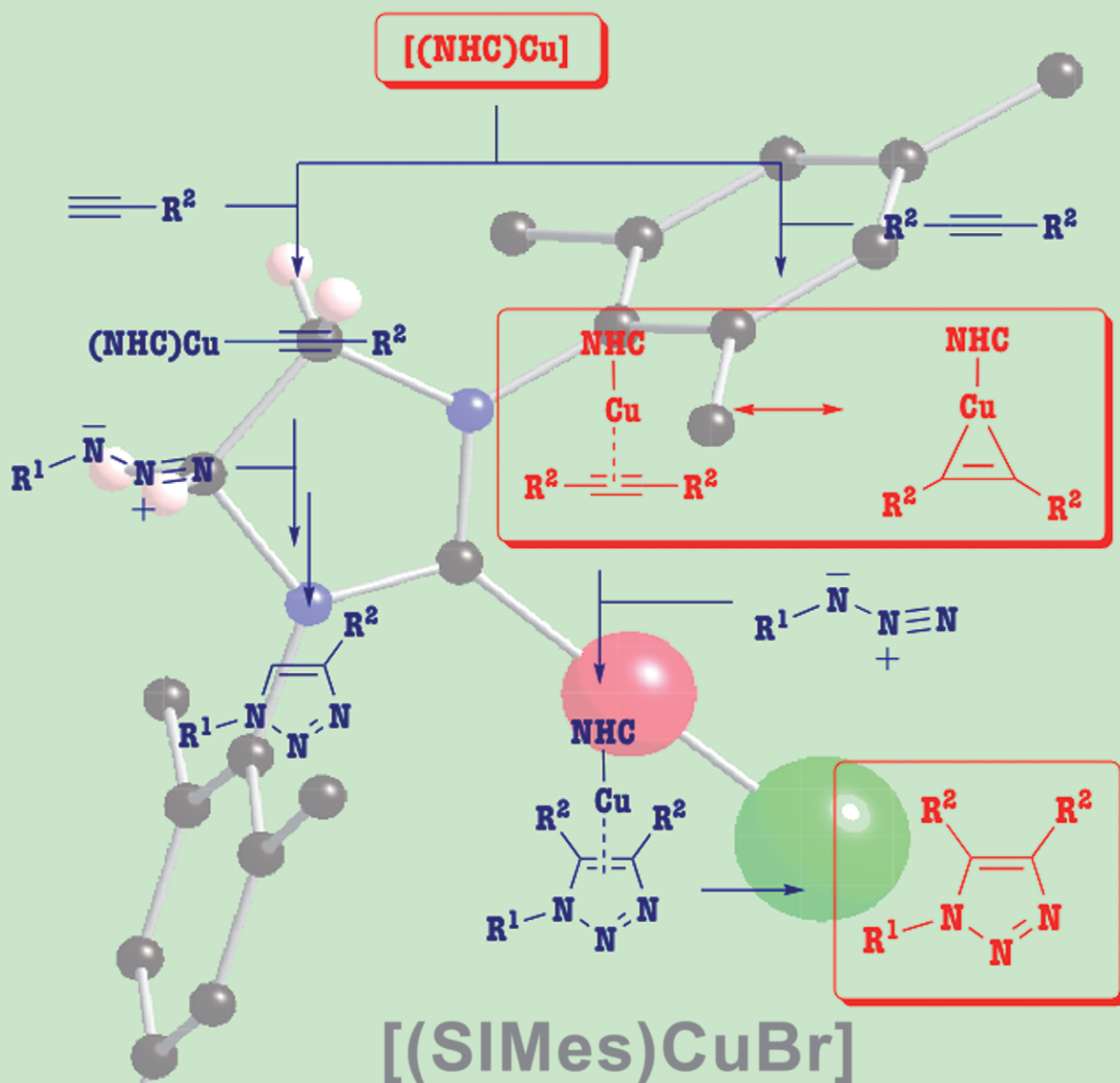


# (NHC)Copper(I)-Catalyzed [3+2] Cycloaddition of Azides and Mono- or Disubstituted Alkynes



The use of N-heterocyclic carbene ligands in click chemistry results in excellent reaction rates and allows for the unprecedented copper-catalyzed cycloaddition of internal alkynes

# (NHC)Copper(I)-Catalyzed [3 + 2] Cycloaddition of Azides and Mono- or Disubstituted Alkynes

Silvia Díez-González,<sup>[a]</sup> Andrea Correa,<sup>[b]</sup> Luigi Cavallo,<sup>[b]</sup> and Steven P. Nolan\*<sup>[a]</sup>

**Abstract:** A versatile and highly efficient catalyst for the Huisgen cycloaddition reaction has been developed. Previously isolated or in situ generated azides yielded 1,2,3-triazoles with differently substituted alkynes in the presence of a [(NHC)CuBr] complex (NHC = N-heterocyclic carbene). Extremely high reaction rates and excel-

lent yields were obtained in all cases. This catalytic system fulfils the requirements of “click chemistry” with its mild and convenient conditions, nota-

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bly in water or solvent free reactions and simple isolation with no purification step. Furthermore, for the first time, an internal alkyne was successfully used in this copper-catalyzed cycloaddition reaction. DFT calculations on this particular system allowed for the proposition of a new mechanistic pathway for disubstituted alkynes.

