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Efficient synthesis of propargylamines from terminal alkynes, dichloromethane and tertiary amines over silver catalysts†

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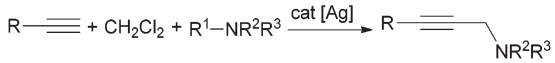
A simple, efficient and highly functional group compatible method for the synthesis of propargylamines from terminal alkynes, dichloromethane and tertiary amines using silver catalysts has been developed.

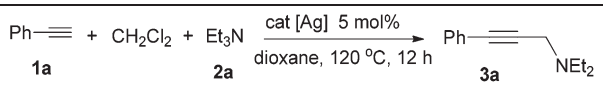
Propargylamines have attracted considerable attention over the past few decades due to their wide applications in medical and synthetic chemistry.[1,2] Conventional synthetic procedures for the preparation of propargylamines involve the use of stoichiometric amounts of alkynylmetal reagents which are highly moisture-sensitive, and the harsh conditions hinder their wide application.[3] Direct oxidative cross-coupling of tertiary amines with terminal alkynes represents an alternative route for the synthesis of propargylamines,[4] but the approach is far from ideal due to the use of dangerous peroxides and extra additives. Recently, the three-component coupling reaction of alkynes and aldehydes (or dihalomethanes) with primary (or secondary) amines provided a more efficient and attractive method to produce propargylamines.[5,6] Although these protocols represent approaches that are more straightforward for the synthesis of propargylamines, the reactions are limited to primary (secondary) amines, and some functional groups such as the carbonyl group are generally sensitive to these amines. Compared with primary and secondary amines, tertiary amines are inexpensive, commercially available and relatively stable to many functional groups. Herein, for the first time a silver-catalyzed reaction of alkyne, dichloromethane and tertiary amine is reported for the formation of propargylamines in high to excellent yields *via* the selective cleavage of C–N bonds (eqn (1)). The method is highly tolerant to functional groups and can be applied to both aromatic and aliphatic alkynes. As an alternative method for the production of propargylamines, we believe that the protocol has a great deal of applicability.



(1)

First, phenylacetylene, dichloromethane and triethylamine were chosen as model reactants for the optimization of reaction conditions, and selected results are shown in Table 1. Using 5 mol% AgOAc as a catalyst, we screened parameters such as the amounts of CH_2Cl_2 and Et_3N (Table 1, entries 1–4), and the best result is obtained under the conditions of 1 mmol of phenylacetylene, 15 mmol of CH_2Cl_2 and 3 mmol of Et_3N in 1 mL dioxane at 120 °C for 12 h. The effect of AgOAc loading was also investigated. When 1 mol% of AgOAc is used, only 62% yield of **3a** is obtained (Table 1, entry 5). However,

Table 1 Optimization of the reaction conditions[a]



Entry	CH_2Cl_2 (mmol)	Et_3N (mmol)	Catalyst	Yield[b] (%)
1	1	3	AgOAc	Trace
2	3	3	AgOAc	10
3	7	3	AgOAc	38
4	15	3	AgOAc	98
5[c]	15	3	AgOAc	62
6[d]	15	3	AgOAc	98
7[e]	15	3	AgOAc	40
8	15	3	$AgNO_3$	88
9	15	3	Ag_2CO_3	80
10	15	3	$AgOSO_2CF_3$	80
11	15	3	$AgBF_4$	90
12	15	3	$AgClO_4$	70
13	15	3	$AgOSO_2C_4F_9$	92
14	15	3	AgCl	85
15	15	3	—	Trace

[a] Reaction conditions: phenylacetylene (1.0 mmol), CH_2Cl_2 (1–15 mmol), Et_3N (3 mmol), dioxane (1 mL), N_2, 120 °C, 12 h, a sealed tube. [b] Reported yields were based on phenylacetylene and determined by GC using dodecane as an internal standard. [c] AgOAc (1 mol%). [d] AgOAc (7 mol%). [e] 100 °C.

