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Copper(II) Triflate-Catalyzed Three-Component Coupling of Aldehydes, Alkynes and Carbamates

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Abstract: A simple and efficient synthesis of propargylcarbamates was developed through a copper(II) triflate-catalyzed coupling of aldehydes, alkynes and carbamates. No co-catalyst or ligand is required.

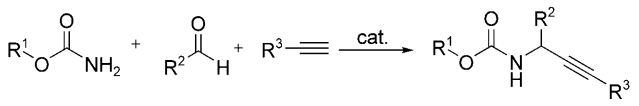
Keywords: A^3-coupling; aldehydes; alkynes; carbamates; copper(II) triflate

Propargylic amine is an important structural motif in organic synthesis[1] and has been widely used in creating biomimetic polymers[2] and producing various biologically active compounds (e.g., natural products, therapeutic drug molecules, herbicides, and fungicides).[3]

One of the most convenient methodologies for the synthesis of these compounds is *via* the three-component couplings of aldehydes, alkynes and amines (A^3-coupling) with water as the only theoretical by-product, which has undergone great progress in recent years. We and others have reported various highly efficient A^3-couplings catalyzed by copper, silver, gold and other catalysts to afford various propargylamines.[4,5] Recently, we and Wang's group also demonstrated that cheap, readily available iron complexes can serve as highly active catalysts for this transformation.[6] By using a chiral copper catalyst, a highly enantioselective addition of alkynes to imines to afford optically active propargylamines (AA^3-coupling) in water or organic media has also been developed.[7] While a great deal of progress has been made in the A^3-coupling reaction, thus far the A^3-coupling reaction has been limited mostly to secondary and aromatic amines, other aliphatic primary amines and amine derivatives are challenging substrates that are often not viable for this transformation.

Propargylcarbamates are important members of propargylic amine family,[8] and the synthesis of these compounds *via* the A^3-coupling reaction has not been accomplished. In the field of propargylcarbamate synthesis, traditional methods often required demanding reaction conditions and stepwise operations with poor functional group compatibility, which limited their application in organic synthesis.[9] In order to circumvent these obstacles, we have developed the first copper-mediated (and catalyzed) direct nucleophilic addition of alkynes to reactive *N*-acylimines and *N*-acyliminium ions (generated *in situ* from α-amido sulfones or methoxy groups as stable precursors) to generate propargylcarbamates in water.[10] Alternatively, we, Arndtsen, and Carreira reported gold-, copper-, and zinc-catalyzed couplings of imines, acid chlorides, and alkynes to provide rapid accesses to propargylcarbamates and propargylic amides in excellent yields.[11] In addition, we also developed a general method for the site-specific functionalization of free-(NH) peptides and glycine derivatives *via* C–H bond activation, through a copper-catalyzed addition of terminal alkynes and other nucleophiles to *in situ* generated acyliminium intermediates.[12]

Based on our extensive interest in A^3-coupling reactions, we envisioned that the simplest and most direct protocol for the synthesis of propargylic carbamates is *via* the three-component coupling of aldehydes, alkynes, and carbamates (Scheme 1).[13] However, to the best of our knowledge, such a coupling reaction has not been achieved. Herein, we report our

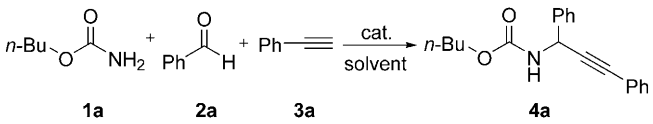


Scheme 1. Synthesis of propargylcarbamates *via* the coupling of aldehydes, alkynes and carbamates.

research results on the direct coupling of aldehydes, alkynes, and carbamates which afforded propargylcarbamates efficiently.

Due to the high catalytic activity of copper catalysts in the A^3-coupling reactions in our previous work, several copper salts were examined in a model reaction employing *n*-butyl carbamate (**1a**), benzaldehyde (**2a**), and phenylacetylene (**3a**) as substrates in our initial studies, and the results are summarized in Table 1. The copper salts (10 mol%) CuBr, $CuBr_2$ and CuCl can all catalyze the reaction to give a trace amount of the corresponding propargylcarbamate (entries 1–3, Table 1). However, no product was detected when employing $CuCl_2$, $Cu(OAc)_2$, $Cu(acac)_2$ and CuI as catalysts under the identical reaction conditions (entries 4–7). To our delight, when the CuOTf·toluene complex and $Cu(OTf)_2$ were used as catalysts, desired product **4a** was obtained in high yields (entries 8 and 9, Table 1). This reaction can also be catalyzed by HOTf or $CuCl_2$/HOTf; however, low yields were obtained (entries 10 and 11). Lowering the loading of the catalyst decreased the yield (entry 12). The reaction temperature was also found to be important in this transformation and a lower yield was obtained when the reaction was conducted at 70 °C (entry 13). Other solvents such as THF, DCE, and CH_3CN afforded the coupling products in low yields (entries 14–16). No desired product was obtained in polar solvents (entries 17–20). It is worth mentioning that a moderate yield of the desired product was obtained under neat conditions (entry 21). The addition of TMEDA impeded the coupling reaction completely (entry 22). The use of some nitrogen-based ligands such as 2,2′-bipyridine and 1,10-phenanthroline decreased the yield significantly (entries 23 and 24). Finally, the optimized reaction conditions were determined to be 1.0 equivalent of aldehyde, 1.2 equivalents of carbamate, 1.5 equivalents of alkyne and 10 mol% of $Cu(OTf)_2$ in toluene at 100 °C under N_2.

