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The synthesis of tetrasubstituted propargylamines from cyclohexanone by solvent-free copper(II) catalysis

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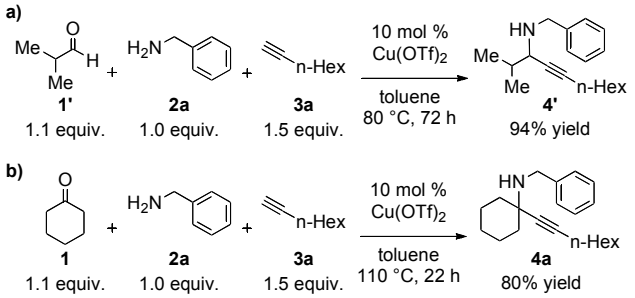
Copper(II) chloride catalyzes the three-component coupling of cyclohexanone, amines, and alkynes to produce tetrasubstituted propargylamines. As a wide range of substrates react without solvent, excess starting material, or other additives, water is the sole by-product. Studies demonstrate that this reaction is first order in copper, cyclohexanone, amine, and alkyne. These mild conditions allow for the first direct, catalytic synthesis of silyl-protected tetrasubstituted propargylamines.

Introduction

Background

Three-component couplings of aldehydes, alkynes, and amines are the most efficient method of forming trisubstituted propargylamine building blocks for rapid access to biologically active targets.[1-4] By circumventing the synthesis and isolation of imine intermediates for subsequent alkynylation,[3] these multicomponent[5] reactions reduce waste.[6] Most of these methods are optimized for the conversion of aldehydes to trisubstituted propargylamines and fail to convert ketones to tetrasubstituted propargylamines.[1] The ketimine formed in situ from the condensation of an amine and a ketone is a less reactive electrophile for nucleophilic attack than its aldimine counterpart.[7,8] Cyclohexanones represent an especially reactive class of ketones due to strain release upon attack.[9-11] In fact, cyclohexanones have been known to react under catalytic conditions developed for aldehydes.[12]

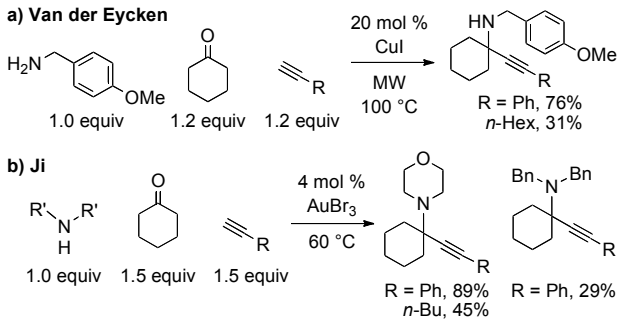


Scheme 1. Similar conditions allow for the three-component coupling of an aldehyde to **4'** or of cyclohexanone to **4a**.

For example, copper(II) triflate catalyzes the three-component coupling of 2-methyl-propanal (**1'**), benzylamine (**2a**), and 1-octyne (**3a**) in toluene (1.0 M) at 80 °C for a 94% yield of trisubstituted propargylamine **4'** (Scheme 1a). Scheme 1b demonstrates that by heating an additional 30 °C, the aldehyde can be replaced with cyclohexanone (**1**), and the same $Cu(OTf)_2$ catalyst, solvent, amine (**2a**), and terminal alkyne (**3a**) provides an 80% yield of tetrasubstituted propargylamine **4a**.[12]

The first catalytic propargylamine synthesis developed specifically to incorporate cyclohexanones was reported by Van der Eycken (Scheme 2a).[13] In analogy to ubiquitous A^3 (Aldehyde-Amine-Alkyne) couplings, they abbreviate this Ketone-Amine-Alkyne coupling as a KA^2 reaction. The microwave activated KA^2 coupling of primary benzylamines and phenylacetylene with cyclohexanones utilizes 20 mol% CuI at 100 °C.[13] The following year Ji reported that a lower 4 mol% loading of $AuBr_3$ catalyzes a similar three-component coupling of cyclic secondary amines at 60 °C (Scheme 2b).[14]

By operating solvent-free, both the methods of Van der Eycken and Ji (Scheme 2) produce significantly less waste than reactions carried out in toluene (Scheme 1b).[12-14] As solvents represent the largest amount of "auxiliary waste," discussions on atom economy[15] often highlight classes of greener solvents.[16] However, solvent-free reactions leave a smaller environmental footprint[17] and should be pursued and appear more frequently in publications on green chemistry.[16]



Scheme 2. The first three-component couplings designed for cyclohexanones

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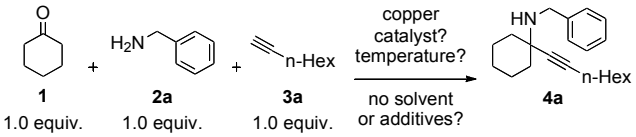
Ideally, the substrate scope in both of the methods dedicated to cyclohexanones (Scheme 2) would be expanded to include primary and secondary amines and non-aryl terminal alkynes. Both methods exhibit a precipitous drop in yield when alkyl alkynes are used in place of aryl alkynes. In the reaction of *p*-methoxybenzylamine with cyclohexanone catalyzed by 20 mol % CuI with microwave (MW) heating, phenylacetylene provides a 76% yield while 1-octyne provides a 31% yield (Scheme 2a).[13] Scheme 2b shows that the yield drops from 89% with phenylacetylene to 45% with 1-hexyne in the gold-catalyzed KA^2 reaction of morpholine and cyclohexanone.[14] In neither case is the lower yield with alkyl alkynes explained. When phenylacetylene is maintained in the reaction with cyclohexanone, the yield drops three-fold when acyclic *N,N*-dibenzylamine is utilized instead of cyclic morpholine (Scheme 2b).[14] In addition, although $AuBr_3$ is utilized at one-fifth the loading of CuI, it is over 100-times more expensive.[18]

Goal of green catalysis with expanded substrate scope

Lower catalyst loadings are a major focus in green chemistry,[6] but reducing waste from excess starting material receives little attention.[16] Starting material waste must be considered more seriously when a method is to be applied in total synthesis. When one or more of the coupling partners is a result of multiple synthetic steps, wasting any of this precious material due to a procedure that requires an excess of two of the three starting materials should be avoided. All three methods waste between 0.4–1.0 equivalents of starting materials (Schemes 1 and 2).[12-14] Therefore, in addition to removing solvent, another condition imposed upon the discovery of a more environmentally friendly three-component coupling was to use one equivalent of each reactant to avoid starting material waste. The formation of water as a by-product would then be the sole by-product of this KA^2 reaction of cyclohexanone.