## Introduction

The reaction of azides and alkynes yielding 1,2,3-triazoles<sup>[1]</sup> is the most popular Huisgen 1,3-dipolar cycloaddition.<sup>[2]</sup> Since the recent discovery of copper(I) as an efficient and regioselective catalyst for this process,<sup>[3]</sup> it has become the best “click” reaction<sup>[4]</sup> to date and found a myriad of applications in chemical synthesis, biology and material science.<sup>[5]</sup> Most often, catalytic systems enabling this transformation consist of a copper(II) salt and a reducing agent. Metallic copper<sup>[3b]</sup> or clusters<sup>[6]</sup> can also be employed but little attention has been paid to cuprous salts due to their inherent thermodynamic instability and the formation of undesired alkyne-alkyne coupling products observed in their presence.<sup>[3a]</sup> On the other hand, nitrogen-<sup>[7]</sup> or phosphorus-based<sup>[8]</sup> ligands have been shown to protect Cu<sup>I</sup> during the cycloaddition

reaction and even modulate the reactivity of the copper salt.<sup>[9]</sup>

As part of our continuing efforts to broaden the scope of NHC-containing (NHC = N-heterocyclic carbene) transition-metal complexes,<sup>[10]</sup> we recently reported the efficiency of [(NHC)CuCl] complexes in the hydrosilylation of carbonyl compounds.<sup>[11]</sup> The remarkable stability of these complexes toward heat, oxygen and moisture prompted us to test them in the Huisgen cycloaddition.

## Results and Discussion

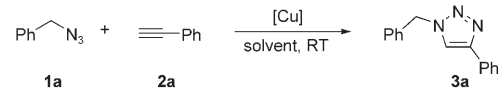
First, the two most commonly used carbene ligands, IPr (*N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and IMes (*N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), were tested (Table 1). While reaction of benzyl azide and phenylacetylene in the presence of [(IPr)CuCl]<sup>[11b]</sup> under standard cycloaddition conditions only led to partial conversion to triazole **3a**, an important increase in yield was observed with [(IMes)CuCl]<sup>[12]</sup> (entries 1 and 2). Interestingly, its saturated analogue, [(SIMes)CuCl]<sup>[11a]</sup> (SIMes = *N,N'*-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene), was even more efficient (entry 3). Moreover, replacing the chloride on the copper center by a bromide further accelerated the reaction (entry 4). Poor conversions were obtained with organic solvents such as THF, CH<sub>2</sub>Cl<sub>2</sub> or *t*BuOH, but pleasantly, a strong acceleration was observed in water (entry 5). It is well recognized that Diels–Alder reactions can be greatly accelerated in water,<sup>[13]</sup> but there are fewer

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Table 1. Catalyst optimization studies.<sup>[a]</sup>



Entry	[Cu] (mol %)	Solvent [mL]	<i>t</i> [h]	Yield [%]
1	[(IPr)CuCl] (5)	water/ <i>t</i> BuOH (3)	18	18
2	[(IMes)CuCl] (5)	water/ <i>t</i> BuOH (3)	18	65
3	[(SiMes)CuCl] (5)	water/ <i>t</i> BuOH (3)	18	93
4	[(SiMes)CuBr] (5)	water/ <i>t</i> BuOH (3)	9	95
5	[(SiMes)CuBr] (5)	water (1)	0.5	98
6	[(SiMes)CuBr] (0.8)	neat	0.3	98
7	CuBr	neat	1	0

[a] Isolated yields are the average of at least two runs.

examples of 1,3-dipolar cycloadditions in aqueous media with no organic co-solvents.<sup>[14]</sup>

It is important to note that according to “click laws”,<sup>[4]</sup> no precautions to exclude oxygen were taken in any of these reactions. No copper disproportionation with precipitation of metal copper, was observed in aqueous medium which shows the high ability of NHC groups to stabilize Cu<sup>I</sup> species. Furthermore, neat reactions proceeded smoothly with no detectable formation of undesirable byproducts (entry 6).<sup>[15]</sup> The catalyst loading could be lowered to 0.8 mol % with no loss of activity, ensuring straightforward reaction workups. Under optimized conditions, no formation of **3a** was observed with CuBr (entry 7), even after prolonged reaction time and higher catalyst loading, highlighting the key role of the ligand.