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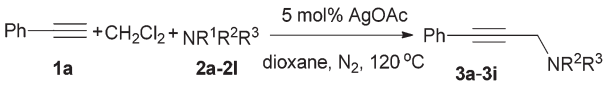
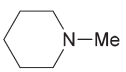
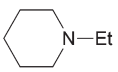
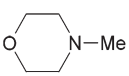
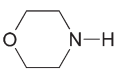
further increase of AgOAc to 7 mol% does not improve the yield of **3a** (Table 1, entry 6). The reaction is found to be sensitive to temperature, *e.g.* at 100 °C, only 40% **3a** is produced under similar conditions (Table 1, entry 7). Other silver catalysts are also effective for this three-component coupling reaction (Table 1, entries 8–14). It should be noted that the addition of the silver catalyst is essential; in the absence of the silver catalyst, only a trace amount of **3a** is detected under similar reaction conditions (Table 1, entry 15).

The method can be successfully applied to other terminal alkynes and tertiary amines, indicating that the reaction is generally applicable to production of propargylamines (Tables 2 and 3). Under the optimized conditions described above, we find that a variety of tertiary amines **2a–2i**, both symmetrical and unsymmetrical, react readily with phenylacetylene and dichloromethane to give the corresponding propargylamines *via* C–N bond cleavage (Table 2). For a symmetrical tertiary amine, only one of the three C–N bonds is cleaved to give the product (Table 2, entries 1–5). The three-component coupling reaction seems to be strongly affected by the alkyl chain length of amines. It is found that the increase of alkyl chain length has a negative effect on the yield of products; namely, the longer the alkyl chain length, the lower the yield. For unsymmetrical amines, a high selectivity to C–N bond cleavage is observed over the tertiary amines. For example, a high selectivity to N–Me cleavage is observed using the substrate of dimethylcyclohexylamine **2f** and the yield of product **3f** is 89% (Table 2, entry 6). The high selectivity to C–N bond cleavage is also detected over cyclic amines, such as piperidine-derived tertiary amine (**2g**, **2h**) and morpholine-derived tertiary amine **2i** (Table 2, entries 7–9). Under similar reaction conditions, secondary amines are also good substrates, and higher yields (95–96%) of the corresponding products *via* selective N–H cleavage are obtained in comparison to those of the previously reported catalytic systems (Table 2, entries 10–12).[6]

Besides the tertiary amines, a variety of alkynes can be smoothly converted to the corresponding propargylamines under the optimized conditions. As compiled in Table 3, the silver-catalyzed system is effective for both aromatic and aliphatic alkynes. It is worth noting that the reaction shows wide functional-group tolerance; functional groups such as ether (Table 3, entry 5), Br (Table 3, entry 6), Cl (Table 3, entry 7), F (Table 3, entry 8), CF_3 (Table 3, entry 9), NO_2 (Table 3, entry 10), CN (Table 3, entry 11), and ester (Table 3, entry 16) are all compatible, and the corresponding propargylamines are

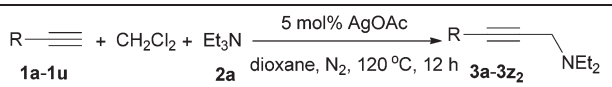
Table 2 Substrate scope of amines[a]

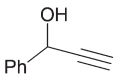
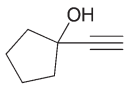
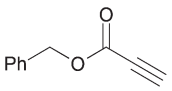
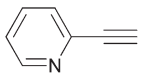
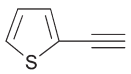


Entry	Amine		Time (h)	Product	Yield[b] (%)
1		R_3N			
	2a	R = Et	12	**3a**	93
2	**2b**	R = *n*-Pr	36	**3b**	88
3	**2c**	R = allyl	40	**3c**	86
4	**2d**	R = *n*-Bu	60	**3d**	85
5	**2e**	R = *n*-Oct	96	**3e**	70
6	**2f**		8	**3f**	89
7	**2g**		10	**3g**	85
8	**2h**		12	**3g**	87
9	**2i**		10	**3h**	88
10[c]	**2j**	$(n\text{-}C_2H_7)_2N\text{–}H$	7	**3b**	96
11[d]	**2k**	$Cy_2N\text{–}H$	12	**3i**	95
12[e]	**2l**		7	**3h**	96

