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Copper(I)-Catalyzed Ketone, Amine, and Alkyne Coupling for the Synthesis of 2-Alkynylpyrrolidines and -piperidines

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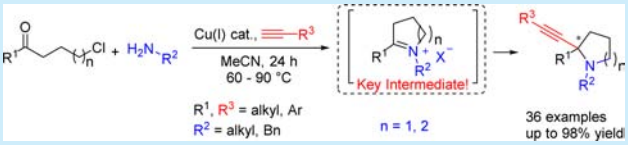
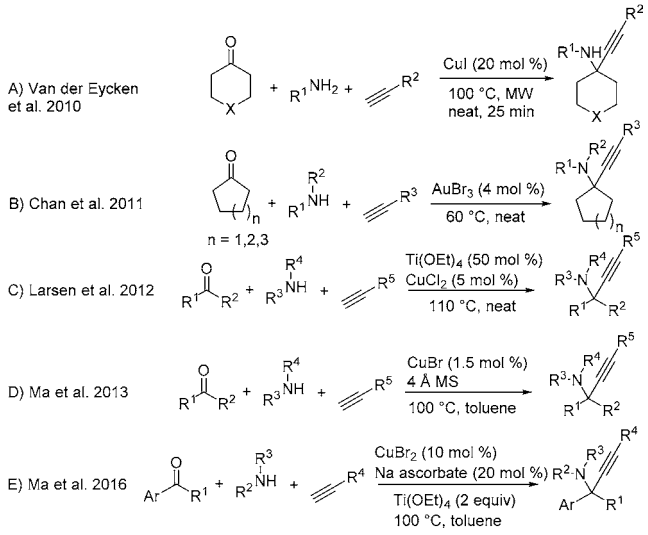
Supporting Information

ABSTRACT: A Cu(I)-catalyzed coupling of a ω-chloro ketone, a primary amine, and an alkyne is described. This protocol allows for the synthesis of α-quaternary carbons in 2-alkynyl-substituted *N*-heterocycles. The key step is the in situ generation of a cyclic ketiminium species, which has enhanced reactivity for alkynylation compared to acyclic ketiminium species.



Propargyl amines are an interesting class of molecules. This is underlined by the overwhelming attention that the reaction providing these molecules, the A^3 reaction, has received in the past decades.[1a] Other traditional methods for the synthesis of propargyl amines include amination of propargylic triflates, propargylic phosphates, propargylic esters, oxyphosphonium salts, and propargylic halides.[1b−f] Not only does the propargyl amine moiety appear in natural products and therapeutics such as rasagiline,[2a] selegiline,[2b] and efavirenz,[2c] but propargyl amines also serve as useful intermediates in the synthesis of allyl amines, pyrroles, pyrrolidines, pyrazoles,[3a] oxazoles,[3b] 2-imidazolones,[3c] and so on. Ever since the first report of the A^3 reaction by Dyatkin et al. in 1998,[4] this reaction has been well established, and only few challenges are left. One of these challenges is the substitution of the aldehyde component by a less reactive ketone. This leads to propargylamines bearing quaternary carbon centers, and a first synthesis was reported by Van der Eycken et al. in 2010, who abbreviated this coupling as a KA^2 coupling (ketone, amine, alkyne).[5] With CuI as a catalyst and under microwave irradiation aryl/alkyl alkynes, benzylic amines and cyclohexanone derivatives were coupled efficiently (Scheme 1, A). Acyclic ketones could not be used due to their lower reactivity compared to cyclohexanone. In 2011, Chan et al. proved that secondary amines can also be coupled using a $AuBr_3$ catalyst (Scheme 1, B).[6] Next to cyclic ketones, few acyclic aliphatic ketones could also be coupled, but aromatic ketones gave no KA^2 reaction. Later, in 2012, Larsen et al. established a dual catalytic system using 50 mol % of $Ti(OEt)_4$ and 5 mol % of $CuCl_2$ (Scheme 1, C).[7] With this system, acyclic aliphatic ketones could be coupled with primary/secondary amines and alkynes. Aromatic ketones, however, remained unreactive. In an attempt to expand the scope of the KA^2 coupling, Ma et al. found a new system consisting of CuBr and 4 Å MS for the synthesis of propargyl amines from acyclic and aromatic ketones (Scheme 1, D).[8] However, the scope is limited to the use of secondary amines. In 2016, Ma et al. published new reaction conditions consisting of a $CuBr_2$/sodium ascorbate and $Ti(OEt)_4$ as the catalytic system and used this combination for the coupling of a broad scope of aromatic ketones (Scheme 1, E).[9] Again, primary amines cannot be used in this coupling.