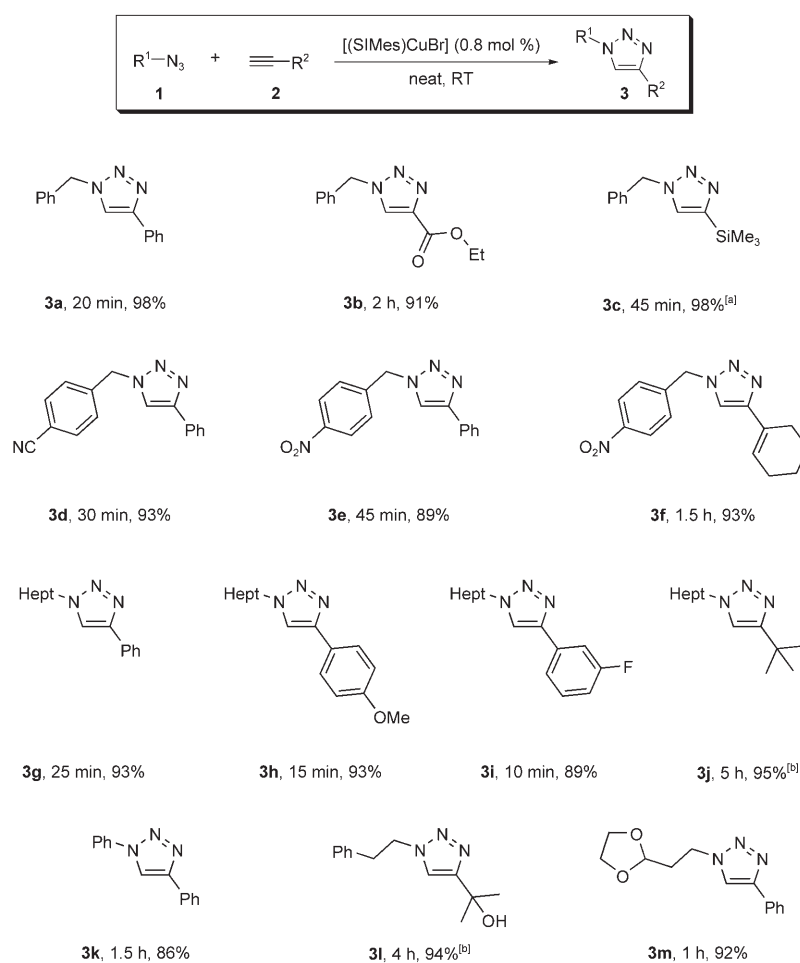
We then investigated the scope of this catalytic system. Results are presented in Scheme 1. All reactions proceeded smoothly to completion after short reaction times and triazoles **3** were isolated in excellent yield and high purity after simple filtration or extraction.

Electron-rich, electron-poor and/or hindered alkynes gave good yields. Enynes were also good reaction partners. For the organic azides, benzylic but also alkyl and aryl azides reacted in very short reaction times. In general, no significant difference of reactivity was observed when examining reactants with varied electronic properties, as required for click reactions. This is probably due to the high

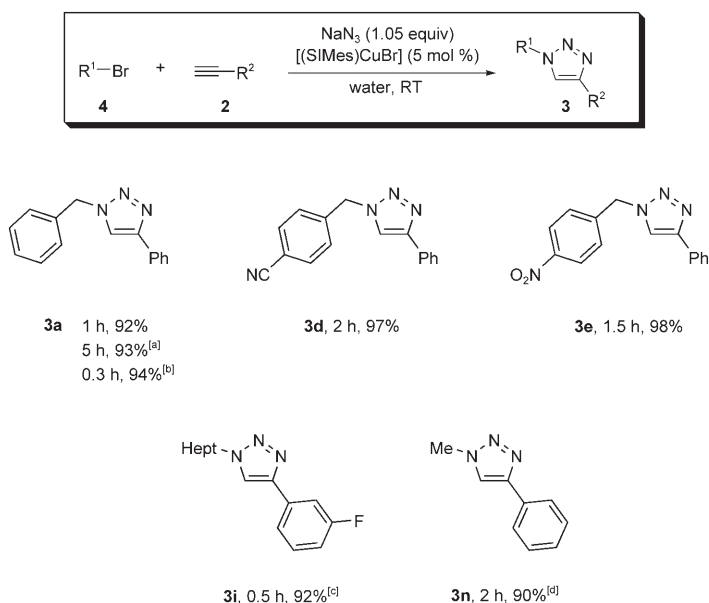
reactivity of [(SiMes)CuBr]. Only oily or low melting-point triazoles led to long or incomplete reactions. In these instances improved results were obtained by either increasing the reaction temperature (**3c**) or increasing the catalyst loading (**3j**).

Although organic azides are generally safe and stable toward water and oxygen,<sup>[16]</sup> those of low molecular weight can be difficult to handle.<sup>[17]</sup> Therefore, a methodology that avoids their isolation is desirable.<sup>[18]</sup> Pleasantly, azides generated in situ from the corresponding halides reacted at room temperature to efficiently yield triazoles **3** (Scheme 2). Again, water was the best solvent for this transformation.<sup>[19]</sup> To ensure short reaction times and, in the case of benzylic halides, minimize any decomposition of the starting material, 5 mol % of copper complex was used. However, at lower catalyst loading the reaction still proceeded to completion with excellent yields. For example, from benzyl bromide, **3a** was isolated in 86% yield after 3 h of reaction in the presence of 3 mol % of [(SiMes)CuBr] or 86% yield after 18 h in the presence of 2 mol % of copper complex.

Benzyl chloride was successfully used in the preparation of **3a**; methyltriazole **3n** could easily be prepared from methyl iodide avoiding the hazardous methyl azide. No



Scheme 1. Solvent-free [(SiMes)CuBr]-catalyzed formation of triazoles. [a] Reaction at 45°C. [b] 2 mol % [(SiMes)CuBr].



Scheme 2. [(SIMes)CuBr]-Catalyzed formation of triazoles from in situ generated azides. [a] From benzyl chloride. [b] From benzyl chloride,  $T = 70^\circ\text{C}$ . [c] Reaction at  $45^\circ\text{C}$ . [d] From methyl iodide.

competitive formation of N–H triazoles, resulting from the addition of an inorganic azide to the alkyne, was detected with this catalytic system.