[a] Reaction conditions: phenylacetylene (1.0 mmol), CH_2Cl_2 (15 mmol), amines (3 mmol), dioxane (1 mL), N_2, 120 °C, a sealed tube. [b] Isolated yield. [c] Di-*n*-propylamine. [d] Dicyclo hexylamine. [e] Morpholine.

Table 3 Substrate scope of terminal alkynes[a]



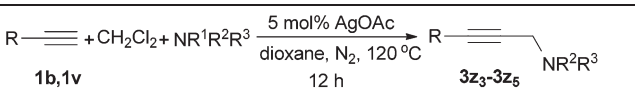
Entry	Terminal alkyne		Product	Yield[b] (%)
1	**1a**	C_6H_5—	**3a**	93
2	**1b**	*p*-Me-C_6H_4—	**3j**	88
3	**1c**	*t*-Bu-C_6H_4—	**3k**	89
4	**1d**	*n*-C_5H_{11}-C_6H_4—	**3l**	89
5	**1e**	*p*-MeO-C_6H_4—	**3m**	90
6	**1f**	*p*-Br-C_6H_4—	**3n**	92
7	**1g**	*p*-Cl-C_6H_4—	**3o**	90
8	**1h**	*p*-F-C_6H_4—	**3p**	89
9	**1i**	*p*-F_3C-C_6H_4—	**3q**	91
10	**1g**	*p*-O_2N-C_6H_4—	**3r**	92
11	**1k**	*p*-NC-C_6H_4—	**3s**	90
12[c]	**1q**	—C_6H_4—	**3t**	88
13	**1l**	HO—C_4H_8—	**3u**	87
14	**1m**		**3v**	89
15	**1n**		**3w**	80
16	**1o**	*m*-HO-C_6H_4—	—	—
17	**1p**		**3x**	91
18	**1r**	Me_3Si—	**3y**	82
19	**1s**	*n*-C_8H_{17}—	**3z**	83
20	**1t**		**3z$_1$**	88
21	**1u**		**3z$_2$**	87

[a] Reaction conditions: terminal alkynes (1.0 mmol), CH_2Cl_2 (15 mmol), Et_3N (3 mmol), dioxane (1 mL), N_2, 120 °C, 12 h, a sealed tube. [b] Isolated yield. [c] 1,4-Diethynylbenzene (1.0 mmol), AgOAC (10 mol%), CH_2Cl_2 (30 mmol), Et_3N (6 mmol), dioxane (1 mL), 20 h.

produced in high to excellent yields. In addition, two amino groups can be easily introduced into diyne as exemplified by the alkylation of aromatic diyne **1q** (Table 3, entry 12). Furthermore, aliphatic alkynes are good substrates, giving the corresponding propargylamines in good yields (Table 3, entries 13–15, 16–19). Especially the yields are still good when aliphatic alkynes bearing active hydroxyl groups are used as substrates (Table 3, entries 13–15). Unfortunately, ethynylphenol fails to give the propargylamine product perhaps due to the acidity (Table 3, entry 15). The heteroaryl alkynes such as 2-ethynylpyridine and 2-ethynylpyridine are also good substrates, and products **3z$_1$** and **3z$_2$** are obtained in good yields (Table 3, entries 20–21).