Scheme 1. Overview of KA^2 reactions until present



From these reported methods, it can be concluded that Cu(I) and Cu(II) salts are the preferred catalysts for the KA^2 coupling. Not surprisingly, efforts were made to synthesize Cu-based heterogeneous catalysts, as these catalysts are easy to recover and can be used multiple times. Some examples of such catalysts, used for simple KA^2 couplings of cyclic ketones and secondary amines, are, for example, Cu_2O on TiO_2 nanoparticles,[10a] Cu_2O on nano-ZnO particles,[10b] a Cu_2O on nano-$CuFe_2O_4$ system which is magnetically recoverable,[10c] a Cu(II)−hydromagnesite nanomaterial,[10d] which was also used in the first decarboxylative KA^2 coupling, and a polystyrene-supported *N*-phenylpiperazine−Cu(II) complex.[10e]

KA^2 couplings generally work better with secondary amines, generating in situ ketiminium species **A**. Since we would like to expand the scope by using primary amines and to make an entry toward interesting alkynyl-substituted *N*-heterocycles **D**, it was

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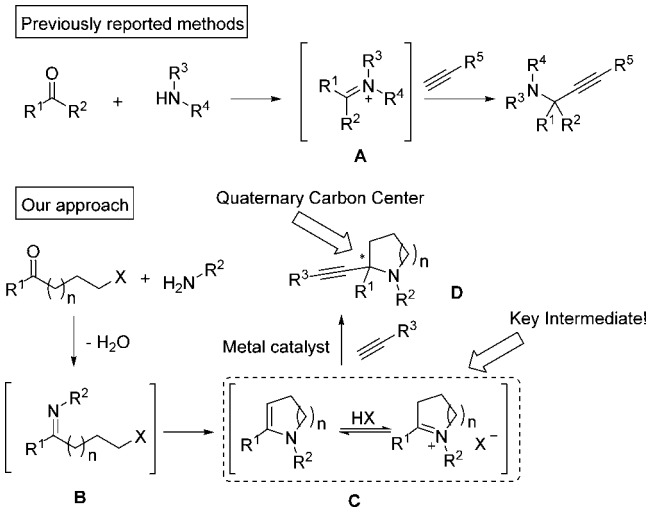
reasoned that adding a ω-halo atom to the ketone might result in a cyclic ketiminium species **C** by substitution of the ω-halo atom by the in situ generated imine **B** (Scheme 2). This is supported by previous work[11] from our group that shows that ω-chlorinated aldimines upon standing become solid due to the formation of iminium chlorides.

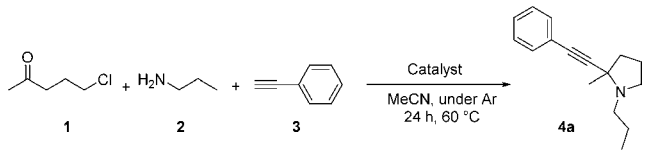
Scheme 2. New Approach toward 2-Alkynyl *N*-Heterocycles



The 2-alkynyl *N*-heterocycles **D** have been synthesized previously via an intramolecular hydroamination of aminoalkyl acetylenes followed by alkynylation.[12a,b] However, these approaches require the prior synthesis of the aminoalkynes, involving a two-step synthesis from either alkynyl alcohols or from alkynoic acids. In this work, we report a straightforward entry to 2-alkynyl-substituted *N*-heterocycles, starting from commercially available starting materials via a one-pot, three-component synthesis.

