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Copper catalysed alkynylation of tertiary amines with CaC_2 via sp^3 C-H activation

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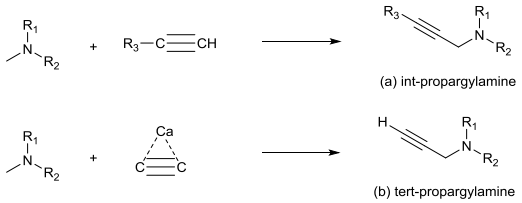
A mild and easy-to-handle protocol to produce propargylamines with terminal alkyne through catalytic cross-coupling of tertiary amines and calcium carbide has been developed. The reaction preceeds via sp^3 C-H bond activation and C-C coupling. Good to excellent yields were obtained for the corresponding propargylamines with both alkyl and aryl substitutions. The development for these functionalized propargylamines with a terminal alkyne group will offer a wider application for the synthesis of natural or pharmaceutical products due to its unique sp C-H reactivity.

Propargylamines and their derivatives are versatile key building blocks for the preparation of many biologically active compounds with wide applications in pharmaceutical and synthetic chemistry.[1] Various reported methods using stoichiometric nucleophilic alkynylation[2] and transition metal-catalyzed three-component coupling of aldehydes/halides, alkynes, and amines[3,4] are indeed effective methods; however, these methods require the presence of a suitable leaving group or pre-functionalized substrates. Hence, direct C-C bond formation of terminal alkynes with tertiary amines via sp^3 C-H activation is a more practical approach. Notably, Li and co-workers reported an efficient copper-catalyzed alkynylation of aryl- or benzyl- substituted tertiary amines in the presence of *t*-BuOOH.[5] Catalytic coupling of aliphatic tertiary amines with terminal alkynes was also demonstrated.[6,7] In all cases, the substrates used in these methods are limited to substituted terminal alkynes and hence produce propargylamines with internal alkynes (Scheme 1). Though important, the internal structure may hinder further synthetic applications. Propargylamines with terminal alkynes, on the other hand may offer wider applications due to the unique reactivity of the sp C-H bond which is susceptible to nucleophilic, electrophilic, radical and cycloaddition reactions.[8]

To date, the preparation of propargylamines with terminal alkynes via catalytic cross-coupling of tertiary amines has not been reported. In recent years, calcium carbide has been used increasingly by our group[8,9] and others[10,11] as a sustainable,[12] easy-to-handle, and cheap feedstock in organic synthesis. Hence, it would be highly desirable to prepare the useful *tert*-propargylamines via one-step catalytic cross-coupling of tertiary amines with calcium carbide. The C-C bond formation via sp^3 C-H bond activation methodology has gained increasing attention in recent years [13, 14] and it eliminates the need to prepare functional groups, making it a direct, quick and efficient method for C-C bond formations. Herein, we report a simple and mild catalytic protocol for the synthesis of *tert*-propargylamines via sp^3 C-H bond activation and C-C coupling with the sustainable calcium carbide. It represents the first example of direct C-C coupling of calcium carbide with a C-H bond.



Scheme 1. Propargylamine with (a) internal and (b) terminal alkyne.

To begin our study, an aliphatic amine; N,N-Dimethylcyclohexylamine was used as the model substrate for optimization. Various copper catalysts and oxidants were investigated (Table 1 and S1). Both Cu(I) and Cu(II) salts showed comparable activities (Table 1, entries 3 – 8) with CuBr found to be the most effective catalyst. The choice of oxidants was of great importance. Besides diethylazodicarboxylate (DEAD), hydroperoxide oxidants worked moderately well (Table S1, entries 1 – 6). Di-*t*-butyl peroxide and H_2O_2 however only gave trace amount of product. Other oxidants like $KMnO_4$, NBS and I_2 does not work in this system.