Traditionally, the starting point of the catalytic cycle for the copper-catalyzed Huisgen reaction is considered to be the formation of a Cu–acetylide complex,<sup>[3a,20]</sup> which precludes internal alkynes as cycloaddition partners. Moreover, DFT calculations have shown that a hypothetical activation toward cycloaddition via coordination of the copper(I) to the alkyne (without its deprotonation) implies a higher energetic barrier than the one without metal catalyst.<sup>[21]</sup> Synthesis of 4,5-disubstituted triazoles can be achieved thermally<sup>[22]</sup> although regioselective reactions are limited in scope.<sup>[23]</sup> Other reported approaches to the preparation of this family of triazoles rely on different metals<sup>[24]</sup> or Lewis acids as catalysts<sup>[25]</sup> or on ring strain release from cyclooctyne.<sup>[26]</sup>

The high activity of [(SIMes)CuBr] in the Huisgen cycloaddition prompted us to test its reactivity with internal alkynes. In a preliminary experiment, we noticed that the reaction of benzyl azide with diphenylacetylene proceeded smoothly at  $70^\circ\text{C}$ , even under copper-free conditions. From a less activated alkyne, triazoles **3o–p** were formed in fair to good yields after heating at this temperature for 48 h (Table 2).<sup>[27]</sup> Optimization studies showed that both, copper salt and NHC ligand are essential for this transformation. While **3o** was formed in 34% conversion when the reaction was carried out with 5 mol % of CuBr, no significant formation of **3o** or **3p** (<5%) was

Table 2. [(SIMes)CuBr]-Catalyzed 1,3-dipolar cycloadditions of benzyl azides and 3-hexyne.<sup>[a]</sup>

R	Copper free	[(SIMes)CuBr] (5 mol %)
H	> 5 %	80 %
<i>p</i> -NO <sub>2</sub>	> 5 %	59 %

[a] NMR conversion.

observed in the absence of copper. To the best of our knowledge, this work represents the first intermolecular copper-catalyzed [3+2] cycloaddition of an azide and an internal alkyne.

For internal alkynes, no acceleration rate was observed in water. This fact might indicate distinct mechanistic pathways for terminal and internal alkynes.

Although the copper ion is generally considered a poor  $\pi$ -back-donating ion, a very recent report from Thompson and Bradley showed the essential role of ancillary ligands in determining its coordination to alkynes.<sup>[28]</sup> DFT calculations on the [(SIMes)Cu(EtC≡CEt)]<sup>+</sup> complex and, for the sake of comparison, [(MeCN)<sub>2</sub>Cu(EtC≡CEt)]<sup>+</sup> are used to shed light on the different catalytic behavior of these systems with respect to internal alkynes.

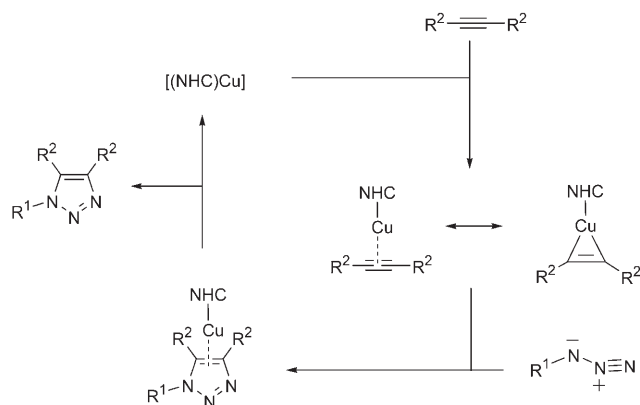
The binding energies,  $\Delta E_{\text{bind}}$ , reported in Table 3, indicate that  $\pi$ -coordination of the internal EtC≡CEt alkyne to [(SIMes)Cu]<sup>+</sup> is favored by almost 25 kcal mol<sup>-1</sup> relative to coordination to [(MeCN)<sub>2</sub>Cu]<sup>+</sup>. Decomposition of the total binding energy as  $\Delta E_{\text{bind}} = \Delta E_{\text{prep}} + \Delta E_{\text{inter}}$  indicates that the major difference between the two cationic Cu systems derives from the  $\Delta E_{\text{prep}}$  contribution, which is some 25 kcal mol<sup>-1</sup> higher for the [(MeCN)<sub>2</sub>Cu]<sup>+</sup> system. This energy difference is reasonable since alkyne coordination to [(MeCN)<sub>2</sub>Cu]<sup>+</sup> requires the noticeable bending of the [(MeCN)<sub>2</sub>Cu]<sup>+</sup> fragment from the strongly preferred linear geometry<sup>[29]</sup> to a MeCN–Cu–NCMe angle of  $105.2^\circ$  in [(MeCN)<sub>2</sub>Cu(EtC≡CEt)]<sup>+</sup>. This is in contrast to the [(SIMes)Cu]<sup>+</sup> system where very little structural rearrangement is required for  $\pi$ -coordination of the alkyne, with the final complex reaching the preferred linear two-coordination.<sup>[29]</sup> However, the interaction energy,  $\Delta E_{\text{inter}}$ , between the deformed EtC≡CEt and the deformed [(SIMes)Cu]<sup>+</sup> or [(MeCN)<sub>2</sub>Cu]<sup>+</sup> systems is rather similar. This indicates that the  $\pi$ -bonding/backbonding contribution to the Cu–alkyne

Table 3. DFT derived properties for free EtC≡CEt and for the [(SIMes)Cu(EtC≡CEt)]<sup>+</sup> and [(MeCN)<sub>2</sub>Cu(EtC≡CEt)]<sup>+</sup> complexes.