As a starting point for the optimization of the reaction under investigation commercially available 5-chloropentan-2-one (**1**), *n*-propylamine (**2**) and phenylacetylene (**3**) were reacted in the presence of various metal catalysts in acetonitrile to give 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**). An excess of 3.5 equiv of *n*-propylamine was used, as *n*-propylamine also acts as a base to trap the equivalent of HCl that is formed and because of its volatility. A small excess of 1.2 equiv of phenylacetylene was used because in all cases traces of the Glaser homocoupling product were observed. Classical A^3 catalysts such as Zn, Fe, Al, Ni, and Sc salts were not able to catalyze this transformation (see Table S1). Remarkably, even $In(OTf)_3$, which worked well for chlorinated imines, was not able to catalyze this reaction.[11,13] $AuPPh_3Cl$ (Table 1, entry 1) and AgOTf (Table 1, entry 2) gave low yields of 18 and 46% of 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine. CuCl (77%, Table 1, entry 3) gave a lower yield than $CuCl_2$ (87%, Table 1, entry 4), while when the counteranion was changed to triflate (83%, Table 1, entry 5) no improvement of the yield was observed. Changing to Cu_2O (87%, Table 1, entry 6) was equally good, while CuO showed less catalytic activity (50%, Table 1, entry 7). When the catalyst loading was lowered to 5 mol %, only 65% yield of 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**) was obtained (Table 1, entry 8), while by increasing the catalyst loading to 25 mol % the yield became nearly quantitative (Table 1, entry 9). The coupling reaction proved also feasible with magnetically recoverable $CuFe_2O_4$, albeit in lower yield

Table 1. Evaluation of Different Catalysts for the KA^2 Coupling of 5-Chloropentan-2-one, *n*-Propylamine, And Phenylacetylene



1 2 3 4a

entry[a]	catalyst (mol %)	yield of **4a**[b] (%)
1	$AuPPh_3Cl$ (20)	18
2	AgOTf (20)	46
3	CuCl (20)	77
4	$CuCl_2$ (20)	87
5	$Cu(OTf)_2$ (20)	83
6	Cu_2O (10)	87
7	CuO (20)	50
8	Cu_2O (5)	65
9	Cu_2O (25)	99
10	$CuFe_2O_4$ (20)	42
11	copper(I) phenylacetylide (20)	80

[a]All reactions were carried out with 1 mmol of 5-chloropentan-2-one, 3.5 mmol of *n*-propylamine, 1.2 mmol of phenylacetylene, catalyst, and 2 mL of acetonitrile. [b]Determined from the ^{1}H NMR spectrum with 1,3,5-trimethoxybenzene as internal standard.

(42%, Table 1, entry 10), and is comparable to CuO (50%, Table 1, entry 7). This yield could probably be improved if Cu_2O is impregnated on the $CuFe_2O_4$ nanoparticles as reported previously.[10c] When the presumable actual catalyst was used, i.e., copper phenylacetylide instead of a precatalyst, the yield was slightly lower (80%, Table 1, entry 11) probably due to difficult breaking of the copper phenylacetylide polymeric structure.[14] The advantage of using copper phenylacetylide is that for largescale applications this catalyst can easily be recovered by filtration after basic workup of the reaction. For screening purposes, however, this catalyst will not be used as the catalyst should be prepared separately for every other alkyne.

The reaction was then further optimized with regard to the solvent. Solvents such as EtOAc, THF, 2-MeTHF, TBME, DMSO, DMF, DCM, EtOH, toluene, and dioxane were also well tolerated, giving yields ranging from 56 to 99% (see Table S2). Water as a solvent still gave a yield of 12%, most likely because of a disfavored ketone−iminium equilibrium, as water is a byproduct of the reaction. This observation allows the use of nondried solvents. Finally, the optimized reaction conditions for the formation of 2-methyl-2-(phenylethynyl)pyrrolidines **4** were established as follows: 1 equiv of 5-chloropentan-2-one, 3.5 equiv of *n*-propylamine, 1.2 equiv of phenylacetylene, and 0.2 equiv of Cu_2O in acetonitrile for 24 h at 60 °C.