Melding the different advantages of each of these three methods[12-14] into one synthetic protocol requires: 1) no solvent, 2) lower loadings of an inexpensive catalyst, 3) no other additives, 4) efficient reaction of primary and secondary amines, 5) high yields for aryl- and non-aryl alkynes, and 6) equimolar amounts of all three starting materials (Scheme 3).



Scheme 3. Basis for developing a green KA^2 with broader substrate scope.

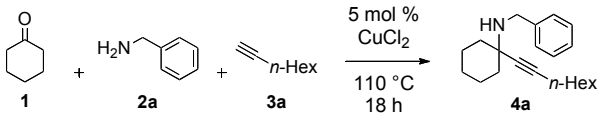
Herein, we report rate studies to elucidate the role of each constituent in our $CuCl_2$-catalyzed KA^2 reaction.[19] This direct formation of tetrasubstituted propargylic amines appears to be first order in each reaction component: copper, cyclohexanone, amine, and alkyne. Moreover, this efficient three-component coupling of cyclohexanone with either primary or secondary amines now produces an expanded range of silyl-protected propargylamines. The six goals set for atom economy[15] are achieved as the sole additive is the copper catalyst and the only by-product is one equivalent of water. Beginning the development of this reaction from a platform of green chemistry was the key to its discovery.

Results and discussion

Optimization of synthetic procedure

While copper(II) triflate catalyzes the reaction of a primary benzylamine, cyclohexanone, and an alkyl alkyne in high yield (Scheme 1b), removing the toluene solvent was the first condition for the development of a greener KA^2 reaction (Scheme 2). In a solution of toluene, the high reactivity of $Cu(OTf)_2$ results in excellent conversion to product **4a**, but side products appear under the same 10 mol % loading of catalyst in the absence of solvent. Thus, the development of a greener method began by testing a wide array of copper catalysts at half the catalyst loading (5 mol%) under solvent-free conditions, and with equimolar amounts of cyclohexanone **1**, benzylamine **2a**, and 1-octyne **3a**.

Table 1.[19] Cu halides are superior to triflates under solvent-free conditions



Entry	Copper Source	GC yield (%)
1	Cu(II) triflate	59
2	Cu(II) acetate	72
3	Cu(II) bromide	72
4	**Cu(II) chloride**	**99**
5	Cu(II) perchlorate hexahydrate	50
6	Cu(II) sulfate	38
7	Cu(II) ethoxide	52
8	Cu(II) bis(hexafluoroacetoacetonato) hydrate	27
9	Cu(II) hydroxide	32
10	Cu(I) triflate tetrakisacetonitrile	45
11	Cu(I) acetate	56
12	Cu(I) bromide	72
13	Cu(I) chloride	89
14	Cu(I) bromide dimethylsulfide	94
15	Cu(I) thiophene-2-carboxylate	70
16	Cu(I) iodide	81
17	Cu(I) hexafluorophosphate tetrakisacetonitrile	46

[a] Reactions were carried out with cyclohexanone (1.0 mmol), amine (1.0 mmol), 1-octyne (1.0 mmol), and copper source (0.05 mmol).

Copper(I) and copper(II) catalysts were tested at 5 mol% loading rather than the 10% or 20% previously reported in these KA^2 reactions (Table 1).[19] A control reaction carried out with no catalyst over 3 days confirms that a copper source is necessary for formation of propargylamine **4a**. Under solvent-free conditions, the catalytic activity does not appear to be correlated to the oxidation state of the copper source. Cu(II) bromide and Cu(I) bromide have identical GC yields (72% and 72%, entries 3 and 12), but Cu(II) chloride is superior to Cu(I) chloride (99% and 89%, entries 4 and 13). The sole pattern apparent is that both copper (I) and copper(II) halides consistently provide greater than 70% GC yield of propargylamine **4a** (Table 1, entries 3, 4, 12, 13, 14, and 16). Although $CuCl_2$ and $CuBr{\bullet}Me_2S$ afford the highest overall GC yields at 18h, $CuCl_2$ provides a faster initial rate.[19] Entry 1 versus entry 4 allows for a direct comparison

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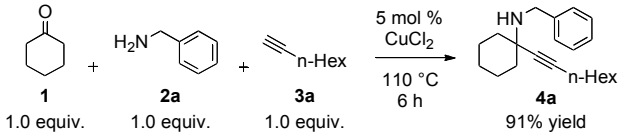
of the catalytic activity of 5 mol % $Cu(OTf)_2$ versus 5 mol % $CuCl_2$ for the three-component coupling of cyclohexanone **1**, benzylamine **2a**, and 1-octyne **3a** under solvent-free conditions. Whereas $CuCl_2$ provides 99% GC yield of fully-substituted propargylamine **4a**, $Cu(OTf)_2$ provides a significantly lower 59% GC yield in the same time frame of 18 h (Table 1, entries 4 and 1). When the standard reaction of cyclohexanone, benzylamine, and 1-octyne is carried out with 5 mol % $CuCl_2$ neat at 110 °C, tetrasubstituted propargylamine **4a** is isolated in 91% yield after 6 h (Scheme 4).