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a** **4a**

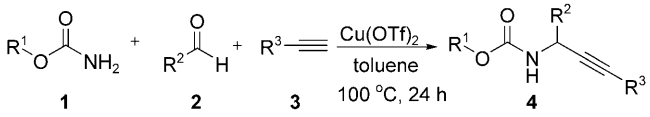
Entry	Catalyst	Solvent	Yield [%][b]
1	CuBr	toluene	trace
2	$CuBr_2$	toluene	trace
3	CuCl	toluene	trace
4	$CuCl_2$	toluene	0
5	$Cu(OAc)_2$	toluene	0
6	$Cu(acac)_2$	toluene	0
7	CuI	toluene	0
8	CuOTf·toluene	toluene	77
9	$Cu(OTf)_2$	toluene	87
10[c]	HOTf	toluene	28
11[d]	$CuCl_2$/HOTf	toluene	28
12[e]	$Cu(OTf)_2$	toluene	61
13[f]	$Cu(OTf)_2$	toluene	37
14	$Cu(OTf)_2$	THF	39
15	$Cu(OTf)_2$	DCE	44
16	$Cu(OTf)_2$	CH_3CN	32
17	$Cu(OTf)_2$	EtOH	0
18	$Cu(OTf)_2$	DMF	0
19	$Cu(OTf)_2$	DMSO	0
20	$Cu(OTf)_2$	H_2O	0
21	$Cu(OTf)_2$	neat	53
22[g]	$Cu(OTf)_2$	toluene	0
23[h]	$Cu(OTf)_2$	toluene	18
24[i]	$Cu(OTf)_2$	toluene	20

[a] Benzaldehyde (0.2 mmol), phenylacetylene (0.3 mmol), carbamate (0.24 mmol), copper catalyst (10 mol%), and solvent (0.4 mL).
[b] NMR yield using an internal standard.
[c] HOTf (20 mol%).
[d] $CuCl_2$ (10 mol%) and HOTf (20 mol%).
[e] $Cu(OTf)_2$ (5 mol%).
[f] At 70 °C.
[g] Tetramethylethylenediamine (TMEDA, 10 mol%) was added.
[h] 2,2′-Bipyridine(10 mol%) was added.
[i] 1,10-Phenanthroline(10 mol%) was added.

With the optimized reaction conditions in hand, we began to examine the scope of this coupling reaction with various aldehydes, alkynes and carbamates (Table 2). Firstly, we examined the effect of varying the carbamate component on the reaction. When it was changed from the *n*-butyl carbamate to a benzyl carbamate, the yields of the desired products were slightly decreased (**4a**, **4b**, **4c**, and **4d**). Next, we examined the effect of different aldehydes on this transformation. Both electron-withdrawing and electron-donating substituted aromatic aldehydes gave similar yields (**4e**, **4f**, **4g** and **4h**), while a lower yield was obtained when 4-(trifluoromethyl)benzaldehyde was the substrate (**4i**). Aliphatic aldehydes, such as hydrocinnamaldehyde, hexanal and cyclohexylcarboxaldehyde, were also investigated under the optimized reaction conditions. It was found that only cyclohexylcarboxaldehyde gave a low yield of the desired product (**4k**) and the corresponding propargylcarbamates were not detected using either hydrocinnamaldehyde or hexanal as a substrate. Finally, the alkyne component of the three-component coupling reaction was examined, which showed that electron-poor aromatic alkynes gave better yields than the electron-rich ones (**4l**, **4m**, **4n**, **4o**, and **4p**). Aliphatic alkynes examined (e.g., 1-tetradecyne and 1-decyne) gave much lower yields, possibly due to their decreasing acidity.