With these in hand, the reaction conditions were further optimized (Table 1). The reaction of this substrate in CH_3CN with calcium carbide (2.5 equiv.) in the presence of CuBr (10 mol%) and DEAD (1.5 equiv.) was carried out at 80 °C for 16 h (Entry 1). Under this dry condition, only trace amount of product was formed due to the poor solubility of calcium carbide in organic solvents.[11,15] Recent

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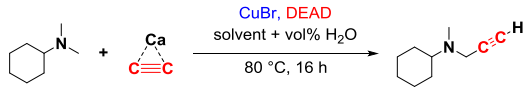
studies have shown that adding a controlled amount of water can resolve this issue by breaking down the polymeric structure of calcium carbide.[8,9,16] Hence, trace amount of water was added into the system, thereby affording 96% yield, as determined from ^{1}H NMR spectroscopy (Entry 3). The reaction proceeded efficiently in a wide range of solvents, including the less polar 1,4-dioxane and polar protic isopropanol (Entries 14 – 17)

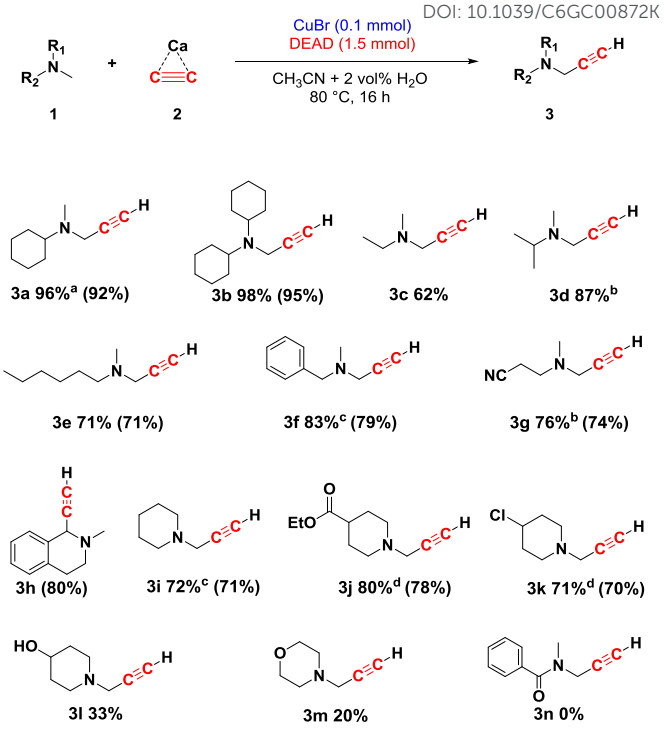
Table 1. Direct alkynylation of tertiary amines with CaC_2: optimization of reaction conditions. [a]



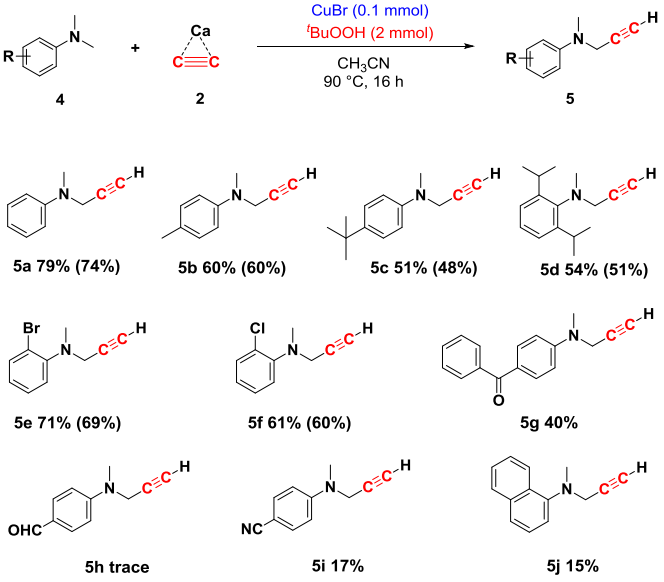
Entry	Catalyst (mol%)	DEAD (eq.)	Solvent	H_2O (vol%)	Yield [%][b]
1	CuBr (10)	1.5	CH_3CN	-	Trace
2	CuBr (10)	1.5	CH_3CN	1	80
3	CuBr (10)	1.5	CH_3CN	2	96
4	CuCl (10)	1.5	CH_3CN	2	93
5	CuI (10)	1.5	CH_3CN	2	95
6	CuCN (10)	1.5	CH_3CN	2	84
7	$Cu(OAc)_2$ (10)	1.5	CH_3CN	2	90
8	$CuBr_2$ (10)	1.5	CH_3CN	2	87
9	--	1.5	CH_3CN	2	NR
10	CuBr (10)	--	CH_3CN	2	NR
11	CuBr (5)	1.5	CH_3CN	2	88
12	CuBr (15)	1.5	CH_3CN	2	91
13	CuBr (10)	1.0	CH_3CN	2	78
14	CuBr (10)	1.5	DMF	2	80
15	CuBr (10)	1.5	THF	2	54
16	CuBr (10)	1.5	dioxane	2	88
17	CuBr (10)	1.5	IPA	2	63

