cu with respect to the substrates in the A³ coupling, but only 0.47 mol.-% (ca. 0.5 mol.-%) with allowance for the fact that the copper is mainly in the form of copper(I) oxide. This catalyst loading is considerably lower than those previously reported with other catalytic systems based on CuNPs (10–15 mol.-%).^[10]

Three-Component Coupling of Aldehydes, Amines, and Alkynes Catalyzed by CuNPs/TiO₂

All reactions were performed with ca. 0.5 mol.-% CuNPs/TiO₂ at 70 °C in the absence of solvent. A control experiment under the above conditions but in the presence only of titania (without copper) gave no trace of the corresponding propargylamine after 24 h. This result confirms the essential role of copper and practically rules out any catalytic effect of the support.

A series of commercially available aldehydes, secondary amines, and alkynes were subjected to the title reaction (Table 2). Firstly, benzaldehyde (**1a**) and phenylacetylene (**3a**) were coupled with different cyclic amines such as piperidine (**2a**), morpholine (**2b**), and 4-methylpiperidine (**2c**),

leading to **4aaa** and **4aba** in high yields, and **4aca** in moderate yield, respectively. Propargylamine **4ada**, derived from 2-methylpiperidine (**2d**), required prolonged heating and was obtained with moderate diastereoselectivity, whereas *N*-methylbenzylamine (**2e**) reacted more rapidly and with higher conversion into **4aea**.

Next, the nature of the alkyne was modified with the aldehyde and the amine kept constant. Arylacetylenes bearing either electron-donating (**4aab**) or electron-withdrawing groups (**4aac**) were examined, with the latter giving some side reactions; cyclohexylacetylene furnished **4aad** in a yield intermediate between those of **4aab** and **4aac**. The structure of the aldehyde seemed to have more pronounced effects both on the reaction time and on the isolated yield. Longer reaction times and lower yields were observed for the derivatives of 4-methoxybenzaldehyde (**4baa**) and 2-naphthaldehyde (**4eaa**), for instance, whereas much better results were achieved with 2-iodobenzaldehyde (**4caa**), 3-nitrobenzaldehyde (**4daa**), and benzofuran-2-carbaldehyde (**4faa**). Several aliphatic aldehydes were then subjected to the A³ coupling. Decanal (**4g**) and cyclohexanecarbaldehyde (**4h**), when coupled with piperidine (**2a**) and phenylacetylene (**3a**), afforded the propargylamines **4gaa** and **4haa** in high yields, though the reaction time was much shorter in the second case. *N*-Methylaniline (**2f**) and *N*-methyl- α -methylbenzylamine (**2g**) behaved similarly in reactions with cyclohexanecarbaldehyde (**4h**) and phenylacetylene (**3a**), with the products **4hfa** and **4hga** being obtained in good yields but with low diastereoselectivity in the latter case. An alkyl- and cycloalkyl-substituted propargylamine (**4hae**) could be also prepared in high yield. We were delighted to see that even the simplest aldehyde, formaldehyde (**1i**, 37% in H₂O/MeOH solution), reacted nicely with diethylamine (**2h**) and phenylacetylene (**3a**), thus giving access to a propargylamine unsubstituted at the propargyl position (**4iia**). (*S*)-(-)-Citronellal (**4j**) was coupled with piperidine (**2a**) and phenylacetylene (**3a**), with the expected product **4jaa** being obtained in a relatively short reaction time, in a high yield, and with some diastereoselectivity. In this case, the two diastereoisomers could be separated by column chromatography.

In view of the low to moderate diastereoselectivities observed for 2-methylpiperidine (**2d**) and *N*-methyl- α -methylbenzylamine (**2g**), we speculated that use of proline derivatives might give better results. Indeed, (*R*)-2-(methoxymethyl)pyrrolidine (**2i**, Scheme 2) afforded the benzaldehyde derivative **4aia** in 84% yield and 94:6 *dr*, this ratio matching the values obtained for *ent*-**4aia** with other methodologies.^[17] A slightly lower isolated yield and diastereoselectivity were recorded when decanal was used as the aldehyde (Scheme 2, compound **4gia**). In this case, the relative (*R,R*) stereochemistry assigned for the major diastereoisomer was established by correlation of the chemical shifts of the NCH propargylic hydrogen atoms in the two diastereoisomers with those of **4aia**. Finally, it is noteworthy that the coupling of benzaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**) was demonstrated to be scalable to 5 mmol, giving rise to propargylamine **4aaa** in 67% isolated yield.

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Table 2. Three-component coupling of aldehydes, amines, and alkynes catalyzed by CuNPs/TiO₂.^[a,b]

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), CuNPs/TiO₂ (0.5 mol-%), neat, 70 °C. [b] Isolated yield. [c] Diastereomeric ratio measured by GC from the reaction crude.

Stability and Recycling of the Catalyst

The catalyst could be handled in air and all the experiments were carried out without air exclusion; these are advantages that make the process operationally simple. It is worth mentioning that, despite the fact of the small amount of catalyst utilized (20 mg), it could easily be recovered by filtration (after addition of diethyl ether) and reused. Good catalyst

performance in the coupling of benzaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**) was observed over four consecutive cycles (Figure 1).

The copper level in the aqueous solution between cycles was detected to be 40 ppb (ICP-MS), which practically rules out any loss of catalytic activity through metal leaching. More probably, loss of catalyst mass during filtration (through a fritted glass filter) could account for the decrease

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Scheme 2. Diastereoselective synthesis of propargylamines **4aia** and **4gia**. Figure 1. Recycling of CuNPs/TiO₂ in the synthesis of propargylamine **4aaa**.

ing tendency in the conversion observed in the recycling experiments. Although the above analysis points to a process that is heterogeneous in nature, we cannot in principle dismiss the possibility that the support acts as a reservoir for metal species that leach into solution and readsorb. Processes of this kind, however, have mainly been shown to occur for nanoparticle suspensions of the catalytically active group VIII transition metals.^[18]

Comparison with Other Catalysts

Any laboratory-made catalyst should, as a matter of principle, be more efficient than commercially available catalysts used for the same purpose, and so we undertook a comparative study of the reactivity of CuNPs/TiO₂ with those of different commercially available copper sources (Table 3). The standard conditions were applied to the reaction of benzaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**) at different catalyst loadings. Copper metal, CuO, and Cu₂O (10 mol-%) gave rise to the expected propargylamine **4aaa** with moderate levels of conversion (Table 3, Entries 1–3). CuCl and CuCl₂ (both at 10 mol-%)

were the best commercial catalysts, although prolonged heating was necessary and the levels of conversion were not as high as desirable (Table 3, Entries 4 and 6). The levels of conversion for CuCl and CuCl₂ dropped when the catalyst loading was reduced to 1 mol-%, with concomitant formation of the diyne derived from **3a** (Table 3, Entries 5 and 7). A similar trend was observed for CuBr and CuI at 1 mol-% (Table 3, Entries 8 and 9). Therefore, the nanosized character of our catalyst and its distribution on the support seem to play decisive roles in its higher performance (Table 3, Entry 10). Furthermore, the easy catalyst preparation, lower metal loading, lower reaction temperature, lack of requirement for an inert atmosphere, and absence of solvent are some clear advantages with respect to other catalysts based on CuNPs^[10] or other heterogeneous catalysts.^[7d]

Table 3. Synthesis of propargylamine **4aaa** catalyzed by different copper catalysts.^[a]

Entry	Cu catalyst	[Mol-%]	<i>t</i> [h]	Conversion [%] ^[b]
1	Cu	10	24	49
2	CuO	10	24	55
3	Cu ₂ O	10	24	63
4	CuCl	10	24	80
5	CuCl	1	24	63 ^[c]
6	CuCl ₂	10	24	76
7	CuCl ₂	1	24	64 ^[c]
8	CuBr	1	24	51 ^[d]
9	CuI	1	24	62 ^[d]
10	CuNPs/TiO ₂	0.5	7	98

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), catalyst, neat, 70 °C. [b] Levels of conversion determined by GC. [c] A 31% yield of the diyne derived from **3a** was obtained. [d] 15–26% yields of the diyne derived from **3a** were obtained.