Property	Free EtC≡CEt	NHC–Cu <sup>+</sup> EtC≡CEt	(MeCN) <sub>2</sub> Cu <sup>+</sup> EtC≡CEt
EtC≡CEt bond [Å]	1.226	1.254	1.263
C≡C freq [cm <sup>-1</sup> ]	2281	2120	2069
C≡C–Et angle [°]	180.0	167.0	161.7
Cu–C bond [Å]	–	2.049	2.016
$\Delta E_{\text{bind}}$ [kcal mol <sup>-1</sup> ]	–	–41.0	–17.6
$\Delta E_{\text{prep}}$ [kcal mol <sup>-1</sup> ]	–	+4.8	+31.0
$\Delta E_{\text{inter}}$ [kcal mol <sup>-1</sup> ]	–	–45.8	–48.6

interaction is similar between the two systems. Insight can be obtained from structural and spectroscopic properties such as those reported in Table 3.<sup>[28,30]</sup> In both complexes the C≡C triple bond is significantly longer than in the free alkyne, and a remarkable deviation of the C≡C–Et angle from linearity, some 15–20°, occurs. Moreover, the C≡C stretching frequency in the two Cu complexes is about 150–200 cm<sup>-1</sup> lower than in the free alkyne. This indicates that π-backbonding is quite remarkable in both complexes, and in line with similar strong π-backbonding contributions reported for other Cu<sup>I</sup> complexes.<sup>[28]</sup> Finally, comparison between the properties of the [(SIMes)Cu(EtC≡CEt)]<sup>+</sup> and [(MeCN)<sub>2</sub>Cu(EtC≡CEt)]<sup>+</sup> complexes indicates that π-backbonding should be more relevant for the latter complex.

It is clear that the presence of a strong σ-donor ligand on the copper center enhances its catalytic activity in this cycloaddition reaction. We believe that the widely accepted reaction pathway for terminal alkynes<sup>[3a,21]</sup> is still applicable with our system. However, the beneficial effect of the NHC allows for the activation of disubstituted alkynes to proceed by a π-alkyne complex (Scheme 3).



Scheme 3. Proposed mechanism for the cycloaddition of internal alkynes.

## Conclusion

We have developed a versatile and highly efficient catalytic system for the Huisgen cycloaddition. Previously isolated or in situ generated azides yield 1,2,3-triazoles in water or solvent-free conditions in extremely short reaction times. The unprecedented use of an internal alkyne in this copper-catalyzed transformation has also been described. Further synthetic applications and mechanistic studies addressing the role of the NHC ligand in this transformation are currently ongoing in our laboratories.

## Experimental Section

**General considerations:** All reagents were used as purchased. Copper(I) bromide and sodium *tert*-butoxide were stored under argon in a glovebox. 1,3-Bis-(2,4,6-trimethylphenyl)imidazolium chloride (SIMes-HCl) was synthesized according to literature procedures<sup>[31]</sup> or can be purchased

from Strem. Flash column chromatography was performed on silica gel 60 (230–400 mesh). <sup>1</sup>H and <sup>13</sup>C Nuclear Magnetic Resonance (NMR) spectra were recorded on a 300 MHz spectrometer at room temperature. Chemical shifts (δ) are reported with respect to tetramethylsilane as internal standard in ppm. Assignments of some <sup>1</sup>H and <sup>13</sup>C NMR signals rely on COSY and/or HMBC experiments. Elemental analyses were performed at Robertson Microлит Laboratories, Inc., Madison, NJ, USA.

**[(SIMes)CuBr]:** In an oven-dried vial, copper(I) bromide (0.522 g, 3.63 mmol), SIMes-HCl (0.86 g, 2.52 mmol) and sodium *tert*-butoxide (0.243 g, 2.52 mmol) were loaded inside a glovebox and stirred in dry THF (18 mL) overnight at room temperature outside of the glovebox. After filtration of the reaction mixture through a plug of Celite, the filtrate was mixed with hexane to form a precipitate. A second filtration afforded the title complex as an off-white solid (0.808 g, 71%). <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]acetone): δ = 7.01 (s, 4H, H<sup>Ar</sup>), 4.16 (s, 4H, NCH<sub>2</sub>), 2.37 (s, 12H, ArCH<sub>3</sub>), 2.29 (s, 6H, ArCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 202.6 (C, NCN), 138.5 (C, C<sup>Ar</sup>), 135.3 (CH, C<sup>Ar</sup>), 135.0 (C, C<sup>Ar</sup>), 129.7 (CH, C<sup>Ar</sup>), 51.0 (CH<sub>2</sub>, NCH<sub>2</sub>), 21.0 (CH<sub>3</sub>, ArCH<sub>3</sub>), 18.0 (CH<sub>3</sub>, ArCH<sub>3</sub>); elemental analysis calcd (%) for C<sub>21</sub>H<sub>26</sub>BrCuN<sub>2</sub> (449.89): C 56.06, H 5.83, N 6.23; found: C 55.98, H 5.64, N 6.21.

**General procedure for the [3+2] cycloaddition of azides and terminal alkynes:** In a vial fitted with a screw cap, azide **1** (1.0 mmol), alkyne **2** (1.05 mmol) and [(SIMes)CuBr] (3.6 mg if 0.8 mol % or 9 mg if 2 mol %) were loaded. The reaction was allowed to proceed at room temperature (unless otherwise noted) and monitored by <sup>1</sup>H NMR analysis of aliquots. After total consumption of the starting azide, the solid product was collected by filtration and washed with water and pentane. When the corresponding triazole was an oil or a low-melting point solid, the reaction mixture was poured in an aqueous NH<sub>4</sub>Cl/diethyl ether mixture. After extraction of the aqueous phase with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated. In all examples, the crude products were estimated to be greater than 95% pure by <sup>1</sup>H NMR. Reported yields are isolated yields and are the average of at least two runs.