[a] Reaction conditions: Amine (1 mmol), CaC_2 (2.5 mmol), solvent + H_2O (5 mL), 80 °C, 16 h. [b] NMR yield. DMF = N,N-dimethylformamide; THF = tetrahydrofuran; IPA = *iso*-propanol.

Subsequently, various aliphatic tertiary amines were screened for this reaction system. Good to excellent yields were obtained for most of the aliphatic substrates including the bulky amine, straight or branched chain amines (Scheme 2, **3a – 3e**), reactive benzylamine (**3f**) and amines with additional functional groups, such as -CN, -COOEt, -OH and halide (**3g, 3j, 3k, 3l**). We were delighted to find that this system also worked well for N-methyl-1,2,3,4-tetrahydro-isoquinoline and N-methyl-piperidine as they are important structural features for pharmaceutical synthesis (Scheme 2, **3h – 3l**). The benzylic position of benzyldimethylamine is usually more susceptible to reactions. However, alkynylation at the methyl position was observed in this system (**3f**). This phenomenon is similar to the anodic methoxylation of the amine.[17] In contrast, alkynylation of tetrahydroisoquinoline (**3h**) took place exclusively at the benzyl position instead of the methyl position, as confirmed by COSY NMR (Figure S1). No desired product was obtained when *N,N*-dimethylbenzamide (Scheme 2, **3n**).



Scheme 2. Substrate scope of aliphatic tertiary amines with CaC_2. NMR yield. Isolated yield is in parentheses. Reaction conditions: Amine (0.5 mmol), CaC_2 (2.5 mmol), CuBr (0.1 mmol), DEAD (1.5 mmol), CH_3CN + H_2O (5 mL), 80 °C, 16 h [a] 1 mmol amine; [b] 2 mmol DEAD; [c] 4 h; [d] 90 °C, 2 mmol DEAD.



Scheme 3. Substrate scope of aromatic tertiary amines with CaC_2. NMR yield. Isolated yield is in parentheses. Reaction conditions: Amine (0.5 mmol), CaC_2 (2.5 mmol), CuBr (0.1 mmol), ^{t}-BuOOH (2 mmol), CH_3CN (5 mL), 90 °C, 16 h