Some Mechanistic Aspects

Tentative mechanisms for copper-catalyzed A³ coupling have been proposed. They normally invoke the participation of copper acetylides, which react with the iminium ions generated in situ from the aldehydes and secondary amines to give the corresponding propargylamines.^[19] This class includes the mechanism reported by Lakshmi Kantam et al. when nanocrystalline CuO was used as catalyst.^[10b] The mechanism depicted by Kidwai et al. however, is somewhat dubious because, on one hand, Cu⁰NPs seem to undergo oxidative addition to the alkyne to give a mixed copper hydride acetylide, followed by deprotonation to afford the copper acetylide.^[10a] On the other hand, though, the authors suggested that the reaction might proceed through a free radical mechanism.

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We performed different experiments in order to gain an insight into the reaction mechanism of the A^3 coupling catalyzed by CuNPs. We observed that the addition of radical traps such as norbornene, cumene, or 2,6-di-*tert*-butylphenol did not inhibit the standard reaction, and no products originated from their reaction with alkynyl radicals were detected. Use of TEMPO led to some side reactions, although its coupling with the alkyne moiety was not observed either. Because the presence of free radicals might compromise the existence of the (originally) formyl hydrogen atom in the product (tertiary benzylic and propargylic N–C–H), two deuterium-labeling experiments were conducted (Scheme 3). The reaction of benzaldehyde (**1a**) with piperidine (**2a**) and deuterated phenylacetylene (**D₁-3a**) did not show any incorporation of deuterium into the product **4aaa** (Scheme 3, a), whereas the coupling of deuterated benzaldehyde (**D₁-1a**) with piperidine (**2a**) and phenylacetylene (**3a**) yielded the propargylamine **D₁-4aaa** with quantitative deuterium incorporation (Scheme 3, b). These results indicate that the reaction mechanism of the A^3 coupling catalyzed by CuNPs very likely does not involve free radicals.

Scheme 3. Deuterium-labeling experiments in the CuNPs/TiO₂-catalyzed A^3 coupling.

We have recently experimentally demonstrated that copper(I) acetylides are the true intermediate species in copper-catalyzed azide/alkyne cycloadditions involving unsupported CuNPs in the presence of triethylamine and THF as solvent.^[13b] We also showed that, in the absence of base, CuNPs enhance the acidity of a terminal alkyne in water, by coordination to the carbon–carbon triple bond, thus enabling the formation of the corresponding copper(I) acetylide. When phenylacetylene was allowed to react with the CuNPs/TiO₂ catalyst at 70 °C a yellow color attributable to copper(I) phenylacetylide (**5a**) appeared over the support (Scheme 4).^[20] This organocopper compound displayed great stability and insolubility, not undergoing any noticeable change after exposure to air for several weeks. It is generally recommended that copper acetylides be preserved under inert atmosphere in the dark, so we cannot rule out a stabilization effect arising from the fact that **5a** remains

anchored to the heterogeneous catalyst (**5a**/TiO₂); some Cu–O bonding between Cu atoms and the O of TiO₂ has been reported on specific surfaces.^[21] When **5a**/TiO₂ was washed with diethyl ether, in order to remove any trace of phenylacetylene, and warmed to 70 °C, the corresponding diyne **6a** was formed and the yellow color on the solid vanished. Addition of benzaldehyde (**1a**) and piperidine (**2a**) to that solid furnished the A^3 product **4aaa** together with a minor amount of diyne **6a**. These experiments therefore imply that copper(I) acetylides are the true intermediates in this methodology and suggest a process that is heterogeneous in nature.

Scheme 4. Formation of copper(I) phenylacetylide from CuNPs/TiO₂.

On the basis of the experiments described above and our previous experience in acetylene chemistry and CuNPs, we propose an ionic reaction mechanism (Scheme 5) that includes: a) coordination of the alkyne to the CuNPs with concomitant activation of the C–H bond, b) formation of the corresponding copper(I) acetylide on the titania support (the acetylenic hydrogen might form a hydroxy group with a surface oxygen atom or might be attached to a bridging oxygen of the support),^[22] and c) addition of the copper(I) acetylide to the iminium ion generated in situ from the aldehyde and the amine, with the subsequent formation of the propargylamine, water, and regeneration of the catalytically active species.

The Ketone/Amine/Alkyne (KA²) Coupling

Ketones are much more reluctant than aldehydes to react in the three-component reaction. In fact, the KA² coupling remained unknown until the recent discovery by the group of Van der Eycken, in which microwave irradiation was found to assist this process with CuI catalysis (20 mol-%) at 100 °C in the absence of solvent.^[23] Only cyclohexanone and its derivatives were reported to be reactive enough to produce the expected propargylamines in moderate to good yields. More recently, a wider substrate scope has been achieved with the aid of gold catalysis.^[24] We studied the CuNPs/TiO₂-catalyzed KA² coupling of cyclohexanone (**1k**, Scheme 6) with piperidine (**2a**) and phenylacetylene (**3a**) and observed that, under the above solvent-free conditions, maximum yields of ca. 35% were recorded. The yields

Scheme 5. Proposed reaction mechanism for the A³ coupling catalyzed by CuNPs/TiO₂.

could be substantially improved [also in the case of *N*-methylbenzylamine (**2e**)] by use of dichloromethane as solvent (Scheme 6). In contrast, pentan-3-one could be coupled with *N*-methylbenzylamine and phenylacetylene in only 30% yield, even with use of dichloromethane as solvent.

Scheme 6. KA² coupling catalyzed by CuNPs/TiO₂.

Conclusions

A series of catalysts composed of copper nanoparticles on different supports have been tested in three-component couplings of aldehydes, secondary amines, and terminal alkynes. The CuNPs/TiO₂ catalyst, in which copper is present mainly as Cu₂O, manifested the best performance in this reaction at 70 °C under solvent-free conditions. An array of structurally different propargylamines has been synthesized, in moderate to excellent yields (52–99%) and with low metal loadings (0.5 mol-%), from all sorts of aryl-, alkyl-,

and cycloalkyl-substituted substrates. The catalyst could be recycled, with negligible leaching (40 ppb), and reused over four cycles, providing excellent to good yields of the product (98–79%). Moreover, higher catalytic activity with less byproduct formation was observed for CuNPs/TiO₂ than for some commercial copper sources. In addition, two examples of ketone/amine/alkyne coupling have been reported, in this case in the presence of dichloromethane as solvent. Finally, different experiments ruled out a free-radical mechanism and unveiled the participation of copper(I) acetylides as reaction intermediates in a process that is heterogeneous in nature.