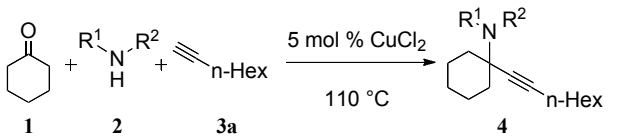
Scheme 4. No solvent and less catalyst for a faster reaction and higher yield

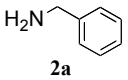
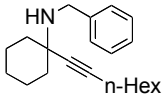
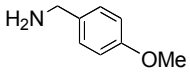
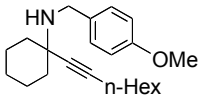
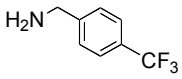
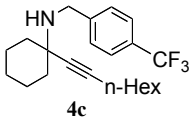
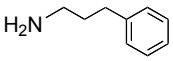
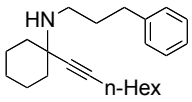
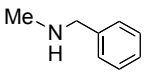
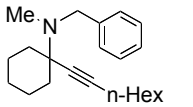
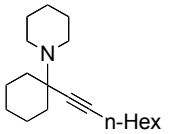
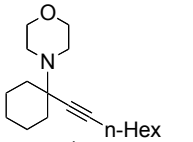
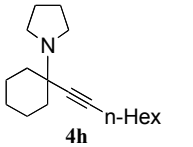
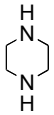
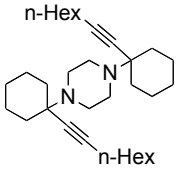
The goal of a greener method without solvent was critical to the identification of copper(II) chloride as the superior catalyst for this KA^2 reaction. When cyclohexanone, benzylamine, and 1-octyne are heated with catalyst at 110 °C for 18 hours, no conversion was observed in a range of solvents at 0.1 M concentration: acetone, acetonitrile, chloroform, dichloroethane, dioxane, dimethylformamide, dimethyl sulfoxide, ethyl acetate, hexanes, methanol, tetrahydrofuran, toluene, and water. No difference in reactivity is observed under an atmosphere of nitrogen versus argon. In air, the reaction proceeds cleanly but conversion is 18% less than under inert atmosphere.

As previous cyclohexanone KA^2 reactions were limited to either primary[13] or secondary[14] amines coupled mostly with phenylacetylene, investigations began by surveying the amine substrates operable with 1-octyne in this solvent-free catalytic method (Table 2).[19] Entries 2-4 show that additional primary amines produce *N*-4-methoxybenzyl (**4b**), *N*-4-(trifluoromethyl)benzyl (**4c**) and *N*-propylphenyl (**4d**) propargylamines in good yield. The 87% yield of **4b** is almost triple the previous report of 31% yield that required a four-fold higher catalyst loading.[13] In contrast to Scheme 2b where an acyclic secondary amine provides a yield three-times lower than cyclic,[14] an 88% yield of **4e** from *N*-methylbenzylamine is nearly identical to the 88-92% yields of **4f**-**4h** from cyclic piperidine, morpholine, and pyrrolidine (Table 2, entries 5-8). Under the same conditions, 2 equivalents of 1-octyne and 2 equivalents of cyclohexanone react with cyclic diamine piperazine to produce tricyclic bis-propargylamine **4i** (Table 2, entry 9).

A broad scope in the alkyne component is exhibited in Table 3.[19] In contrast to Scheme 2 where application of 1-octyne instead of phenylacetylene resulted in half the yield, under the new conditions reported herein, 1-octyne and phenylacetylene (**4f** and **4j**, 90% and 89%, entries 1 and 2) react with nearly identical yields. Products bearing propylphenyl (**4k**), 3-methylbutyl (**4l**), and *tert*-butyl (**4m**) substituents also form in good yield from piperidine and cyclohexanone (entries 3-5). Finally, propargylic morpholines bearing a *tert*-butyldimethylsilyl-protected alkyne (**4n**) or alcohol (**4o**) are produced in 91% and 84% yield, respectively. To the best of our knowledge,[16-18] these represent the first silyl and silyloxy tetrasubstituted propargylamines obtained from a direct, catalytic reaction of cyclohexanone.[3a]

Table 2.[19] Range of amines for KA^2 with cyclohexanone and 1-octyne



Entry	Amine	time (h)	Product	Yield (%)
1	 **2a**	6	 **4a**	91
2		5	 **4b**	87
3		5	 **4c**	74
4		6	 **4d**	82
5		4	 **4e**	88
6		3	 **4f**	90
7		3	 **4g**	92
8		2	 **4h**	88
9		16	 **4i**	68[b]

[a] All reactions were carried out with cyclohexanone (1.0 mmol), amine (1.0 mmol), 1-octyne (1.0 mmol), and $CuCl_2$ (0.05 mmol).
[b] Cyclohexanone (2.0 mmol) and 1-octyne (2.0 mmol) were used.

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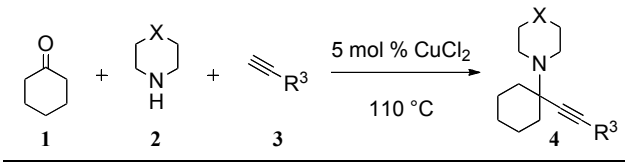
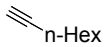
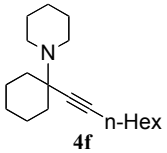
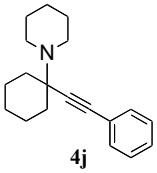
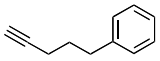
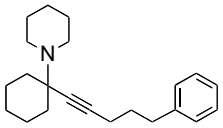
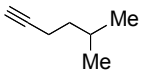
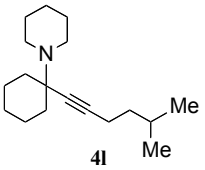
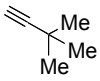
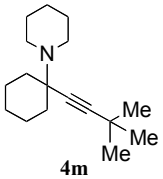
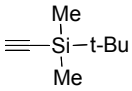
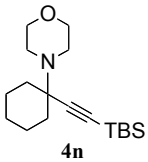
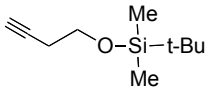
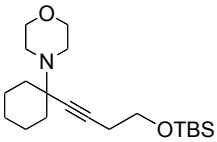
Table 3.[19] Mild copper catalysis for alkyl, aryl, siloxy, and silyl alkynes