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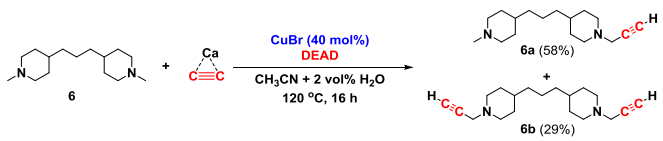
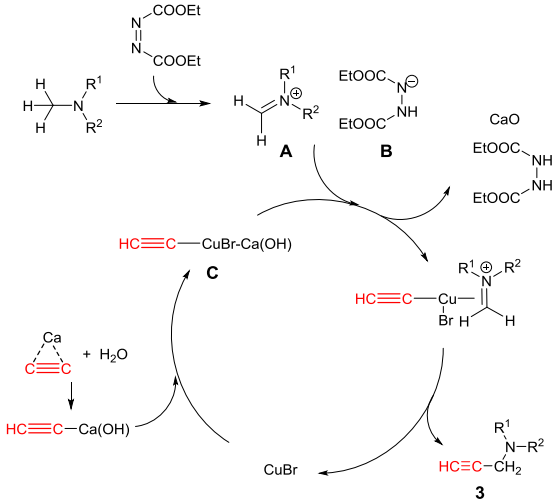
We next screened aromatic amines as substrates under the above reaction condition. We noted that the adduct of DEAD with *N,N*-dimethylaniline was observed from GCMS which is similar to the reaction of *N,N*-dimethylaniline with phenylacetylene in the presence of DEAD.[6] When a different oxidant, *t*-BuOOH was used, trace amount of product was observed with secondary amine N-methylaniline as a major side product. Attempts to optimize the reaction condition for *N,N*-dimethylaniline (Table S2) led us to improve the yield to 79% by not adding water into the system. Here the reaction could be self-accelerated as water is produced during the reaction.[5] Under this set of optimized conditions, moderate to good yields were generally obtained for aromatic amines substituted with bulky groups and halides (Scheme 3, **5a – 5f**). While the reaction for the aromatic amines with electron-withdrawing substituents gave low yields (Scheme 3, **5g – 5j**).

It is noted that only one methyl group of tertiary amines undergoes alkynylation with CaC_2 in all these reactions.[5,7] When using **3a** as the substrate, further alkynylation on another methyl group did not proceed with excess calcium carbide remaining. When diamine **6** was used as the substrate, the reaction proceeded to give a mixture of mono- and di- product (Scheme 4). The reaction was not selective despite the use of harsher conditions (Table S3).

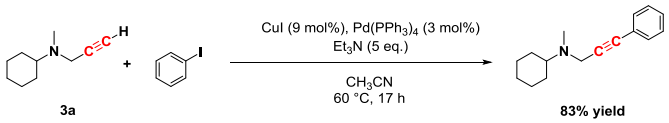


Scheme 4. Alkynylation of diamine with CaC_2.

It is proposed that the current reaction has a similar pathway as reported reactions with terminal alkynes (Scheme 5).[6,18] The oxidant DEAD undergoes nucleophilic addition reaction with tertiary amine forming an adduct. The adduct then cleaves to form the imine cation **A** and DEAD anion **B**. Thereafter, coupling of the *in-situ* generated copper acetylide **C** and the imine cation **A** results in the desired product **3** and regenerates the copper catalyst. It is also possible that copper catalyzes the formation of the imine intermediate through sp^3 C-H activation.[5]



Scheme 5. Proposed mechanism for the catalytic alkynylation of tertiary amine with CaC_2.



Scheme 6. Sonogashira coupling of propargylamine **3a** with iodobenzene.

Herein, the application of the synthesized propargylamine **3a** was successfully demonstrated via the Sonogashira coupling with iodobenzene, forming *N*-methyl-*N*-(3-phenylprop-2-yn-1-yl)cyclohexanamine in 83% yield.

In conclusion, we have developed a mild and easy-to-handle protocol for affording propargylamines with terminal alkyne through catalytic cross-coupling of tertiary amines with the inexpensive and renewable calcium carbide. Good to excellent yields were obtained for the corresponding propargylamines, with the aliphatic ones working particularly well. The development for these functionalized propargylamines with a terminal alkyne group will offer a wider application for the synthesis of natural or pharmaceutical products due to its unique sp C-H reactivity. The synthetic application of this work is under investigation.

Acknowledgements

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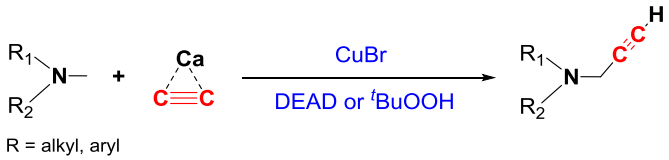

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