Experimental Section

General: Anhydrous copper(II) chloride (97%, Aldrich), lithium powder (MEDALCHEM S. L.), and DTBB (4,4'-di-*tert*-butylbiphenyl, Aldrich) were commercially available. Degussa P25 TiO₂ (60% anatase, 40% rutile) with a surface area of 50 m² g⁻¹ was used as support, after being calcined in air at 500 °C for 5 h. All the starting materials and other reagents were commercially available of the best grade (Aldrich, Acros, Alfa Aesar) and were used without further purification. 1-Deuterio-2-phenylacetylene (D₁-**3a**) was prepared by stirring phenylacetylene (**3a**) and D₂O at 70 °C overnight, followed by a standard extraction workup.^[14c] 1-Deuterio-1-phenylmethanone (D₁-**1a**) was obtained from ethyl benzoate by reduction with LiAlD₄^[25] (THF, 0 °C, 4 h, room temp.) and oxidation with Dess–Martin's reagent (CH₂Cl₂, 2 h, room temp.). THF was dried in a Sharlab PS-400-3MD solvent purification system with an alumina column. All reactions were carried out with a multireactor apparatus and the corresponding reactor tubes. Melting points were obtained with a Reichert Thermovar apparatus. Optical rotations were measured with a Perkin–Elmer 341 polarimeter with a thermally jacketed 5-cm cell at approximately 20 °C. Concentrations (*c*) are given in g/100 mL and [*α*] values are given in units of 10⁻¹ deg cm² g⁻¹. NMR spectra were recorded with Bruker Avance 300 and 400 spectrometers (300 and 400 MHz for ¹H NMR; 75 and 100 MHz for ¹³C NMR); peak assignments were achieved on the basis of DEPT experiments and estimation with the ACD/Laboratories 6.0 program; chemical shifts (*δ*) are given in parts per million and coupling constants (*J*) in Hertz. Infrared analysis was performed with a Jasco 4100LE (Pike MIRacle ATR) spectrophotometer; wavenumbers (*ν*) are given in cm⁻¹. Mass spectra (EI) were obtained at 70 eV with an Agilent 5973 spectrometer; fragment ions in *m/z* with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV with a Finnigan MAT95S spectrometer. The purities of volatile compounds and the chromatographic analyses (GLC) were determined with a Hewlett–Packard HP-5890 instrument and an Agilent 5973 GC–MS apparatus. Retention times (*t_R*) were obtained with the latter under the following conditions: HP5MS capillary column (30 m, 0.25 mm diameter, 0.25 μm film thickness) with helium (54.1 mL min⁻¹) as carrier gas, *T*_{injector} = 250 °C, *T*_{column} = 60 °C (3 min) and 60–270 °C (15 °C min⁻¹). Column chromatography was performed with silica gel 60 of 40–60 microns (hexane/EtOAc as eluent).

Typical Procedure for the Preparation of CuNPs/TiO₂: Anhydrous copper(II) chloride (135 mg, 1 mmol) was added at room temperature under argon to a suspension of lithium (14 mg, 2 mmol) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) in THF (2 mL). The reaction mixture, which was initially dark blue, rapidly

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changed to black, indicating that the suspension of copper nanoparticles had been formed. This suspension was diluted with THF (18 mL) followed by addition of TiO_2 (1.28 g). The resulting mixture was stirred for 1 h at room temperature and filtered, and the solid was washed with THF (20 mL) and dried under vacuum.

General Procedure for the A^3 Coupling Catalyzed by CuNPs/ TiO_2 :

The aldehyde **1** (1.0 mmol), amine **2** (1.0 mmol), and alkyne **3** (1.0 mmol) were placed in a reactor tube containing CuNPs/ TiO_2 (20 mg, ca. 0.5 mol-%) without solvent. The reaction mixture was warmed to 70 °C without exclusion of air and monitored by TLC and/or GLC until total conversion of the starting material. EtOAc (2 mL) was added to the resulting mixture, followed by filtration through celite and washing with additional EtOAc (4 mL). The crude reaction product was purified by column chromatography (silica gel, hexane/EtOAc), except for compounds **4haa** and **4iha**, which were obtained in suitably pure states, to give the corresponding propargylamines **4**.

1-(1,3-Diphenylprop-2-yn-1-yl)piperidine (4aaa):^[26] Yellow solid. R_f = 0.44 (hexane/EtOAc 9:1); m.p. 65.9–66.4 °C. t_R = 16.90. ^1H NMR (300 MHz, CDCl_3): δ = 1.35–1.49 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.50–1.67 (m, 4 H, $2 \times \text{CH}_2\text{CH}_2\text{N}$), 2.55 (t, J = 5.4 Hz, 4 H, $2 \times \text{NCH}_2$), 4.79 (s, 1 H, NCH), 7.23–7.39 (m, 6 H, $6 \times \text{ArH}$), 7.48–7.55 (m, 2 H, $2 \times \text{ArH}$), 7.60–7.68 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 24.6, 26.3, 50.8 ($5 \times \text{CH}_2$), 62.5 (NCH), 86.2 (CHC $\equiv$ C), 87.9 (CHC $\equiv$ C), 123.5 (ArC), 127.6, 128.2, 128.4, 128.7, 131.9 ($10 \times \text{ArCH}$), 138.7 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 3060, 2934, 2923, 2114, 1596, 1487, 1447, 1299, 1273, 1200, 757, 724, 693 cm^{-1} . MS (70 eV): m/z (%) = 275 (45) $[\text{M}]^+$, 274 (29), 232 (15), 199 (27), 198 (100), 192 (48), 191 (100), 190 (13), 189 (59), 165 (19), 115 (24).

4-(1,3-Diphenylprop-2-yn-1-yl)morpholine (4aba):^[26] Yellow oil. R_f = 0.16 (hexane/EtOAc 9:1). t_R = 16.40. ^1H NMR (400 MHz, CDCl_3): δ = 2.50–2.78 (m, 4 H, $2 \times \text{OCH}_2$), 3.60–3.85 (m, 4 H, $2 \times \text{NCH}_2$), 4.79 (s, 1 H, NCH), 7.24–7.41 (m, 6 H, $6 \times \text{ArH}$), 7.46–7.56 (m, 2 H, $2 \times \text{ArH}$), 7.58–7.70 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 50.0 ($2 \times \text{NCH}_2$), 62.2 (NCH), 67.3 ($2 \times \text{OCH}_2$), 85.2 (CHC $\equiv$ C), 88.7 (CHC $\equiv$ C), 123.1 (ArC), 127.9, 128.3, 128.5, 128.7, 131.9 ($10 \times \text{ArCH}$), 137.9 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 3059, 3029, 2853, 2820, 2361, 2331, 1597, 1489, 1450, 1284, 1245, 1114, 754, 724, 690 cm^{-1} . MS (70 eV): m/z (%) = 277 (15) $[\text{M}]^+$, 200 (21), 191 (100), 189 (25).

1-(1,3-Diphenylprop-2-yn-1-yl)-4-methylpiperidine (4aca):^[27] Yellow oil. R_f = 0.78 (hexane/EtOAc 8:2). t_R = 17.42. ^1H NMR (300 MHz, CDCl_3): δ = 0.89 (d, J = 6 Hz, 3 H, CH_3), 1.07–1.22 (m, 1 H, CHCH_3), 1.29–1.45, 1.49–1.74 ($2 \times$ m, 4 H, $2 \times \text{CH}_2\text{CH}_2\text{N}$), 2.18 (td, J = 11.7, 2.7 Hz, 1 H, NCHH), 2.50 (td, J = 11.1, 2.7 Hz, 1 H, NCHH), 2.59–2.72 (m, 1 H, NCHH), 2.88–3.01 (m, 1 H, NCHH), 4.81 (s, 1 H, NCH), 7.24–7.42 (m, 6 H, $6 \times \text{ArH}$), 7.47–7.55 (m, 2 H, $2 \times \text{ArH}$), 7.59–7.68 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 22.1 (CH_3), 30.9 (CHCH_3), 34.5, 34.9, 47.6, 52.8 ($4 \times \text{CH}_2$), 62.2 (NCH), 86.2 (CHC $\equiv$ C), 87.9 (CHC $\equiv$ C), 123.5 (ArC), 127.6, 128.2, 128.4, 128.6, 131.9 ($10 \times \text{ArCH}$), 138.8 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 3059, 3029, 2947, 2920, 1489, 1449, 1321, 1273, 754, 722, 690 cm^{-1} . MS (70 eV): m/z (%) = 289 (22) $[\text{M}]^+$, 288 (16), 213 (14), 212 (80), 192 (32), 191 (100), 189 (24), 115 (10).

1-(1,3-Diphenylprop-2-yn-1-yl)-2-methylpiperidine (4ada):^[28] Diastereoisomer mixture (5.9:1). Brown oil. R_f = 0.45, 0.55 (hexane/EtOAc 9:1).