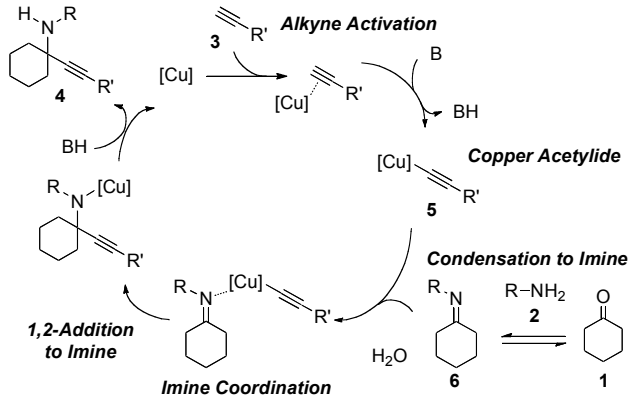


Entry	Alkyne	time (h)	Product	Yield (%)
1	 **3a**	3	 **4f**	90
2		2	 **4j**	89
3		4	 **4k**	78
4		3	 **4l**	92
5		2	 **4m**	81
6		5	 **4n**	91
7		6	 **4o**	84

[a] All reactions were carried out with cyclohexanone (1.0 mmol), amine (1.0 mmol), 1-octyne (1.0 mmol), and $CuCl_2$ (0.05 mmol).

Reaction mechanism and rates

A mechanism by which copper(II) chloride can catalyze the three-component coupling of cyclohexanone (**1**), an amine (**2**), and a terminal alkyne (**3**) is shown in Scheme 5. Beginning with alkyne activation in which the alkyne terminus is acidified by binding to copper, deprotonation by base (B) forms the copper acetylide nucleophile (**5**). The ketimine electrophile (**6**) is formed from the condensation of a primary amine and cyclohexanone. Imine coordination to the copper acetylide is believed to precede attack of the imine formed from the condensation of a primary amine and cyclohexanone.[1c,3] 1,2-Addition to the ketimine forms the tetrasubstituted propargylamine product (**4**), and liberates the copper to re-enter the catalytic cycle (Scheme 5).



Scheme 5. Catalytic cycle for cyclohexanone-amine-alkyne coupling.

Condensation to ketimine is reversible (Scheme 5), and a steady-state concentration of ketimine is observed in KA[2] reactions of benzylamine. This is not surprising as imines derived from cyclohexanone and primary amines have been well-studied for over half a century.[21] The ketimine formed from primary benzylamine is detectible by GC analysis of reaction aliquots and correlated to samples of ketimine synthesized separately and confirmed by proton NMR.[22] Interestingly, the addition of one to three equivalents of water has little effect on the reaction. At five to ten added equivalents of water, product formation is reduced. The additional water should shift the equilibrium to disfavor ketimine formation, favoring ketimine hydrolysis to starting materials. As a secondary amine forms a ketiminium upon condensation with cyclohexanone, this cationic intermediate is not expected to be observable by GC. Attempts to detect positively-charged ketiminia in the crude reaction mixture by NMR (without flushing though silica) are hampered by the paramagnetic nature of the copper(II) catalyst.

Cyclohexanone (**1**) and amine (**2**) are incorporated into the ketimine (**6**) that is attacked by the copper acetylide (**5**) formed from the copper catalyst and terminal alkyne (**3**). Thus, if acetylide addition to ketimine is the rate-determining step for the formation of product (**4**), then the overall reaction should be first order in copper catalyst, in cyclohexanone, in amine, and in alkyne.

To determine the order in each component, the rate of product formation (**4a**) is measured while varying the concentration of each constituent in the reaction of cyclohexanone (**1**), benzylamine (**2a**), and 1-octyne (**3a**). Though it is an optimal catalyst under solvent-free conditions, $CuCl_2$ is rendered inactive upon significant dilution in solvent. However, as the total reaction time is a 2-6 h, a slower reaction rate is required for reasonable sampling intervals during the first 10% of product formation. Diluting to 1.0 M instead of 0.1 M does not maintain reactivity in coordinating solvents like acetonitrile. Toluene is ideal in that it cuts the rate of reaction in half.[20]

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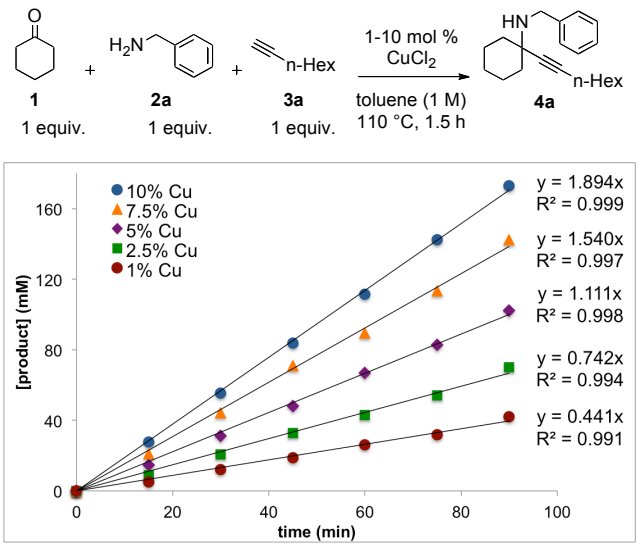

Figure 1. The formation of product over time at catalyst loadings from 1-10 mol% $CuCl_2$ each provide a linear plot with $R^2 > 0.99$.