**General procedure for the [3+2] cycloaddition of in situ-generated azides and terminal alkynes:** The procedure described above was followed using an alkyl halide **4** (1.0 mmol), NaN<sub>3</sub> (68 mg, 1.05 mmol) and an alkyne **2** (1.05 mmol) in water (1 mL).

**4-Cyclohexenyl-1-(4-nitrobenzyl)-1H-1,2,3-triazole (3f):** Using the general procedure, from 4-(azidomethyl)-4-nitrobenzene (**1e**) (0.176 g) and 1-ethynylcyclohex-1-ene (**2f**) (0.118 mL), the title compound was isolated as a light yellow solid after filtration (0.263 g, 93%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.17 (d, *J* = 8.6 Hz, 2H, H<sup>Ar</sup>), 7.41 (s, 1H, NCH=), 7.40 (d, *J* = 8.6 Hz, 2H, H<sup>Ar</sup>), 6.51 (brs, 1H, =CHCH<sub>2</sub>), 5.62 (s, 2H, NCH<sub>2</sub>), 2.40–2.23 (m, 2H, cyclohexenyl), 2.23–2.11 (m, 2H, cyclohexenyl), 1.80–1.56 (m, 4H, cyclohexenyl); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 150.2 (C, NC=), 147.8 (C, C<sup>Ar</sup>), 142.1 (C, C<sup>Ar</sup>), 128.3 (CH, C<sup>Ar</sup>), 126.8 (C, C=CHCH<sub>2</sub>), 125.5 (CH, C=CHCH<sub>2</sub>), 124.1 (CH, C<sup>Ar</sup>), 118.5 (CH, NCH=), 52.8 (CH<sub>2</sub>, NCH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 22.0 (CH<sub>2</sub>); elemental analysis calcd (%) for C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub> (284.31): C 63.37, H 5.67, N 19.71; found: C 63.49, H 5.36, N 19.35.

**1-Heptyl-4-phenyl-1H-1,2,3-triazole (3g):** Using the general procedure from 1-azidoheptane (**1g**) (0.176 g) and phenylacetylene (**2a**) (0.11 mL), the title compound was isolated as a white solid after filtration (0.225 g, 93%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.85 (d, *J* = 7.1 Hz, 2H, H<sup>Ar</sup>), 7.75 (s, 1H, NCH=), 7.48–7.40 (m, 2H, H<sup>Ar</sup>), 7.40–7.29 (m, 1H, H<sup>Ar</sup>), 4.40 (t, *J* = 7.2 Hz, NCH<sub>2</sub>), 2.04–1.88 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 1.43–1.19 (m, 8H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.87 (t, *J* = 6.7 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 147.5 (C, NC=), 130.6 (C, C<sup>Ar</sup>), 128.7 (CH, C<sup>Ar</sup>), 127.9 (CH, C<sup>Ar</sup>), 125.5 (CH, C<sup>Ar</sup>), 119.4 (CH, NCH=), 50.2 (CH<sub>2</sub>, NCH<sub>2</sub>), 31.4 (CH<sub>2</sub>, heptyl), 30.2 (CH<sub>2</sub>, heptyl), 28.6 (CH<sub>2</sub>, heptyl), 26.3 (CH<sub>2</sub>, heptyl), 22.4 (CH<sub>2</sub>, heptyl), 13.9 (CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub> (243.35): C 74.03, H 8.70, N 17.27; found: C 73.79, H 8.60, N 17.18.

**1-Heptyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (3h):** Using the general procedure from 1-azidoheptane (**1g**) (0.176 g) and 1-ethynyl-4-methoxybenzene (**2g**) (0.136 mL), the title compound was isolated as a white solid after filtration (0.255 g, 93%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.76 (d, *J* = 8.8 Hz, 2H, H<sup>Ar</sup>), 7.66 (s, 1H, NCH=), 6.96 (d, *J* = 8.8 Hz, 2H,

H<sup>Ar</sup>), 4.37 (t,  $J=7.2$  Hz, NCH<sub>2</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 2.00–1.83 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 1.42–1.21 (m, 8H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.88 (t,  $J=6.8$  Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=159.4$  (C, C<sup>Ar</sup>), 147.5 (C, NC=), 126.9 (CH, C<sup>Ar</sup>), 123.4 (C, C<sup>Ar</sup>), 118.6 (CH, NCH=), 114.1 (CH, C<sup>Ar</sup>), 55.2 (CH<sub>2</sub>, NCH<sub>2</sub>), 50.3 (CH<sub>3</sub>, OCH<sub>3</sub>), 31.5 (CH<sub>2</sub>, heptyl), 30.3 (CH<sub>2</sub>, heptyl), 28.6 (CH<sub>2</sub>, heptyl), 26.4 (CH<sub>2</sub>, heptyl), 22.5 (CH<sub>2</sub>, heptyl), 14.0 (CH<sub>2</sub>CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>O (273.37): C 70.30, H 8.48, N 15.37; found: C 69.98, H 8.79, N 15.24.