Major diastereoisomer: t_R = 16.98. ^1H NMR (300 MHz, CDCl_3): δ = 1.18–1.28 (d, J = 6.0 Hz, 3 H, CH_3CH), 1.30–1.54, 1.57–1.79

($2 \times$ m, 6 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 2.14–2.37, 2.41–2.51 ($2 \times$ m, 2 H, NCH_2), 2.53–2.75 (m, 1 H, CHCH_3), 5.31 (s, 1 H, NCH), 7.20–7.40, 7.44–7.57, 7.58–7.74 ($3 \times$ m, 10 H, $10 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 20.9 (CH_3), 25.2, 26.4, 35.7 ($3 \times \text{CH}_2$), 47.0 (NCH_2), 55.3 (NCH), 56.2 (CHCH_3), 85.1 (CHC $\equiv$ C), 88.3 (CHC $\equiv$ C), 123.6, 139.8 ($2 \times \text{ArC}$), 127.3, 128.0, 128.2, 128.3, 128.4, 128.6, 131.9, 132.0 ($10 \times \text{ArCH}$) ppm. IR (neat): $\tilde{\nu}$ = 3055, 3025, 2929, 1598, 1489, 1448, 754, 722, 690 cm^{-1} . MS (70 eV): m/z (%) = 289 (18) $[\text{M}]^+$, 275 (33), 274 (100), 212 (46), 192 (76), 191 (100), 190 (14), 189 (56), 165 (19), 115 (11).

Selected data for the minor diastereoisomer: t_R = 17.18. ^1H NMR (300 MHz, CDCl_3): δ = 1.07–1.15 (d, J = 6.3 Hz, 3 H, CH_3CH), 3.05–3.23 (m, 1 H, CHCH_3), 5.06 (s, 1 H, NCH) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 26.7, 34.9 ($2 \times \text{CH}_2$), 54.5 (NCH), 58.6 (CHCH_3) ppm. MS (70 eV): m/z (%) = 289 (5) $[\text{M}]^+$, 274 (41), 212 (18), 192 (26), 191 (100), 189 (20).

N-Benzyl-N-methyl-1,3-diphenylprop-2-yn-1-amine (4aca):^[27] Yellow oil. R_f = 0.64 (hexane/EtOAc 9:1). t_R = 17.82. ^1H NMR (400 MHz, CDCl_3): δ = 2.24 (s, 3 H, CH_3), 3.68 (AB system, J = 13.2 Hz, 2 H, CH_2), 4.92 (s, 1 H, NCH), 7.22–7.44 (m, 11 H, $11 \times \text{ArH}$), 7.53–7.61 (m, 2 H, $2 \times \text{ArH}$), 7.65–7.71 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 38.2 (CH_3), 59.1 (CH_2), 59.7 (NCH), 84.9 (CHC $\equiv$ C), 88.8 (CHC $\equiv$ C), 123.4 (ArC), 127.2, 127.6, 128.3, 128.5, 129.2, 132.0 ($15 \times \text{ArCH}$), 139.2, 139.5 ($2 \times \text{ArC}$) ppm. IR (neat): $\tilde{\nu}$ = 3060, 3028, 2842, 2791, 1598, 1489, 1450, 1326, 1274, 1017, 754, 734, 690 cm^{-1} . MS (70 eV): m/z (%) = 311 (14) $[\text{M}]^+$, 234 (41), 220 (13), 192 (22), 191 (100), 189 (21), 91 (25).

1-[3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-yl]piperidine (4aab):^[26] Yellow oil. R_f = 0.42 (hexane/EtOAc 9:1). t_R = 17.93. ^1H NMR (300 MHz, CDCl_3): δ = 1.37–1.48 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.51–1.69 (m, 4 H, $2 \times \text{CH}_2\text{CH}_2\text{N}$), 2.55 (t, J = 5.3 Hz, 4 H, $2 \times \text{NCH}_2$), 3.81 (s, 3 H, CH_3), 4.77 (s, 1 H, NCH), 6.81–6.91 (m, 2 H, $2 \times \text{ArH}$), 7.22–7.38 (m, 3 H, $3 \times \text{ArH}$), 7.42–7.49 (m, 2 H, $2 \times \text{ArH}$), 7.60–7.66 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 24.6, 26.3, 50.8 ($5 \times \text{CH}_2$), 55.5 (OCH_3), 62.6 (NCH), 84.7 (CHC $\equiv$ C), 87.7 (CHC $\equiv$ C), 114.0, 127.5, 128.1, 128.7, 133.3 ($9 \times \text{ArCH}$), 115.6, 138.9, 159.5 ($3 \times \text{ArC}$) ppm. IR (neat): $\tilde{\nu}$ = 3059, 3028, 2932, 2218, 1604, 1508, 1491, 1450, 1289, 1271, 1244, 830, 805, 740, 699 cm^{-1} . MS (70 eV): m/z (%) = 305 (23) $[\text{M}]^+$, 304 (13), 228 (38), 222 (38), 221 (100), 207 (15), 179 (10), 178 (28).

1-{1-Phenyl-3-[4-(trifluoromethyl)phenyl]prop-2-yn-1-yl}piperidine (4aac): Yellow oil. R_f = 0.54 (hexane/EtOAc 9:1). t_R = 16.68. ^1H NMR (300 MHz, CDCl_3): δ = 1.38–1.51 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.51–1.68 (m, 4 H, $2 \times \text{CH}_2\text{CH}_2\text{N}$), 2.55 (t, J = 5.3 Hz, 4 H, $2 \times \text{NCH}_2$), 4.80 (s, 1 H, NCH), 7.26–7.41 (m, 3 H, $3 \times \text{ArH}$), 7.55–7.65 (m, 6 H, $6 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 24.6, 26.3, 50.9 ($5 \times \text{CH}_2$), 62.5 (NCH), 86.7 (CHC $\equiv$ C), 89.1 (CHC $\equiv$ C), 124.1 (q, $^1J_{\text{C,F}}$ = 1083 Hz, CF_3), 125.3 (q, $^3J_{\text{C,F}}$ = 15; 2 Hz $\times$ ArCH), 127.3 (ArC), 127.8, 128.3, 128.6, 132.2 ($7 \times \text{ArCH}$), 129.9 (q, $^2J_{\text{C,F}}$ = 129 Hz, ArC), 138.3 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 2934, 1614, 1450, 1321, 1125, 1065, 929, 840, 807, 744 cm^{-1} . MS (70 eV): m/z (%) = 343 (24) $[\text{M}]^+$, 342 (15), 267 (15), 266 (93), 260 (34), 259 (100), 191 (14), 189 (22). HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}$ 343.1548; found 343.1537.

1-(3-Cyclohexyl-1-phenylprop-2-yn-1-yl)piperidine (4aad):^[26] Yellow oil. R_f = 0.48 (hexane/EtOAc 9:1). t_R = 15.63. ^1H NMR (300 MHz, CDCl_3): δ = 1.26–1.60 (m, 12 H, $6 \times \text{CH}_2$), 1.67–1.90 (m, 4 H, $2 \times \text{CH}_2$), 2.38–2.58 (m, 5 H, $2 \times \text{CH}_2$, CHCH_3), 4.55 (d, J = 1.8 Hz, 1 H, NCH), 7.22–7.37 (m, 3 H, $3 \times \text{ArH}$), 7.53–7.59 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 24.7, 24.9, 26.1, 26.3, 33.3, 50.6 ($10 \times \text{CH}_2$), 29.3 (CHCH_3), 62.0 (NCH), 76.0

(CHC≡C), 92.4 (CHC≡C), 127.3, 127.9, 128.7 (5×ArCH), 139.5 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 3060, 3027, 2928, 2852, 2237, 1491, 1448, 1297, 1268, 988, 727, 696 cm⁻¹. MS (70 eV): m/z (%) = 281 (10) [M]⁺, 205 (16), 204 (100), 141 (12), 115 (17), 91 (13).