The initial rate of product formation, measured during the first 10% of product formation, is determined by GC sampling under each set of reaction parameters. Comparison to a dodecane internal standard provides the concentration of propargylamine **4a** over time at 1, 2.5, 5, 7.5, and 10 mol% $CuCl_2$ and is plotted in Figure 1. For each set of conditions, a batch of identical reactions is started at the same time such that every data point represents the sole sample taken from one reaction. The linear plot with $R^2 > 0.99$ at each catalyst loading indicates that the data is reliable and that reactions run in parallel are uniform and reproducible. When each of these initial rates (V_0) is plotted against the concentration of $CuCl_2$, the resulting straight line ($R^2 = 0.998$) demonstrates that the KA^2 reaction is first order in copper catalyst.[20]

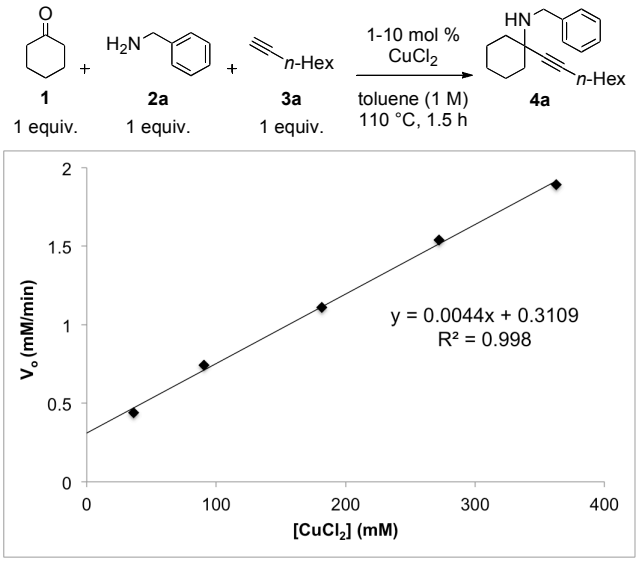

Figure 2. Linear plot indicates first order dependence on copper(II) chloride.

A similar process was followed to determine the order in each of the three reaction components. The individual plots of product formation over time for cyclohexanone, benzylamine, and 1-octyne are provided in the Supplementary Information.[20] Figure 3 graphs the initial rate of product formation (V_0) at each concentration of cyclohexanone for a linear plot with $R^2 = 0.991$, indicating that the reaction is first order in ketone starting material.

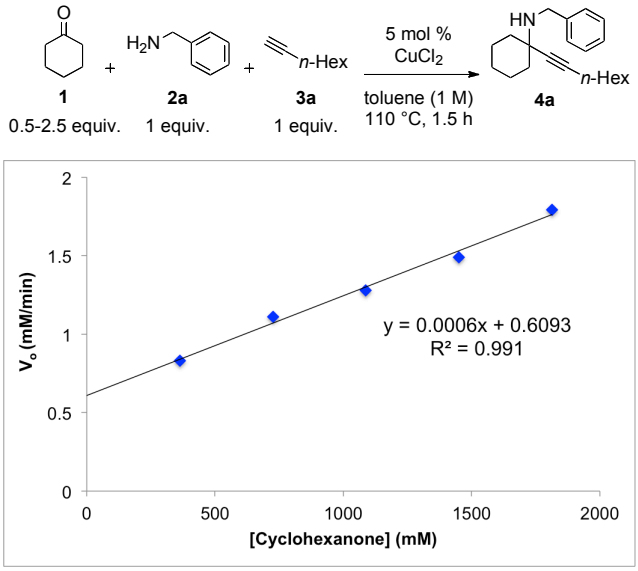

Figure 3. Linear plot indicates first order dependence on cyclohexanone.

When the initial rate of product formation (V_0) at each concentration of benzylamine is graphed in Figure 4,[20] a linear plot with $R^2 = 0.996$ indicates that the KA^2 reaction is first order in this primary amine starting material.

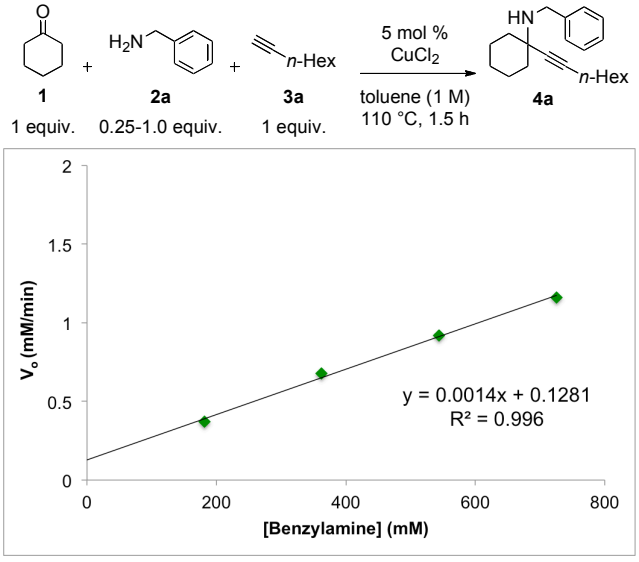

Figure 4. Linear plot indicates first order dependence on amine.

When the initial rate of product formation (V_0) at each concentration of 1-octyne is graphed,[20] a linear plot with $R^2 = 0.994$ indicates that the three-component coupling is first order in the terminal alkyne starting material (Figure 5).