**4-(3-Fluorophenyl)-1-heptyl-1H-1,2,3-triazole (3i):** a) Using the general procedure from 1-azidoheptane (**1g**) (0.176 g) and 1-ethynyl-3-fluorobenzene (**2i**) (0.121 mL), the title compound was isolated as an off-white solid after extraction (0.233 g, 89%). b) Using the general procedure from 1-bromoheptane (**4g**) (0.157 mL) and 1-ethynyl-3-fluorobenzene (**2i**) (0.121 mL), the title compound was isolated as a white solid after extraction (0.240 g, 92%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta=7.76$  (s, 1H, NCH=), 7.65–7.52 (m, 2H, H<sup>Ar</sup>), 7.43–7.34 (m, 1H, H<sup>Ar</sup>), 7.08–6.97 (m, 1H, H<sup>Ar</sup>), 4.41 (t,  $J=7.3$  Hz, NCH<sub>2</sub>), 2.02–1.89 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 1.43–1.20 (m, 8H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.89 (t,  $J=6.7$  Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=160.4$  (d,  $J=244$  Hz, C, C-F), 146.5 (C, NC=), 132.8 (d,  $J=8.5$  Hz, C, C<sup>Ar</sup>), 130.3 (d,  $J=8.5$  Hz, CH, C<sup>Ar</sup>), 121.2 (CH, C<sup>Ar</sup>), 119.8 (CH, NCH=), 114.7 (d,  $J=21$  Hz, CH, C<sup>Ar</sup>), 112.4 (d,  $J=23$  Hz, CH, C<sup>Ar</sup>), 50.4 (CH<sub>2</sub>, NCH<sub>2</sub>), 31.4 (CH<sub>2</sub>, heptyl), 30.2 (CH<sub>2</sub>, heptyl), 28.6 (CH<sub>2</sub>, heptyl), 26.3 (CH<sub>2</sub>, heptyl), 22.4 (CH<sub>2</sub>, heptyl), 13.9 (CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>15</sub>H<sub>20</sub>FN<sub>3</sub> (261.34): C 68.94, H 7.71, N 16.08. Found: C 68.87, H 7.99, N 15.85.

**4-tert-Butyl-1-heptyl-1H-1,2,3-triazole (3j):** Using the general procedure from 1-azidoheptane (**1g**) (0.176 g), 3,3-dimethylbut-1-yne (**2j**) (0.13 mL), and 2 mol % [(SImes)CuBr], the title compound was isolated as a light yellow oil after extraction (0.212 g, 95%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta=7.19$  (s, 1H, NCH=), 4.21 (t,  $J=7.4$  Hz, 2H, NCH<sub>2</sub>), 1.84–1.74 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 1.33–1.21 (m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.26 (s, CCH<sub>3</sub>) (17H), 0.80 (t,  $J=6.8$  Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=157.2$  (C, NC=), 118.1 (CH, NCH=), 49.8 (CH<sub>2</sub>, NCH<sub>2</sub>), 31.3 (CH<sub>2</sub>, heptyl), 30.4 (C, CCH<sub>3</sub>), 30.1 (CH<sub>3</sub>, CCH<sub>3</sub>), 28.4 (CH<sub>2</sub>, heptyl), 26.2 (CH<sub>2</sub>, heptyl), 22.2 (CH<sub>2</sub>, heptyl), 13.8 (CH<sub>2</sub>CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>13</sub>H<sub>25</sub>N<sub>3</sub> (223.36): C 69.91, H 11.28, N 18.81; found: C 70.01, H 11.56, N 18.76.

**2-(1-Phenethyl-1H-1,2,3-triazol-4-yl)propan-2-ol (3l):** Using the general procedure from (2-azidoethyl)benzene (**1l**) (0.147 g) and 2-methylbut-3-yn-2-ol (**2l**) (0.11 mL), the title compound was isolated as a white solid after filtration (0.216 g, 94%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta=7.39$ –7.21 (m, 3H, H<sup>Ar</sup>), 7.19 (s, 1H, NCH=), 7.18–7.02 (m, 2H, H<sup>Ar</sup>), 4.54 (t,  $J=7.6$  Hz, PhCH<sub>2</sub>), 3.19 (t,  $J=7.6$  Hz, NCH<sub>2</sub>), 2.99 (brs, 1H, OH), 1.59 (s, 6H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=155.3$  (C, NC=), 137.0 (C, C<sup>Ar</sup>), 128.7 (CH, C<sup>Ar</sup>), 128.6 (CH, C<sup>Ar</sup>), 127.0 (CH, C<sup>Ar</sup>), 119.5 (CH, NCH=), 68.3 (C, COH), 51.5 (CH<sub>2</sub>, NCH<sub>2</sub>), 36.7 (CH<sub>2</sub>, PhCH<sub>2</sub>), 30.4 (CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O (231.29): C 67.51, H 7.41, N 18.17; fund: C 67.45, H 7.48, N 18.87.