1-[1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl]piperidine (4baa):^[26] Yellow oil. R_f = 0.35 (hexane/EtOAc 8:2). t_R = 18.20. ¹H NMR (400 MHz, CDCl₃): δ = 1.38–1.49 (m, 2 H, CH₂CH₂CH₂N), 1.51–1.67 (m, 4 H, 2×CH₂CH₂N), 2.46–2.63 (m, 4 H, 2×NCH₂), 3.81 (s, 3 H, OCH₃), 4.73 (s, 1 H, NCH), 6.85–6.93 (m, 2 H, 2×ArH), 7.28–7.37 (m, 3 H, 3×ArH), 7.47–7.58 (m, 4 H, 4×ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 24.6, 26.3, 50.7 (5×CH₂), 55.4 (OCH₃), 61.9 (NCH), 86.6 (CHC≡C), 87.7 (CHC≡C), 113.5, 128.1, 128.4, 129.7 (9×ArCH), 123.5, 130.8 (2×ArC), 131.9 (ArCH), 159.1 (ArCOCH₃) ppm. IR (neat): $\tilde{\nu}$ = 3054, 2931, 1609, 1584, 1508, 1488, 1441, 1272, 1244, 1168, 1035, 754, 690 cm⁻¹. MS (70 eV): m/z (%) = 305 (16) [M]⁺, 222 (23), 221 (100), 178 (15).

1-[1-(2-Iodophenyl)-3-phenylprop-2-yn-1-yl]piperidine (4caa): Yellow oil. R_f = 0.79 (hexane/EtOAc 7:3). t_R = 18.48. ¹H NMR (400 MHz, CDCl₃): δ = 1.39–1.62 [m, 6 H, (CH₂)₃CH₂N], 2.44–2.72 (m, 4 H, 2×NCH₂), 4.83 (s, 1 H, NCH), 7.26 (s, 1 H, ArH), 7.29–7.38 (m, 4 H, 4×ArH), 7.47–7.54 (m, 2 H, 2×ArH), 7.70–7.75 (dd, J = 10.8, 1.6 Hz, 1 H, ArH), 7.85–7.92 (dd, J = 10.4, 2.4 Hz, 1 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 24.7, 26.2, 60.6 (5×CH₂), 65.9 (NCH), 85.6 (CHC≡C), 88.8 (CHC≡C), 101.6 (CI), 123.3 (ArC), 127.6, 128.3, 128.4, 129.3, 130.3, 131.9, 140.2 (9×ArCH), 140.9 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 3055, 2930, 1562, 1488, 1461, 1451, 1434, 1298, 1266, 1203, 753, 742, 689 cm⁻¹. MS (70 eV): m/z (%) = 401 (30) [M]⁺, 400 (24), 318 (42), 317 (61), 274 (13), 199 (16), 198 (100), 191 (43), 190 (23), 189 (88), 188 (12), 187 (10), 165 (12), 115 (11). HRMS (EI): m/z calcd. for C₂₀H₂₀IN 401.0640; found 401.0610.

1-[1-(3-Nitrophenyl)-3-phenylprop-2-yn-1-yl]piperidine (4daa):^[29] Yellow oil. R_f = 0.27 (hexane/EtOAc 9:1). t_R = 20.15. ¹H NMR (400 MHz, CDCl₃): δ = 1.38–1.49 (m, 2 H, CH₂CH₂CH₂N), 1.52–1.70 (m, 4 H, 2×CH₂CH₂N), 2.35–2.73 (m, 4 H, 2×NCH₂), 4.87 (s, 1 H, NCH), 7.30–7.42, 7.47–7.61 (2×m, 6 H, 6×ArCH), 8.01 (d, J = 7.7 Hz, 1 H, ArCH), 8.15 (d, J = 7.7 Hz, 1 H, ArCH), 8.55 (s, 1 H, ArCH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 24.4, 26.3, 50.8 (5×CH₂), 61.8 (NCH), 84.3 (CHC≡C), 89.2 (CHC≡C), 122.7, 123.5, 128.5, 128.6, 129.1, 132.0, 134.6 (9×ArCH), 122.8, 141.5, 148.4 (3×ArC) ppm. IR (neat): $\tilde{\nu}$ = 3074, 2934, 2848, 2808, 1736, 1528, 1346, 1091, 754, 727, 690 cm⁻¹. MS (70 eV): m/z (%) = 320 (20) [M]⁺, 319 (12), 277 (10), 236 (45), 199 (18), 198 (100), 190 (26), 189 (48), 115 (13).

1-[1-(Naphthalen-2-yl)-3-phenylprop-2-yn-1-yl]piperidine (4eaa):^[26] Beige solid. R_f = 0.50 (hexane/EtOAc 9:1); m.p. 126.4–127.9 °C. t_R = 21.44. ¹H NMR (300 MHz, CDCl₃): δ = 1.36–1.50 (m, 2 H, CH₂CH₂CH₂N), 1.52–1.71 (m, 4 H, 2×CH₂CH₂N), 2.60 (s, 4 H, 2×NCH₂), 4.94 (s, 1 H, NCH), 7.32–7.40 (m, 3 H, 3×ArH), 7.44–7.52 (m, 2 H, 2×ArH), 7.53–7.61 (m, 2 H, 2×ArH), 7.73–7.79 (m, 1 H, ArH), 7.80–7.92 (m, 3 H, 3×ArH), 8.08 (s, 1 H, ArH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 24.6, 26.3, 60.0 (5×CH₂), 62.7 (NCH), 86.2 (CHC≡C), 88.2 (CHC≡C), 123.5 (ArC), 126.0, 126.1, 126.8, 127.4, 127.7, 127.9, 128.2, 128.5, 132.0 (12×ArCH), 133.1, 133.2, 136.4 (3×ArC) ppm. IR (neat): $\tilde{\nu}$ = 3055, 2934, 2356, 1596, 1507, 1488, 1445, 1435, 1266, 784, 762, 695. MS (70 eV): m/z (%) = 325 (14) [M]⁺, 242 (47), 241 (100), 240 (12), 239 (33), 198 (18).

1-[1-(Benzofuran-2-yl)-3-phenylprop-2-yn-1-yl]piperidine (4faa): Yellow solid. R_f = 0.48 (hexane/EtOAc 9:1); m.p. 93.5–96.9 °C. t_R = 20.13. ¹H NMR (300 MHz, CDCl₃): δ = 1.38–1.52 (m, 2 H, CH₂CH₂CH₂N), 1.53–1.79 (m, 4 H, 2×CH₂CH₂N), 2.66 (t, J =

5.3 Hz, 4 H, 2×NCH₂), 5.01 (d, J = 0.9 Hz, 1 H, NCH), 6.91 (t, J = 0.9 Hz, 1 H, ArH), 7.18–7.38 (m, 5 H, 5×ArH), 7.49–7.60 (m, 4 H, 4×ArH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 24.4, 26.1, 50.8 (5×CH₂), 57.2 (NCH), 83.5 (CHC≡C), 87.1 (CHC≡C), 106.5, 111.7, 121.0, 122.9, 124.3, 128.4, 128.5, 132.0 (10×ArCH), 128.1, 154.7, 155.4 (4×ArC) ppm. IR (neat): $\tilde{\nu}$ = 2936, 2799, 2094, 1313, 1295, 1255, 985, 762, 753, 743, 695 cm⁻¹. MS (70 eV): m/z (%) = 315 (15) [M]⁺, 232 (32), 231 (100), 202 (17), 102 (10). HRMS (EI): m/z calcd. for C₂₂H₂₁NO 315.1623; found 315.1660.

1-(1-Phenyldodec-1-yn-3-yl)piperidine (4gaa): Yellow oil. R_f = 0.44 (hexane/EtOAc 8:2). t_R = 16.90. ¹H NMR (400 MHz, CDCl₃): δ = 0.88 (t, J = 6.8 Hz, 3 H, CH₃), 1.23–1.77 (m, 22 H, 11×CH₂), 2.43–2.56, 2.63–2.77 (2×m, 4 H, 2×NCH₂), 3.41–3.55 (m, 1 H, NCH), 7.26–7.32 (m, 3 H, 3×ArH), 7.40–7.48 (m, 2 H, 2×ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 14.3 (CH₃), 22.8, 24.7, 26.4, 27.1, 29.5, 29.6, 29.7, 32.1, 33.6 (13×CH₂), 58.8 (NCH), 85.7 (CHC≡C), 88.4 (CHC≡C), 123.8 (ArC), 127.9, 128.3, 131.9 (5×ArCH) ppm. IR (neat): $\tilde{\nu}$ = 3064, 3025, 2924, 2853, 1488, 1465, 1098, 754, 689 cm⁻¹. MS (70 eV): m/z (%) = 325 (0.15) [M]⁺, 199 (15), 198 (100), 115 (11). HRMS (EI): m/z calcd. for C₂₃H₃₅N 325.2770; found 325.2731.