To investigate the scope of the reaction, first the primary amine component was varied. With *n*-propylamine, an isolated yield of 91% was obtained for the product **4a**, while the more sterically hindered isopropylamine also was tolerated and gave a yield of 87%. The reaction of 5-chloropentan-2-one with *tert*-butylamine did not yield any reaction product **4c** at 60 °C. By raising the temperature to 90 °C, product **4c** was isolated in 29% yield. This lower yield can be explained by the difficult formation of the ketimine and ring-closing reaction[11] and by the low boiling point of *t*-$BuNH_2$ (46 °C). Amines, with readily removable protecting groups such as allylamine or benzylamine, furnished yields of 77% and 75%, respectively. Molecule **4f** shows that the primary amine reacts exclusively, even in the presence of a

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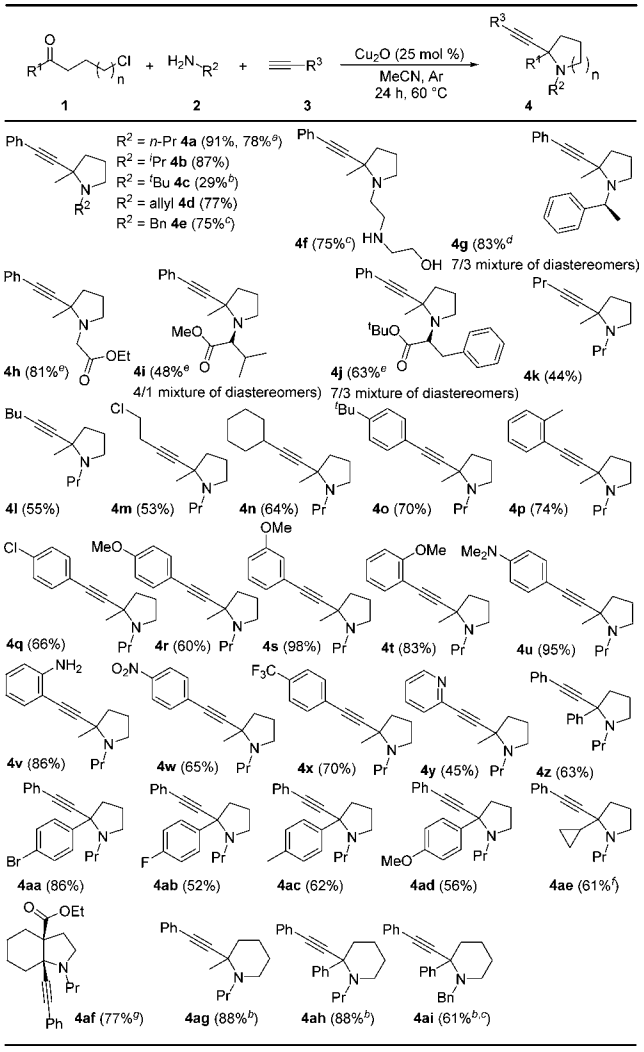
secondary amine and hydroxy function in a reasonable 75% yield. (*S*)-Methylbenzylamine afforded a 7/3 mixture of diastereomers in 83% yield. It is known that α-amino esters are also good coupling partners for KA^2 couplings.[15] Therefore, glycine ethyl ester was used as amine component, and the product **4h** was obtained in 42% yield. By using the more stable glycine ethyl ester hydrochloride in the presence of 2 equiv of triethylamine, the yield increased to 81%. Other α-aminoesters, derived from natural α-amino acids such as L-valine methyl ester hydrochloride and L-phenylalanine *t*-Bu ester hydrochloride, gave under the same reaction conditions (2 equiv of NEt_3) 48% of a 4/1 diastereomeric mixture and a 63% yield of a 7/3 diastereomeric mixture, respectively.