Under the optimized conditions, substituted alkynes react with different tertiary amines smoothly to furnish the desired

Table 4 Scope of alkynes and tertiary amines[a]

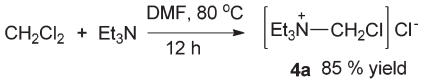


Entry	Alkyne	Amine	Product	Yield[b] (%)
1	R = *p*-Me-C_4H_6— **1b**	**2f**	**3z$_3$**	92%
2	R = Me—C(=O)—C_4H_6— **1v**	**2a**	**3z$_4$**	91%
3	R = Me—C(=O)—C_4H_6— **1v**	**2b**	**3z$_5$**	90%

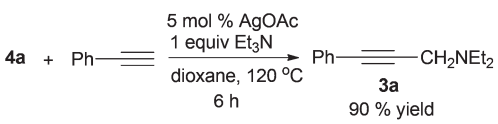
[a] Reaction conditions: alkyne (1.0 mmol), CH_2Cl_2 (15 mmol), tertiary amine (3 mmol), dioxane (1 mL), N_2, 120 °C, a sealed tube. [b] Isolated yield.

products (Table 4). Methyl phenyl acetylene **1b** reacts with *N*,*N*-dimethyl cyclohexylamine **2f** to give the corresponding propargylamine **3z$_3$** in 92% yield (Table 4, entry 1). The carbonyl group is found compatible in this reaction system, *e.g.* 1-(4-ethynylphenyl)ethanone **1v** reacts with **2a** and **2b** to give the corresponding products **3z4–3z$_5$** in 90% and 91% yield respectively (Table 4, entries 2–3).

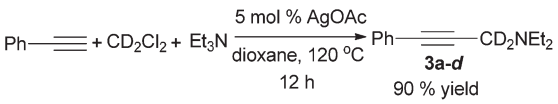
The reaction mechanism was also investigated. Under the adopted reaction conditions, it is found that CH_2Cl_2 reacts with Et_3N to form 1-chloro-*N*,*N*,*N*-triethylmethaniminium chloride (**4a**) in 85% yield as colorless crystals at 80 °C in DMF (eqn (2)). By heating **4a** with an equal amount of phenylacetylene under the conditions of 5 mol% AgOAc in dioxane at 120 °C for 6 h, the corresponding propargylamine **3a** is obtained quantitatively (eqn (3)). An experiment using CD_2Cl_2 instead of CH_2Cl_2 as the substrate confirms that the two protons of the methylene group of dichloromethane are not affected during the reaction, indicating that the proton for the formation of amine hydrochloride comes from alkyne (eqn (4)).



(2)

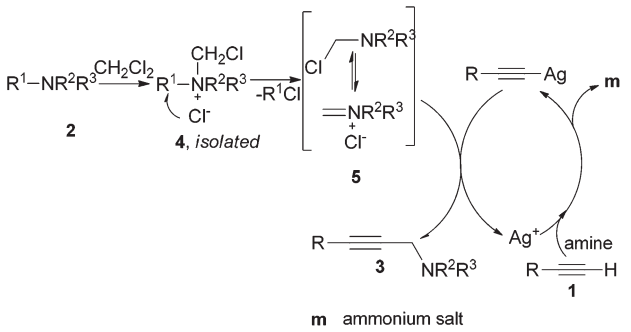


(3)



(4)

According to the reported studies[7–9] and our experimental results, the catalytic reaction pathways for the three-component coupling reaction are proposed as shown in Scheme 1. First, methaniminium chloride **4** is formed by the reaction of $R^1R^2R^3N$ with CH_2Cl_2,[7] and then decomposes *via* R^1Cl dissociation to produce methyleneammonium chloride **5**.[8] It is known that **5** is a Mannich reaction intermediate,[5] which reacts with silver acetylide[9] to give the corresponding propargylamine, with the Ag(I) catalyst being regenerated.[5c]



Scheme 1 A plausible mechanism for the formation of propargylamines.

In conclusion, for the first time, an efficient method for the preparation of propargylamines *via* a silver-catalyzed three-component coupling reaction using tertiary amines as the source of the nitrogen group is demonstrated. The reaction shows high functional-group tolerance and can be conducted without the use of an exotic base, a co-catalyst or an additive. The success of the present studies not only provides a new strategy for the preparation of propargylamines but also suggests a powerful method for C–N bond cleavage.

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