1-(1-Cyclohexyl-3-phenylprop-2-yn-1-yl)piperidine (4haa):^[26] Brown oil. R_f = 0.48 (hexane). t_R = 16.26. ¹H NMR (400 MHz, CDCl₃): δ = 0.87–1.09 (m, 2 H, CH₂), 1.13–1.81 (m, 13 H, 5×CH₂, 2×CHH, CHCH₂), 2.03, 2.10 (2×d, J = 13.2, 11.2 Hz, 2 H, 2×CHH), 2.35–2.45, 2.57–2.68 (2×m, 4 H, 2×NCH₂), 3.10 (d, J = 9.6 Hz, 1 H, NCH), 7.21–7.32 (m, 3 H, 3×ArH), 7.39–7.48 (m, 2 H, 2×ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 24.9, 26.2, 26.4, 26.9, 30.6, 31.5 (8×CH₂), 39.7 (CHCH₂), 50.9 (2×NCH₂), 64.5 (NCH), 86.3 (CHC≡C), 87.9 (CHC≡C), 123.9, 127.7, 128.3, 131.8 (5×ArCH) ppm. IR (neat): $\tilde{\nu}$ = 3054, 3025, 2926, 2849, 1597, 1488, 1443, 1102, 996, 753, 689 cm⁻¹. MS (70 eV): m/z (%) = 281 (0.08) [M]⁺, 199 (16), 198 (100), 115 (18).

N-(1-Cyclohexyl-3-phenylprop-2-yn-1-yl)-N-methylaniline (4hfa):^[30] Yellow oil. R_f = 0.85 (hexane/EtOAc 8:2). t_R = 17.98. ¹H NMR (400 MHz, CDCl₃): δ = 1.06–1.34 (m, 4 H, 2×CH₂), 1.65–1.93 (m, 6 H, 3×CH₂), 2.16–2.18 (m, 1 H, CHCH₂), 2.91 (s, 3 H, CH₃), 4.34 (d, J = 12.8 Hz, 1 H, NCH), 6.72–6.79 (m, 1 H, ArH), 6.84–6.92 (m, 2 H, 2×ArH), 7.23–7.30 (m, 5 H, 5×ArH), 7.36–7.43 (m, 2 H, 2×ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 26.1, 26.3, 26.6, 30.3, 30.8 (5×CH₂), 33.6 (CHCH₂), 41.5 (CH₃), 58.9 (NCH), 85.4 (CHC≡C), 87.6 (CHC≡C), 111.8, 114.4, 117.7, 128.0, 128.3, 129.2, 131.8 (10×ArCH), 123.5, 150.7 (2×ArC) ppm. IR (neat): $\tilde{\nu}$ = 3058, 3030, 2850, 1596, 1502, 1489, 1275, 750, 689 cm⁻¹. MS (70 eV): m/z (%) = 303 (6) [M]⁺, 301 (12), 290 (13), 280 (11), 221 (18), 220 (100), 218 (13), 208 (14), 207 (56), 204 (20), 191 (11), 179 (11), 177 (16), 167 (16), 165 (14), 152 (12), 141 (12), 115 (20), 107 (22), 106 (28), 105 (32), 104 (25), 103 (10), 102 (11), 91 (17), 79 (15), 78 (20), 77 (50), 75 (14), 67 (13), 55 (11), 54 (11), 51 (21).

1-Cyclohexyl-N-methyl-3-phenyl-N-(1-phenylethyl)prop-2-yn-1-amine (4hga): Diastereoisomer mixture (1:0.80). Yellow solid. R_f = 0.85 (hexane/EtOAc 8:2); m.p. 83.8–86.4 °C. t_R = 17.96 and 18.15. ¹H NMR (300 MHz, CDCl₃): δ = 0.59–1.30, 1.38–1.88, 1.91–2.03 (3×m, 20 H, 10×CH₂), 1.33–1.37 (d, J = 6.6 Hz, 6 H, 2×CH₃CH), 2.05, 2.31 (2×s, 6 H, 2×NCH₃), 2.09–2.25 (m, 2 H, 2×CHCH₂), 3.07, 3.59 (2×d, J = 10.2 Hz, 2 H, 2×NCH), 3.61, 3.69 (2×q, J = 6.6 Hz, 2 H, 2×CHCH₃), 7.15–7.52 (m, 20 H, 20×ArH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 21.5, 22.1 (2×CH₃CH), 26.1, 26.2, 26.4, 26.8, 30.3, 31.4, 31.6 (10×CH₂), 33.0, 35.0 (2×CHCH₂), 40.2, 40.4 (2×NCH₃), 57.8, 60.0 (2×NCH), 63.1, 63.2 (2×CHCH₃), 86.3, 86.5 (2×CHC≡C), 87.6, 87.9 (2×CHC≡C), 123.9, 124.0, 126.7, 126.9, 127.5, 127.7,

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127.8, 128.3, 128.4, 131.8, 131.9 ($20 \times \text{ArCH}$), 146.1, 146.9 ($2 \times \text{ArC}$) ppm. IR (neat): $\tilde{\nu} = 3061, 3027, 2930, 2847, 2359, 2342, 1596, 1488, 1449, 753, 700, 689 \text{ cm}^{-1}$. MS (70 eV) ($t_R = 17.96$): m/z (%) = 331 (0.07) $[\text{M}]^+$, 249 (10), 248 (100), 144 (58), 115 (14), 105 (52), 77 (9). MS (70 eV) ($t_R = 18.15$): m/z (%) = 331 (0.09) $[\text{M}]^+$, 249 (20), 248 (100), 144 (61), 115 (15), 105 (56), 77 (10). HRMS (EI): m/z calcd. for $\text{C}_{24}\text{H}_{29}\text{N}$ 331.2300; found 331.2331.

1-(1-Cyclohexylnon-2-yn-1-yl)piperidine (4hae):^[31] Yellow oil. $R_f = 0.79$ (hexane/EtOAc 9:1). $t_R = 15.68$. ^1H NMR (400 MHz, CDCl_3): $\delta = 0.89$ (t, $J = 6.9 \text{ Hz}$, 3 H, CH_3), 1.02–1.82 (m, 23 H, $11 \times \text{CH}_2$, CHCH_2), 1.88–2.08 (m, 2 H, CH_2), 2.19–2.24 (td, $J = 6.9$, $J = 2.1 \text{ Hz}$, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.25–2.35 (m, 2 H, CH_2), 2.48–2.57 (m, 2 H, CH_2), 2.84 (dt, $J = 9.7$, $J = 1.8 \text{ Hz}$, 1 H, NCH) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.2$ (CH_3), 18.8, 22.8, 24.9, 26.3, 26.4, 26.9, 28.7, 29.4, 30.6, 31.3, 31.5 ($13 \times \text{CH}_2$), 39.8 (CHCH_2), 50.7 ($2 \times \text{CH}_2$), 64.1 (NCH), 77.5 ($\text{CHC}\equiv\text{C}$), 85.9 ($\text{CHC}\equiv\text{C}$) ppm. IR (neat): $\tilde{\nu} = 2924, 2851, 1449, 1299, 1261, 1230, 1156, 1102, 996 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 289 (0.21) $[\text{M}]^+$, 207 (31), 206 (100).