Next, different alkynes were evaluated. In general, alkyl-substituted alkynes reacted well in this conversion, resulting in yields of 40−64%. 1-Pentyne as a coupling partner resulted in a low yield of 44%, probably due to its low boiling point (40 °C). When 1-hexyne with a boiling point of 71−72 °C was used, the yield increased to 55%. When 4-chlorobut-1-yne was used, product **4m** was isolated in 53% yield. Trace amounts of 2-(but-3-en-1-yn-1-yl)-2-methyl-1-propylpyrrolidine and 4-(2-methyl-1-propylpyrrolidin-2-yl)-*N*-propylbut-3-yn-1-amine were observed, resulting from the conjugated elimination of HCl and the substitution of chlorine by *n*-propylamine in 2-(4-chlorobut-1-yn-1-yl)-2-methyl-1-propylpyrrolidine (**4m**). The use of cyclohexylacetylene results in the formation of product **4n** in 64%. Next, a range of aromatic alkynes were evaluated. Electron-donating substituents (4-*t*-Bu, 2-Me, 4-Cl, 2-MeO, 3-MeO, 4-MeO) were tolerated well, resulting in yields of 60−98%. 4-Ethynyl-*N*,*N*-dimethylaniline leads to a very high yield of 95%. The reaction of **1** with 2-ethynylaniline also led to the expected alkynylpyrrolidine **4v** in 86% yield. Under these reaction conditions, no additional intramolecular hydroamination, leading to a 2-indolopyrrolidine as previously reported under comparable conditions, was observed.[16] Next to electron-donating groups, electron-withdrawing groups like 4-nitro and 4-trifluoromethyl gave reasonable yields of 65 and 70%. In a special case, the 2-ethynylpyridine could also be coupled, albeit in a moderate yield of 45%.

Next, different ketones were screened. As stated above, aromatic ketones are difficult coupling partners in KA^2 reactions. Under our conditions, the commercially available 4-chlorobutyrophenone could be easily coupled with *n*-propylamine and phenylacetylene leading to 2-phenyl-2-(phenylethynyl)-1-propylpyrrolidine (**4z**) in 63% yield. In addition, substituted 4-chlorobutyrophenones could be coupled, and the corresponding pyrrolidines were isolated in 52−86% yield. In general, the yields are lower than for the aliphatic ketones, probably because of increased steric hindrance in aromatic ketiminium intermediates (Scheme 3). When 1,7-dichloroheptan-4-one was used, solely pyrrolidine **4ae**, which contains a cyclopropyl ring, was obtained in toluene. Besides the commercially available ketones tested above, a wide variety of chloroketones can be accessed by a plethora of literature methods.[17] For example, bicyclic product **4af**, containing an ester moiety, was prepared from ethyl 1-(2-chloroethyl)-2-oxocyclohexanecarboxylate. Lastly, the formation of other nitrogen heterocycles was evaluated. To our delight, the formation of piperidine **4ag** from the commercially available 6-chlorohexan-2-one was possible in 88% yield. The formation of **4ah** from 5-chloro-1-phenylpentan-1-one did not work at 60 °C and required a higher temperature of 90 °C, leading to a comparable yield of 88%. In addition, product **4ai**, which contains a Bn group, was obtained at elevated temperature (90 °C) in 61% yield. Unfortunately, the reaction of 4-chlorobutan-2-one or 7-chloroheptan-2-one with phenylacetylene and Cu_2O under the developed conditions did not lead to any formation of the corresponding 2-alkynylazetidines and -azepanes. In order to show the robustness of the developed method and to prove that the reaction could be scaled up, a gram-scale experiment was conducted. On a 10 mmol scale, the product **4a** could be isolated in 78% yield.

Scheme 3. Scope of the Evaluated KA^2 Reaction



[a]Unless otherwise stated, 3.5 equiv of amine was used. 10 mmol scale. [b]90 °C. [c]2 equiv of amine was used. [d]1 equiv of amine was used; 1 equiv of NEt_3 was added. [e]1 equiv of aminoester·HCl was used, and 2 equiv of NEt_3 was added. [f]Prepared from 1,7-dichloroheptan-4-one in toluene. [g]Prepared from ethyl 1-(2-chloroethyl)-2-oxocyclohexanecarboxylate.