**1-[2-(1,3-Dioxolan-2-yl)ethyl]-4-phenyl-1H-1,2,3-triazole (3m):** Using the general procedure from (2-azidoethyl)-1,3-dioxolane (**1m**) (0.143 g) and phenylacetylene (**2a**) (0.11 mL), the title compound was isolated as a white solid after filtration (0.226 g, 92%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta=7.87$ –7.73 (m, 3H, H<sup>Ar</sup> + NCH=), 7.47–7.28 (m, 3H, H<sup>Ar</sup>), 4.94 (t,  $J=4.3$  Hz, 1H, OCHO), 4.55 (t,  $J=7.2$  Hz, 2H, NCH<sub>2</sub>), 4.04–3.92 (m, 2H, OCH<sub>2</sub>), 3.92–3.84 (m, 2H, OCH<sub>2</sub>), 2.37–2.27 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=147.4$  (C, NC=), 130.6 (C, C<sup>Ar</sup>), 128.7 (CH, C<sup>Ar</sup>), 128.0 (CH, C<sup>Ar</sup>), 125.6 (CH, C<sup>Ar</sup>), 119.8 (CH, NCH=), 101.4 (CH, OCHO), 65.0 (CH<sub>2</sub>, CH<sub>2</sub>O), 45.3 (CH<sub>2</sub>, NCH<sub>2</sub>), 34.0 (CH<sub>2</sub>, NCH<sub>2</sub>CH<sub>2</sub>); elemental analysis calcd (%) for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> (245.28): C 63.66, H 6.16, N 17.13; found: C 63.82, H 6.22, N 16.86.

**General procedure for the [3+2] cycloaddition of azides and 3-hexyne:** In a vial fitted with a screw cap, azide (1.0 mmol), 3-hexyne (0.120 mL, 1.05 mmol) and [(SImes)CuBr] (22 mg, 5 mol %) were loaded. The reaction was allowed to proceed at 70 °C for 48 h. The reaction mixture was allowed to cool down and poured on an aqueous NH<sub>4</sub>Cl/diethyl ether mixture. After extraction of the aqueous phase with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated. Due to their low melting point, triazoles

**3o** and **3p** could not be purified by recrystallization and the crude product was purified by flash chromatography on silica gel.

**1-Benzyl-4,5-diethyl-1H-1,2,3-triazole (3o):** Using the general procedure from benzyl azide **1a** (0.133 g) and after purification by flash chromatography on silica gel (pentane/diethyl ether 1:1), the title compound was isolated as a colorless oil (0.153 g, 71%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta=7.42$ –7.27 (m, 3H, H<sup>Ar</sup>), 7.21–7.18 (m, 2H, H<sup>Ar</sup>), 5.48 (s, 2H, NCH<sub>2</sub>), 2.65 (q,  $J=7.6$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.52 (q,  $J=7.6$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.28 (t,  $J=7.6$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.96 (t,  $J=7.6$  Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=146.39$  (C, NC=), 146.34 (C, NC=), 135.4 (C, C<sup>Ar</sup>), 128.88 (CH, C<sup>Ar</sup>), 128.81 (CH, C<sup>Ar</sup>), 128.1 (CH, C<sup>Ar</sup>), 51.8 (CH<sub>2</sub>, NCH<sub>2</sub>), 18.5 (CH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 15.9 (CH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 13.3 (CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub> (215.29): C 72.52, H 7.96, N 19.52; found: C 72.43, H 7.83, N 19.45.

**4,5-Diethyl-1-(4-nitrobenzyl)-1H-1,2,3-triazole (3p):** Using the general procedure from 4-(azidomethyl)-4-nitrobenzene (**1e**) (0.176 g) and after purification by flash chromatography on silica gel (diethyl ether), the title compound was isolated as a yellow oil (0.130 g, 48%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta=8.21$  (d,  $J=8.7$  Hz, H<sup>Ar</sup>), 7.30 (d,  $J=8.7$  Hz, H<sup>Ar</sup>), 5.58 (s, 2H, NCH<sub>2</sub>), 2.67 (q,  $J=7.5$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.55 (q,  $J=7.5$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.30 (t,  $J=7.5$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.01 (t,  $J=7.5$  Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta=147.71$  (C), 147.66 (C), 147.63 (C), 142.6 (C, C<sup>Ar</sup>), 127.7 (CH, C<sup>Ar</sup>), 124.1 (CH, C<sup>Ar</sup>), 50.7 (CH<sub>2</sub>, NCH<sub>2</sub>), 18.4 (CH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 15.8 (CH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 14.1 (CH<sub>3</sub>), 13.5 (CH<sub>3</sub>); elemental analysis calcd (%) for C<sub>13</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub> (260.29): C 59.99, H 6.20, N 21.52; found: C 60.34, H 6.33, N 21.76.

**Calculation details:** The DFT calculations were performed at the BP86/GGA level using the Gaussian03 package.<sup>[32]</sup> The split-valence + 1 polarization function SVP basis set of Ahlrichs was used for H, C and N.<sup>[33]</sup> The Stuttgart/Dresden relativistic small core pseudopotential was used for Cu.<sup>[34]</sup> The total binding energy  $\Delta E_{\text{bind}}$  was decomposed as  $\Delta E_{\text{bind}} = \Delta E_{\text{prep}} + \Delta E_{\text{inter}}$ , where  $\Delta E_{\text{prep}}$  is the energy required to prepare (deform) the free EtC≡CEt, [(SImes)Cu]<sup>+</sup> and [(MeCN)<sub>2</sub>Cu]<sup>+</sup> systems to the final geometry they have in the [(SImes)Cu(EtC≡CEt)]<sup>+</sup> and [(MeCN)<sub>2</sub>Cu(EtC≡CEt)]<sup>+</sup> complexes, while  $\Delta E_{\text{inter}}$  is the interaction energy between the deformed EtC≡CEt and the deformed [(SImes)Cu]<sup>+</sup> or [(MeCN)<sub>2</sub>Cu]<sup>+</sup> systems.<sup>[35]</sup>

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