N,N-Diethyl-3-phenylprop-2-yn-1-amine (4iha):^[32] Yellow oil. $R_f = 0.42$ (hexane/EtOAc 8:2). $t_R = 16.31$. ^1H NMR (300 MHz, CDCl_3): $\delta = 1.14$ (t, $J = 7.2 \text{ Hz}$, 6 H, $2 \times \text{CH}_3$), 2.67 (q, $J = 6.8 \text{ Hz}$, 4 H, $2 \times \text{CH}_2\text{CH}_3$), 3.68 (s, 2 H, CH_2N), 7.26–7.32 (m, 3 H, $3 \times \text{ArH}$), 7.39–7.46 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 12.5$ ($2 \times \text{CH}_3$), 41.4 ($2 \times \text{CH}_2\text{CH}_3$), 47.4 ($\text{CH}_2\text{C}\equiv\text{C}$), 83.9 ($\text{CHC}\equiv\text{C}$), 85.4 ($\text{CHC}\equiv\text{C}$), 123.3, 128.1, 128.4 ($5 \times \text{ArCH}$), 131.8 (ArC) ppm. IR (neat): $\tilde{\nu} = 3079, 3056, 2969, 2818, 1597, 1488, 1321, 1068, 754, 690 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 187 (10) $[\text{M}]^+$, 172(49), 116 (13), 115 (100).

1-[(5S)-5,9-Dimethyl-1-phenyldec-8-en-1-yn-3-yl]piperidine (4jaa): Diastereoisomer mixture (2.5:1) separated by column chromatography.

Major diastereoisomer: Yellow oil. $R_f = 0.61$ (hexane/EtOAc 9:1). $[\alpha]_D^{20} = -9.1$ ($c = 1.0$, CHCl_3). $t_R = 17.20$. ^1H NMR (400 MHz, CDCl_3): $\delta = 0.96$ (d, $J = 6.4 \text{ Hz}$, 3 H, CHCH_3), 1.09–1.28 (m, 1 H, CHCH_3), 1.36–1.49, 1.50–1.84 ($2 \times \text{m}$, 16 H, $5 \times \text{CH}_2$, $2 \times \text{CH}_3$), 1.90–2.11 (m, 2 H, CHCH_2CH_2), 2.39–2.53, 2.59–2.74 ($2 \times \text{m}$, 4 H, $2 \times \text{NCH}_2$), 3.51–3.63 (dd, $J = 8.4$, 6.8 Hz, 1 H, NCH), 5.06–5.16 [td, $J = 6.4$, $J = 1.5 \text{ Hz}$, 1 H, $\text{CHC}(\text{CH}_3)_2$], 7.22–7.33 (m, 3 H, $3 \times \text{ArH}$), 7.38–7.46 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 17.8$, 20.1, 25.9 ($3 \times \text{CH}_3$), 24.8, 25.6, 26.4, 36.7, 40.5, 50.7 ($8 \times \text{CH}_2$), 29.8 (CHCH_3), 56.4 (NCH), 85.6 ($\text{CHC}\equiv\text{C}$), 88.6 ($\text{CHC}\equiv\text{C}$), 123.8 (ArC), 125.0 ($\text{C}=\text{CH}$), 127.8, 128.3, 131.8 ($5 \times \text{ArCH}$), 131.3 ($\text{C}=\text{CH}$) ppm. IR (neat): $\tilde{\nu} = 2929, 2852, 1488, 1452, 1441, 1155, 1101, 754, 690 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 323 (0.29) $[\text{M}]^+$, 199 (17), 198 (100), 138 (17), 115 (18), 102 (9). HRMS (EI): m/z calcd. for $\text{C}_{23}\text{H}_{33}\text{N}$ 323.2613; found 323.2586.

Minor diastereoisomer: Yellow oil. $R_f = 0.45$ (hexane/EtOAc 9:1). $[\alpha]_D^{20} = -16.9$ ($c = 1.0$, CHCl_3). $t_R = 17.16$. ^1H NMR (400 MHz, CDCl_3): $\delta = 0.95$ (d, $J = 6.5 \text{ Hz}$, 3 H, CHCH_3), 1.18–1.31 (m, 1 H, CHCH_3), 1.33–1.52, 1.53–1.86 (m, 16 H, $5 \times \text{CH}_2$, $2 \times \text{CH}_3$), 1.93–2.09 (m, 2 H, CHCH_2CH_2), 2.40–2.57, 2.63–2.76 ($2 \times \text{m}$, 4 H, $2 \times \text{NCH}_2$), 3.53–3.63 (dd, $J = 10.2$, 4.6 Hz, 1 H, NCH), 5.05–5.18 [td, $J = 6.4$, 1.3 Hz, 1 H, $\text{CHC}(\text{CH}_3)_2$], 7.23–7.33 (m, 3 H, $3 \times \text{ArH}$), 7.39–7.47 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 17.8$, 19.4, 25.8 ($3 \times \text{CH}_3$), 24.8, 25.5, 26.4, 37.7, 40.4, 50.9 ($8 \times \text{CH}_2$), 29.9 (CHCH_3), 56.9 (NCH), 85.9 ($\text{CHC}\equiv\text{C}$), 88.2 ($\text{CHC}\equiv\text{C}$), 123.8 (ArC), 125.0 ($\text{C}=\text{CH}$), 127.9, 128.3, 131.8 ($5 \times \text{ArCH}$), 131.3 ($\text{C}=\text{CH}$) ppm. IR (neat): $\tilde{\nu} = 2929, 2852, 1488, 1452, 1441, 1155, 1102, 754, 690 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 323 (0.25) $[\text{M}]^+$, 199 (17), 198 (100), 138 (15), 115 (18), 102 (10). HRMS (EI): m/z calcd. for $\text{C}_{23}\text{H}_{33}\text{N}$ 323.2613; found 323.2577.

(2R)-1-[(1R)-1,3-Diphenylprop-2-yn-1-yl]-2-(methoxymethyl)-pyrrolidine (4aia): Diastereoisomer mixture (15:1). **Major diastereoisomer:** Pale yellow oil. $R_f = 0.24$ (hexane/EtOAc 9:1). $[\alpha]_D^{20} = +89.8$ ($c = 1.0$, CHCl_3) [ref.^[17a] –107.8 ($c = 0.34$, CHCl_3), *ent*-4aia]. $t_R = 17.41$. ^1H NMR (300 MHz, CDCl_3): $\delta = 1.56$ –1.76, 1.88–2.02 ($2 \times \text{m}$, 4 H, $\text{CH}_2\text{CH}_2\text{CH}$), 2.52–2.64, 2.68–2.81 ($2 \times \text{m}$, 2 H, NCH_2), 3.24–3.36 (m, 1 H, CHCH_2), 3.42 (s, 3 H, OCH_3), 3.43–3.58 (m, 2 H, CH_2O), 5.33 (s, 1 H, NCH), 7.24–7.38, 7.47–7.54, 7.60–7.67 ($3 \times \text{m}$, 10 H, ArH) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 23.2$, 28.8 ($\text{CH}_2\text{CH}_2\text{CH}$), 48.1 (NCH_2), 57.6, 59.3, 60.3 (NCH, OCH_3 , CHCH_2), 77.16 (CH_2O), 86.3 ($\text{CHC}\equiv\text{C}$), 87.7 ($\text{CHC}\equiv\text{C}$), 123.5 (ArC), 127.4, 128.1, 128.2, 128.3, 128.4, 131.9 ($10 \times \text{ArCH}$), 139.9 (ArC) ppm. IR (neat): $\tilde{\nu} = 3059, 3028, 2871, 1598, 1489, 1448, 1104, 1070, 754, 725, 690 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 305 (0.20) $[\text{M}]^+$, 261 (16), 260 (82), 192 (54), 191 (100), 189 (36), 165 (12). HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}$ 305.1780; found 305.1785.