To gain insight into the reaction mechanism, as proposed in Scheme 2, a series of control experiments was set up. First, the reaction of 5-chloropentan-2-one with dipropylamine and phenylacetylene was evaluated. At 85 °C, a complex mixture of substitution product 5-(dipropylamino)pentan-2-one (**5**), the hydroamination product *N*-(1-phenylvinyl)-*N*-propylpropan-1-amine (**6**), and the subsequent alkynylation product 2,4-diphenyl-*N*,*N*-dipropylbut-3-yn-2-amine (**7**) could be distinguished in the ^{1}H NMR spectrum of the reaction mixture (Scheme 4, route a). When the nonchlorinated 2-pentanone was

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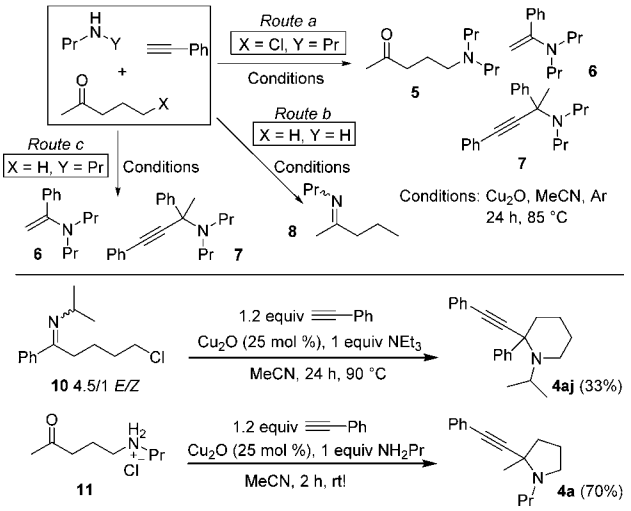
Scheme 4. Control Experiments



reacted with *n*-propylamine and phenylacetylene, besides some imine **8**, no alkynylated product was formed (Scheme 4, route b). When dipropylamine was used instead of *n*-propylamine in combination with nonchlorinated ketone, hydroamination of phenylacetylene, followed by alkynylation of the intermediate formed iminium occurred, as described by Larsen et al. (Scheme 4, route c).[18a,b] However, no incorporation of the ketone component was seen. This proves that both the primary amine and the presence of the ω-chlorine atom on the ketone are necessary for the coupling reaction. Next, ω-chloroimine **10** was synthesized[19] and reacted with phenylacetylene at 90 °C in the presence of 0.25 equiv of Cu_2O and 1 equiv of NEt_3. The corresponding 2-alkynylpiperidine **4aj** was isolated in 33% yield, proving that the proposed reaction mechanism in Scheme 2 is plausible. Alkynylation reactions of enamines have been reported to proceed via the corresponding iminium compounds, thus supporting the proposed reaction mechanism.[20] Preliminary alkylation of the primary amine by the alkyl chloride moiety of **1**, followed by intramolecular iminium formation is more plausible, since 5-aminopentan-2-one **11** (as its ammonium salt), which was prepared independently (see the SI) upon reaction with phenylacetylene, 1 equiv of propylamine and 0.25 equiv of Cu_2O furnished the alkynylpiperidine **4a** in 70% yield already at rt after 2 h.

In conclusion, a new, mild Cu(I)-catalyzed synthesis of 2-alkynylpyrrolidines and -piperidines bearing a quaternary α-carbon center was reported. Different primary aliphatic amines can be used in combination with ω-chlorinated ketones. A broad range of functional groups (Cl, MeO, CF_3, NO_2, NH_2, NMe_2) is well tolerated on the alkyne moiety. Different substituted aromatic ketones, which traditionally are difficult reaction partners, could be coupled. Moreover, this synthesis uses simple, cheap, and commercially available starting materials. The key step is the in situ generation of a cyclic ketiminium species, which has an enhanced reactivity toward alkynylation in comparison to acyclic ketiminium species.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02127.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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