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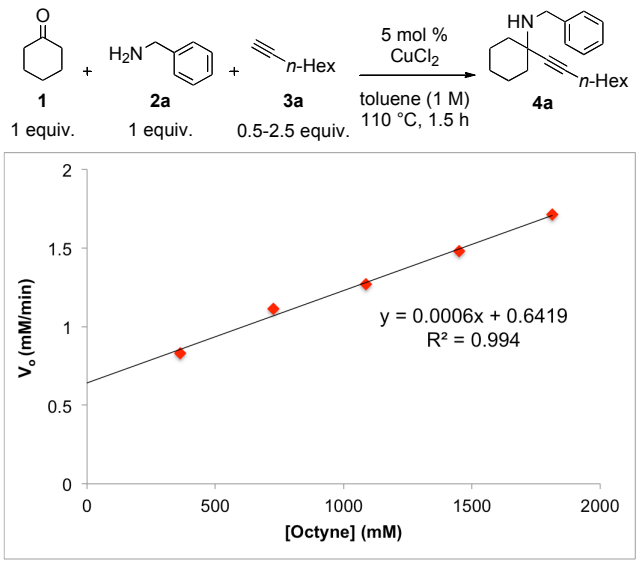

Figure 5. Linear plot indicates first order dependence on alkyne.

The rate-determining step of three-component couplings of amine and alkynes with carbonyl compounds is generally believed to be the addition of the metal acetylide nucleophile to the imine electrophile (Figure 6, intermediates **5** and **6**).[3,4] If the formation and subsequent nucleophilicity of this acetylide is most critical, some difference in rate would be expected between an alkyl acetylide and an aryl acetylide. For a terminal alkyne, a stronger base should accelerate the formation of copper acetylide. In this case, electron-donating substituents on benzylamine would be expected to increase the rate of reaction and electron-withdrawing substituents on benzylamine would be expected to decrease the rate of reaction.

Figure 6 plots the formation of propargylamine over time in the KA^2 reaction of cyclohexanone (**1**) and 1-octyne (**3a**) catalyzed by 5 mol % $CuCl_2$ at 110 °C with *para*-substituted benzylamines. GC analysis of reaction aliquots taken over the first 90 minutes of the reaction in toluene provides the data on the relative rates of product formation for 4-methoxybenzylamine, 4-methylbenzylamine, 4-chloro-benzylamine, and 4-(trifluoromethyl)benzylamine. Contrary to what might be expected, the most electron-poor 4-CF_3-benzylamine reacts an order of magnitude faster than the most electron-rich 4-MeO-benzylamine. 4-Cl-benzylamine reacts almost four-times faster and 4-Me-benzylamine reacts over twice as fast as 4-MeO-benzylamine.

Intriguingly, closer examination of the GC data reveals that a greater steady-state concentration of the cyclohexyl ketimine formed from 4-methoxybenzylamine is observed compared to 4-(trifluoromethyl)benzylamine. During the course of the KA^2 reaction with cyclohexanone (**1**) and 1-octyne (**3a**), the ketimine stabilized by the electron-donating methoxy group forms to a 30% greater extent than the ketimine destabilized by the electron-withdrawing trifluoromethyl group during the course of the reaction. The more stable, electron-rich ketimine (**6**, X = OMe) forms in a higher concentration but is less susceptible to copper acetylide attack. The less stable, electron-poor ketimine (**6**, X = CF_3) forms in a lower concentration but is more susceptible to copper acetylide attack.

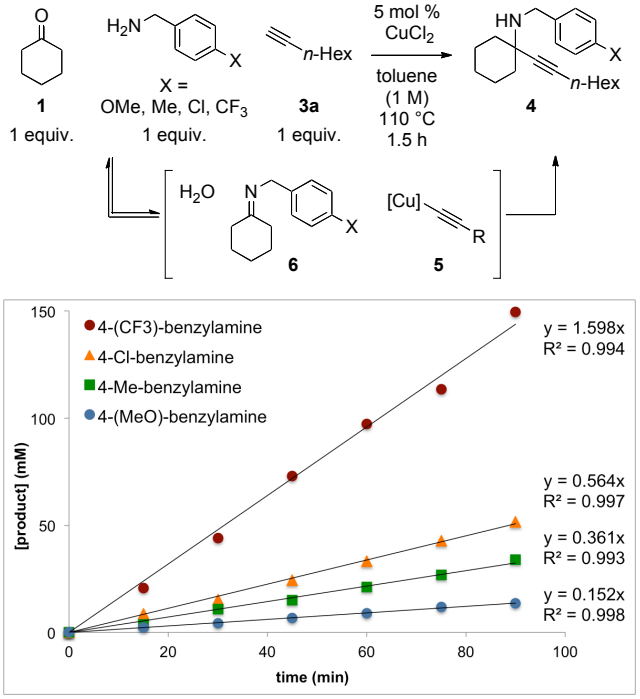

Figure 6. Electron-poor 4-(trifluoromethyl)benzylamine reacts 10.5-times faster in a KA^2 reaction than electron-rich 4-methoxybenzylamine.

Expanded scope of KA^2 reaction of TIPS-acetylene

The synthetic utility of the alkyne portion of these tetrasubstituted products (**4**) can be expanded by utilizing silyl alkynes to form readily deprotectable propargylic amines. A new, more complex terminal alkyne can be unmasked by treatment with a fluoride source.[23] This opens a wide range of reactions beyond the fact that terminal alkynes can be added to imines and other electrophiles.[3a] One of the most ubiquitous reactions of terminal alkynes is the Huisgen 1,3-dipolar cycloaddition reaction with azides for the formation of triazoles via "click" chemistry.[24]

When $Cu(OTf)_2$ was used as the catalyst in toluene for A^3 reactions involving trialkylsilyl alkynes, base was required in equimolar amounts to triflate in order to avoid protodesilylation.[12] Table 4 is a testament to the mildness of these neat $CuCl_2$ conditions for KA^2 reactions[19] compared to those developed with $Cu(OTf)_2$. Demonstrating the scope of these neat $CuCl_2$ conditions, a variety of TIPS-protected propargylamines were prepared from cyclohexanone (**1**), (triisopropylsilyl)acetylene (**3b**), and an amine (**2**). Primary and secondary benzylamines form tetrasubstituted products **4p**–**4r** in 75-80% yield (Table 4, entries 1-3). New amine starting materials also efficiently convert to silyl-protected products. *N*-methylpiperazine forms diamine **4u**, and a near