(2R)-2-(Methoxymethyl)-1-[(3R)-1-phenyldec-1-yn-3-yl]pyrrolidine (4gia): Diastereoisomer mixture (10:1). **Major diastereoisomer:** Yellow oil. $R_f = 0.16$ (hexane/EtOAc 9:1). $[\alpha]_D^{20} = 71.9$ ($c = 1.0$, CHCl_3). $t_R = 18.53$. ^1H NMR (400 MHz, CDCl_3): $\delta = 0.88$ (t, $J = 6.8 \text{ Hz}$, 3 H, CH_3CH_2), 1.22–1.37, 1.39–1.95 ($2 \times \text{m}$, 20 H, $10 \times \text{CH}_2$), 2.74 (q, $J = 8.4 \text{ Hz}$, 1 H, NCH_AH_B), 2.89–2.97 (m, 1 H, NCH_AH_B), 3.07–3.16 (m, 1 H, CHCH_2O), 3.28–3.44 (m, 2 H, CH_2O), 3.37 (s, 3 H, CH_3O), 3.90 (t, $J = 7.4 \text{ Hz}$, 1 H, NCH), 7.25–7.31, 7.39–7.45 ($2 \times \text{m}$, 5 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.3$ (CH_3CH_2), 22.8, 23.3, 26.9, 28.5, 29.5, 29.6, 29.7, 32.1, 35.3, 47.8 ($11 \times \text{CH}_2$), 53.9 (NCH), 59.3 (OCH_3), 60.6 (CHCH_2O), 76.5 (CH_2O), 85.2 ($\text{CHC}\equiv\text{C}$), 88.9 ($\text{CHC}\equiv\text{C}$), 123.7 (ArC), 127.9, 128.3, 131.9 ($5 \times \text{ArCH}$) ppm. IR (neat): $\tilde{\nu} = 3055, 3035, 2922, 2853, 1597, 1488, 1457, 1441, 1106, 754, 722, 690 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 355 (0.19) $[\text{M}]^+$, 311 (29), 310 (100), 229 (10), 228 (65), 143 (13), 129 (16), 128 (20), 117 (19), 115 (28), 95 (13), 91 (26), 70 (49). HRMS (EI): m/z calcd. for $\text{C}_{24}\text{H}_{37}\text{NO}$ 355.2875; found 355.2895.

1-(1-Deuterio-1,3-diphenylprop-2-yn-1-yl)piperidine (D₁-4aaa):^[33] Yellow solid. $R_f = 0.42$ (hexane/EtOAc 9:1); m.p. 55.7–57.6 °C. $t_R = 16.82$. ^1H NMR (300 MHz, CDCl_3): $\delta = 1.30$ –1.42 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.42–1.62 (m, 4 H, $2 \times \text{CH}_2\text{CH}_2\text{N}$), 2.49 (t, $J = 5.3 \text{ Hz}$, 4 H, $2 \times \text{NCH}_2$), 7.16–7.32 (m, 6 H, $6 \times \text{ArH}$), 7.40–7.49 (m, 2 H, $2 \times \text{ArH}$), 7.52–7.60 (m, 2 H, $2 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 24.6$, 26.3, 50.8 ($5 \times \text{CH}_2$), 62.1 (t, $^1J_{\text{C,D}} = 84 \text{ Hz}$, NCD), 86.1 ($\text{CHC}\equiv\text{C}$), 88.0 ($\text{CHC}\equiv\text{C}$), 123.5 (ArC), 127.6, 128.2, 128.4, 128.7, 131.9 ($10 \times \text{ArCH}$), 138.6 (ArC) ppm. IR (neat): $\tilde{\nu} = 3052, 3016, 2934, 2923, 2366, 1953, 1596, 1487, 1446, 1103, 757, 718, 693 \text{ cm}^{-1}$. MS (70 eV): m/z (%) = 277 (10) $[\text{M} + 1]^+$, 276 (50) $[\text{M}]^+$, 275 (22), 200 (26), 199 (100), 193 (43), 192 (100), 191 (12), 190 (40), 189 (11), 166 (12), 116 (17).

General Procedure for the KA² Coupling Catalyzed by CuNPs/TiO₂: Cyclohexanone (**1k**, 0.1 mL, 1.0 mmol), an amine **2** (1.0 mmol), and phenylacetylene (**3a**, 0.1 mL, 1.0 mmol) were placed in a reactor tube containing CuNPs/TiO₂ (20 mg, ca. 0.5 mol-%) and CH_2Cl_2 (2 mL). The reaction mixture was warmed to 70 °C without exclusion of air and monitored by TLC and/or GLC until total conversion of the starting materials. EtOAc (2 mL) was added to the resulting mixture, followed by filtration through celite and washing with additional EtOAc (4 mL). The crude reaction product was purified by column chromatography (silica gel, hexane/EtOAc) to give the corresponding pure propargylamines **4kaa** and **4kea**.

1-[1-(Phenylethynyl)cyclohexyl]piperidine (4kaa):^[24] Pale yellow solid. $R_f = 0.15$ (hexane/EtOAc 9:1); m.p. 35.5–38.9 °C. $t_R = 15.99$. ^1H NMR (300 MHz, CDCl_3): $\delta = 1.07$ –1.79, 1.99–2.15, 3.58–3.78

(3 × m, 20 H, 10 × CH₂), 7.21–7.34, 7.38–7.48 (2 × m, 5 H, 5 × ArCH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 23.2, 24.9, 25.9, 26.8, 35.9, 47.3 (10 × CH₂), 59.4 (NC), 86.2 (C≡CAr), 90.9 (C≡CAr), 123.9 (ArC), 127.7, 128.3, 131.8 (5 × ArCH) ppm. IR (neat): ν̄ = 3055, 2986, 2920, 2851, 1709, 1488, 1443, 1291, 1092, 759, 692 cm⁻¹. MS (70 eV): m/z (%) = 267 (50) [M]⁺, 266 (20), 253 (15), 252 (80), 238 (25), 225 (41), 224 (100), 211 (15), 210 (41), 196 (10), 190 (27), 155 (15), 142 (10), 141 (43), 128 (25), 127 (17), 115 (40), 91 (11), 84 (23).

N-Benzyl-N-methyl-1-(phenylethynyl)cyclohexanamine (4kea): Pale yellow oil. *R*_f = 0.67 (hexane/EtOAc 9:1). *t*_R = 18.23. ¹H NMR (400 MHz, CDCl₃): δ = 1.24–1.42, 1.56–1.83, 2.03–2.14 (3 × m, 10 H, 5 × CH₂), 2.20 (s, 3 H, CH₃), 3.68 (s, 2 H, NCH₂), 7.20–7.25 (m, 1 H, ArH), 7.26–7.35 (m, 5 H, 5 × ArH), 7.36–7.41 (m, 2 H, 2 × ArH), 7.45–7.52 (m, 2 H, 2 × ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 23.0, 25.9, 36.8, 55.8 (6 × CH₂), 35.5 (CH₃), 59.2 (NC), 85.66 (C≡CAr), 90.89 (C≡CAr), 123.9 (ArC), 126.7, 127.8, 128.3, 128.4, 128.9, 131.9 (10 × ArCH), 141.3 (ArC) ppm. IR (neat): ν̄ = 3028, 2929, 2853, 1597, 1489, 1443, 1290, 1057, 754, 735, 690 cm⁻¹. MS (70 eV): m/z (%) = 303 (23) [M]⁺, 302 (11), 288 (38), 274 (11), 261 (23), 260 (100), 247 (21), 246 (44), 226 (14), 142 (19), 141 (14), 128 (13), 127 (12), 115 (31), 102 (23), 91 (83), 77 (10), 68 (10), 65 (11). HRMS (EI): m/z calcd. for C₂₂H₂₅N 303.1987; found 303.1989.

Supporting Information (see footnote on the first page of this article): TEM micrograph and size distribution of the CuNPs/TiO₂ catalyst; ¹H and ¹³C NMR spectra of the propargylamines 4.

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A³ coupling catalyzed by ultrafine copper nanoparticles on titania under solvent-free conditions is described. Some examples of KA² coupling are also reported. The catalyst is reusable and exhibited better per-

formance than commercially available copper catalysts. The participation of copper(I) acetylides in a heterogeneous process has been demonstrated.

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Three-Component Coupling of Aldehydes, Amines, and Alkynes Catalyzed by Oxidized Copper Nanoparticles on Titania

Keywords: Multicomponent reactions / Nanoparticles / Copper / Alkynes / Aldehydes / Amines