A tentative mechanism for the copper-catalyzed aldehyde–alkyne–carbamate coupling is proposed in Scheme 2. Firstly, Cu(II) coordinates to a terminal alkyne and generates a terminal copper-acetylide intermediate. Meanwhile, the carbamate reacts with an

Table 2. Copper(II) triflate-catalyzed three-component coupling of aldehydes, alkynes, and carbamates.[a]



1 2 3 4

Entry	R^1	R^2	R^3	Product	Yield [%][b]
1	*n*-Bu	Ph	Ph	**4a**	71
2	Et	Ph	Ph	**4b**	70
3	Me	Ph	Ph	**4c**	65
4	Bn	Ph	Ph	**4d**	64
5	*n*-Bu	4-CH_3-C_6H_4	Ph	**4e**	68
6	*n*-Bu	4-Cl-C_6H_4	Ph	**4f**	71
7	*n*-Bu	4-Br-C_6H_4	Ph	**4g**	73
8	*n*-Bu	2-Br-5-F-C_6H_3	Ph	**4h**	67
9	*n*-Bu	4-CF_3-C_6H_4	Ph	**4i**	35
10	*n*-Bu	1-naphthyl	Ph	**4j**	51
11	*n*-Bu	Cy	Ph	**4k**	8
12	*n*-Bu	Ph	4-CH_3-C_6H_4	**4l**	53
13	*n*-Bu	Ph	4-*n*-Bu-C_6H_4	**4m**	43
14	*n*-Bu	Ph	4-*t*-Bu-C_6H_4	**4n**	62
15	*n*-Bu	Ph	4-CF_3-C_6H_4	**4o**	71
16	*n*-Bu	Ph	2-F-C_6H_4	**4p**	74
17	*n*-Bu	Ph	4-C_6H_5-C_6H_4	**4q**	45

[a] Aldehyde (0.5 mmol), alkyne (0.75 mmol), carbamate (0.6 mmol), and copper (II) triflate (10 mol%) in toluene (1.0 mL) under N_2.
[b] Isolated yield based on benzaldehyde.

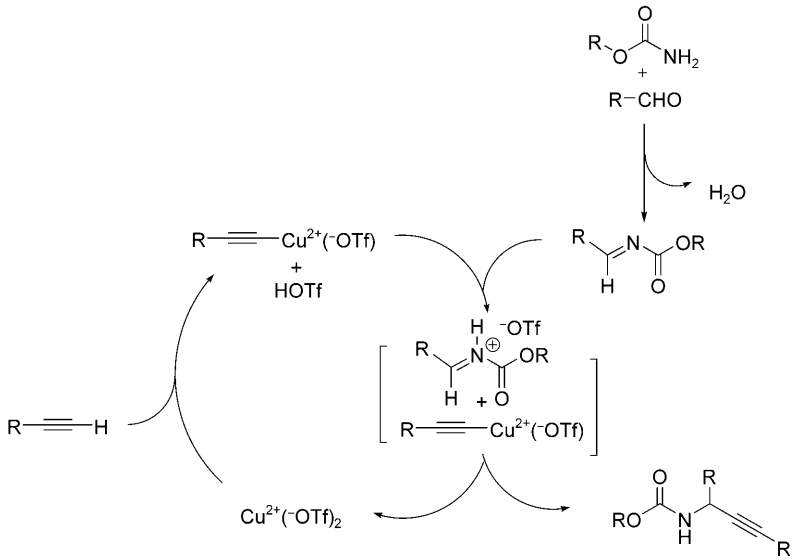
aldehyde to generate an imino amide intermediate, which is protonated by the HOTf generated *in situ* to form the acyl immonium intermediate. Then, a nucleophilic addition of the terminal copper-acetylide to the immonium salt gives the propargylic carbamate product and regenerates the Cu(II). Based on the results obtained, the formation of the imino amide intermediate is likely the rate-determining step. Compared to aliphatic aldehydes, aromatic ones favor the formation of conjugated imino amide intermediates, which can explain the different reactivities between aromatic and aliphatic aldehydes.

In conclusion, we have developed a simple, direct, and effective three-component coupling of aldehydes, alkynes, and carbamates with copper(II) triflate as catalyst. The method allows us to prepare a diverse range of propargylcarbamates in moderate to high yields. In addition, no other co-catalyst or ligand was required in this transformation with water as the only thereotical by-product. Further investigation into the enantioselective version of this process and its extension to other amino derivatives are underway.

Experimental Section

Typical Procedure for the Coupling of *n*-Butyl Carbamate, Benzaldehyde, and Phenylacetylene

An oven-dried reaction vessel was charged with *n*-butyl carbamate (70.3 mg, 0.6 mmol), benzaldehyde (51 μL, 0.5 mmol), and toluene (0.3 mL) under N_2 (1 atm). The resulting mixture was stirred at room temperature for 20 min. Then $Cu(OTf)_2$ (18.1 mg, 0.05 mmol), phenylacetylene (83 μL, 0.75 mmol) and toluene (0.7 mL) were added to the reaction vessel, which was then sealed and the resulting solution was stirred at 100 °C for 24 h. The resulting mixture was cooled to room temperature and the residue was purified by column chromatography (silica gel, hexane/diethyl ether) to give **4a** as a white solid.



Scheme 2. Tentative mechanism.

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