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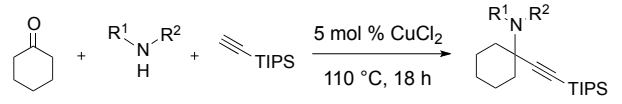
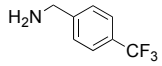
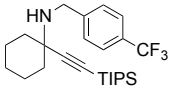
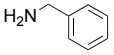
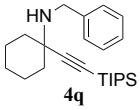
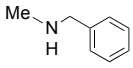
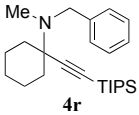
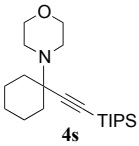
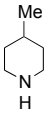
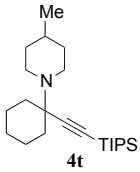
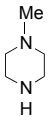
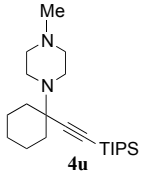
quantitative yield of TIPS-propargylamine **4t** forms from 4-methylpiperidine. In addition to synthetic manipulation of the amine portion and alkyne pi-system,[2,3] the new silyl-protected alkynes in Table 4 provide a new dimension for functionalization of tetrasubstituted propargylamines.[3a]

Table 4. Silyl alkynes react readily with cyclohexanone and a range of amines.



1 **2** **3b** **4**

Entry	Amine	Product	Yield (%)
1		**4p** 	80
2	**2a** 	**4q** 	75
3		**4r** 	76
4		**4s** 	73[b]
5		**4t** 	98
6		**4u** 	70

[a] All reactions were carried out with cyclohexanone (1.0 mmol), amine (1.0 mmol), 1-octyne (1.0 mmol), and $CuCl_2$ (0.05 mmol). [b] 6 hours.

Conclusions

The decision to target solvent-free green chemistry was crucial to the discovery of this mild catalytic procedure. Although the inexpensive copper(II) chloride catalyst is highly reactive in the absence of solvent, dilution in most solvents renders the complex inactive. Next to the removal of solvent, eliminating excess starting materials provides the largest reduction in E factor. As this three-component coupling proceeds by heating the copper(II) chloride catalyst with a 1:1:1 ratio of cyclohexanone, amine, and alkyne, the sole by-product is water. Thus, in addition to a wide substrate scope, none of the aryl, alkyl, silyl, and silyloxy alkynes nor primary and secondary amines are wasted in order to achieve high yields in KA[2] reactions with cyclohexanone. A table of deprotectable triisopropylsilyl propargylamines provides hindered substrates for conversion into the corresponding complex terminal alkyne for triazole formation via click chemistry. The cyclohexanone-amine-alkyne coupling catalyzed by copper(II) chloride is found to be first order in copper source, in cyclohexanone, in amine, and in alkyne.

Experimental

General information

All reactions were set up on the benchtop in oven-dried screw-cap test tubes with Teflon seal inserts and carried out under an atmosphere of N_2 or Ar. Column chromatography was performed using silica purchased from Silicycle. All reagents were obtained through commercial suppliers and purified by distillation before use as in W. L. F. Amerengo and D. D. Perrin, *Purification of Laboratory Chemicals, 4th ed.*, Butterworth-Heineman,: Oxford, U.K., 1996.

^1H and ^{13}C NMR spectra were measured on a Varian Inova 400 (400 MHz) spectrometer using $CDCl_3$ as a solvent at room temperature. Some spectra include tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. Gas chromatography spectra were obtained on an Agilent Technologies 6850 GC System using dodecane as an internal standard. IR spectra were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. Attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in cm^{-1}. Mass spectrometric data was collected on a HP 5989A GC/MS quadrupole instrument. Exact masses were recorded on a Waters GCT Premier ToF instrument using direct injection of samples in acetonitrile into the electrospray source (ESI) and positive ionization.

General procedure

To an oven-dried test tube equipped with magnetic stir bar and Teflon-seal screw cap was added 5 mol % $CuCl_2$. The flask was purged with nitrogen for 5 minutes. Ketone (1.0 equiv), alkyne (1.0 equiv), and amine (1.0 equiv) were added, and the reaction was stirred at 110 °C for 18h. Upon reaction completion as confirmed by GC analysis, the mixture was cooled to room temperature and loaded directly atop a silica gel column. Chromatography with the solvent system indicated afforded the desired product.

New compound characterization data

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1-(oct-1-yn-1-yl)-*N*-(4-(trifluoromethyl)benzyl) cyclohexanamine (**4c**): Prepared according to the general procedure: 4-(trifluoromethyl)benzylamine (142 µL, 1.0 mmol), cyclohexanone (103 µL, 1.0 mmol), octyne (147 µL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 74% yield (0.270 g, 0.74 mmol) after chromatography on silica gel (20% EtOAc in hexanes). IR (film) 2946, 2853, 2155, 1460, 1325, 1174 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.47 (d, J= 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 3.86 (s, 2H), 2.17 (t, J = 6.8 Hz, 2H), 1.75 (d, J = 12 Hz, 2H), 1.60-1.12 (m, 17H), 0.81 (t, J= 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.8, 128.8, 128.7 (2 overlapping carbons), 125.3 (J= 4.0 Hz), 123.15, 84.9, 83.81, 55.0, 47.6, 38.7, 31.5, 29.3, 28.7, 26.1, 23.1, 22.8, 18.9, 14.2. HRMS (ESI) m/z calcd for $[M+H]^+$ requires 366.2403, found 366.2420.

N-(4-(trifluoromethyl)benzyl)-1-((triisopropylsilyl)ethynyl) cyclohexanamine (**4p**): Prepared according to the general procedure: 4-(trifluoromethyl)-benzylamine (142 µL, 1.0 mmol), cyclohexanone (103 µL, 1.0 mmol), (triisopropylsilyl) acetylene (269 µL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 80% yield (0.350 g, 0.80 mmol) after chromatography on silica gel (20% EtOAc in hexanes). IR (film) 2936, 2863, 2155, 1462, 1323, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.46 (d, J= 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 3.90 (s, 2H), 1.78 (d, J = 12 Hz, 3H), 1.58 (m, 6H), 1.33 (m, 2H), 1.13 (m, 2H) 1.02 (d, J= 4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.5, 128.8 (2 overlapping carbons), 125.3 (J= 4.0 Hz) (2 carbons overlapped), 112.1, 84.4, 55.8, 47.8, 38.4, 26.0, 23.1, 18.8, 11.4. HRMS (ESI) m/z calcd for $[M+H]^+$ requires 438.2798, found 438.2775.

N-benzyl-1-((triisopropylsilyl)ethynyl)cyclohexanamine (**4q**): Prepared according to the general procedure: benzylamine (109 µL, 1.0 mmol), cyclohexanone (103 µL, 1.0 mmol), (triisopropylsilyl) acetylene (269 µL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 75% yield (0.277 g, 0.75 mmol) after chromatography on silica gel (10% EtOAc in hexanes). IR (film) 2931, 2862, 2154, 1461, 1279 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.27 (d, J= 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 2H), 7.13 (t, J= 7.2 Hz, 1H), 3.84 (s, 2H), 1.80 (d, J = 16 Hz, 3H), 1.59 (m, 6H), 1.34 (m, 2H), 1.17 (m, 2H) 1.03 (d, J= 4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 141.2, 128.8, 128.6, 127.0, 112.5, 84.2, 55.9, 48.4, 38.4, 26.1, 23.3, 18.9, 11.5. HRMS (ESI) m/z calcd for $[M+H]^+$ requires 370.2925, found 370.2936.

N-benzyl-*N*-methyl-1-((triisopropylsilyl)ethynyl) cyclohexanamine (**4r**): Prepared according to the general procedure: *N*-methyl-benzylamine (129 µL, 1.0 mmol), cyclohexanone (103 µL, 1.0 mmol), (triisopropylsilyl) acetylene (269 µL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 76% yield (0.291 g, 0.76 mmol) after chromatography on silica gel (10% EtOAc in hexanes). IR (film) 2932, 2863, 2153, 1462, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.24 (d, J= 8 Hz, 2H), 7.20 (t, J = 8 Hz, 2H), 7.11 (t, J= 8 Hz, 1H), 3.53 (s, 2H), 2.06 (s, 3H), 1.96 (d, J = 12 Hz, 3H), 1.64 (m, 2H), 1.54 (t, J= 9.6 Hz, 2H), 1.45 (t, J= 12 Hz, 2H), 1.18 (m, 4H) 1.03 (d, J= 4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 141.2, 128.9, 128.2, 126.6, 109.0, 84.7, 59.6, 56.0, 36.98, 35.3, 25.9, 23.1, 18.9, 11.4. HRMS (ESI) m/z calcd for $[M+H]^+$ requires 384.3081, found 384.3089.

4-methyl-1-(1-((triisopropylsilyl)ethynyl)cyclohexyl) piperidine (**4t**): Prepared according to the general procedure: 4-methyl-piperidine (117 µL, 1.0 mmol), cyclohexanone (103 µL, 1.0 mmol), (triisopropylsilyl) acetylene (269 µL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 98% yield (0.354 g, 0.98 mmol) after chromatography on silica gel (20% EtOAc in hexanes). IR (film) 2926, 2863, 2154, 1462, 1258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 2.96 (d, J= 16 Hz, 2H), 2.14 (t, J = 12 Hz, 2H), 1.96 (d, J= 16 Hz, 3H), 1.58 (m, 7H), 1.30 (t, J = 12.4 Hz, 3H), 1.13 (m, 5H), 1.01 (d, J= 4 Hz,18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 108.9, 85.19, 59.4, 46.4, 36.3, 35.0, 31.1, 25.8, 23.2, 21.8, 18.8, 11.4. HRMS (ESI) m/z calcd for $[M+H]^+$ requires 362.3238, found 362.3226.

1-methyl-4-(1-((triisopropylsilyl)ethynyl)cyclohexyl) piperazine (**4u**): Prepared according to the general procedure: *N*-methyl-piperazine (110 µL, 1.0 mmol), cyclohexanone (103 µL, 1.0 mmol), (triisopropylsilyl) acetylene (269 µL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 70% yield (0.253 g, 0.70 mmol) after column chromatography on silica gel (25% methanol in CH_3Cl_3). IR (film) 2932, 2863, 2155, 1456, 1283 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 2.65 (bs, 4H), 2.46 (bs, 4H), 2.22 (s, 3H), 1.91 (d, J= 16 Hz, 3H), 1.56 (m, 6H), 1.32 (t, J= 12 Hz, 2H), 1.12 (m, 2H), 1.00 (d, J= 4 Hz,18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 108.0, 86.2, 58.9, 55.6, 45.8, 45.7, 35.9, 25.6, 22.9, 18.7, 11.3. HRMS (ESI) m/z calcd for $[M+H]^+$ requires 363.3190, found 363.3203.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental details on rate studies and the synthesis of new products as well as copies of the ^1H and ^{13}C NMR spectra for new products. See DOI: 10.1039/b000000x/

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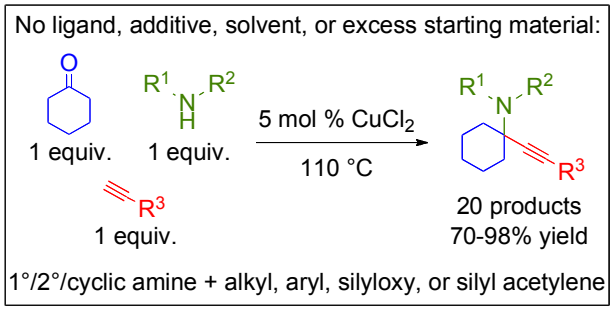

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