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A general and mild copper-catalyzed three-component synthesis of protected homoallyl amines

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ABSTRACT

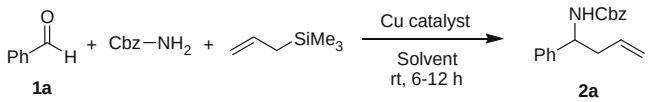
A mild and highly efficient copper-catalyzed, one-pot, three-component reaction is developed for the synthesis of homoallyl amines. Reaction of an aldehyde, a carbamate, and allyltrimethylsilane in the presence of 5 mol % $Cu(OTf)_2$ furnishes the corresponding protected homoallylic amines in good to excellent yields.

Lewis acid-catalyzed allylations of imines or iminium species with allylating reagents, such as allyl silane or borane reagents are effective methods for the introduction of an amino group into carbon frameworks.[1] In addition, homoallyl amines and their derivatives are considered to be useful precursors in natural product synthesis[2] and in β-lactam chemistry[3] and are valuable intermediates in drug discovery.[4] The synthesis of homoallyl amines from aldimines and allyltrimethylsilane or allyltributylstannane, is inefficient due to the requirement of additional synthetic transformations.[5,6] A one-pot, three-component reaction was first reported for the preparation of homoallylamines by Panek.[7] Subsequently, Veenstra reported an improved one-pot, three-component reaction for the synthesis of protected homoallyl amines.[8] The main drawback of this reaction was the use of excess Lewis acid ($BF_3{\cdot}OEt_2$). Yamamoto,[9] Ollevier,[10] Phukan,[11] and Williamson[12] have demonstrated three-component syntheses of homoallyl amines by employing various Lewis acids. All of these methods, while offering some advantages, also suffer from disadvantages in terms of the use of expensive catalysts, incomplete reactions, prior silylation of the carbamate, and limited substrate scope. Furthermore, their scope for enantioselective synthesis using chiral ligands is extremely limited. Hence, the development of new methods that lead to potentially general and convenient procedures for this transformation is still of interest.

In recent years, copper-catalyzed reactions have received considerable attention as they are more affordable, highly active, less toxic, and inexpensive in contrast to classical Lewis acids. Copper complexes have been studied extensively by Pfaltz,[13] Andrus,[14] and Katsuki[15] using chiral bis and tris oxazoline ligands for asymmetric synthesis. Copper(I or II) triflates have been widely used as catalysts for various chemical transformations.[16] To the best of our knowledge, the copper-catalyzed three-component reaction for the synthesis of homoallyl amines has not been studied. Herein, we report a mild and efficient synthesis of homoallyl amines using copper(II) triflate as an inexpensive copper catalyst.

We first optimized the reaction conditions for the copper-catalyzed, one-pot, three-component allylation of in situ-generated imines. The results are summarized in Table 1. Initially, 10 mol % of CuOTf was utilized to promote the reaction of benzaldehyde, benzyl carbamate ($CbzNH_2$), and allyltrimethylsilane in different solvents. The results were disappointing when dichloromethane and acetonitrile were used as solvents with yields of only 20% and 35% being obtained, respectively (entries 1 and 2). When 10 mol % of $Cu(OTf)_2$ was used in acetonitrile at room temperature the desired homoallyl amine was obtained in 80% yield (Table 1, entry 3). Further investigation of the reaction conditions revealed that acetonitrile was the best solvent and a catalyst loading as low as 5 mol % could be used to afford the highest yield of 92% (entry 4).[17] Changing the solvent to dichloromethane reduced

Table 1
Optimization of the copper-catalyzed one-pot, three-component allylation of in situ-generated imines



1a **2a**

Entry	Catalyst	mol %	Solvent	Time (h)	Yield (%)
1	CuOTf	10	CH_2Cl_2	24	20
2	CuOTf	10	CH_3CN	24	35
3	$Cu(OTf)_2$	10	CH_3CN	12	80
4	**$Cu(OTf)_2$**	**5**	CH_3CN	**10**	**92**
5	$Cu(OTf)_2$	5	CH_2Cl_2	24	40
6	$Cu(OTf)_2$	20	CH_3CN	12	70

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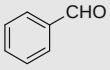
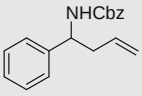
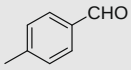
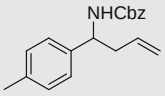
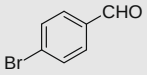
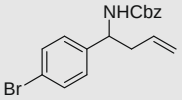
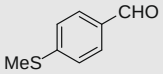
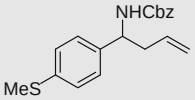
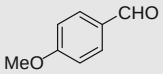
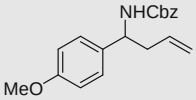
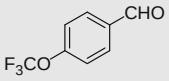
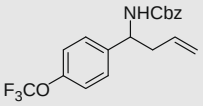
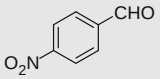
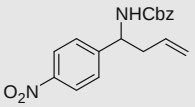
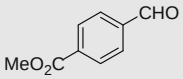
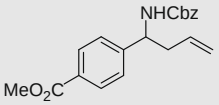
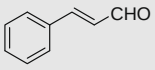
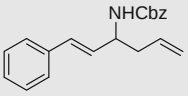
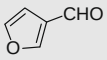
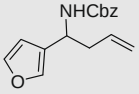
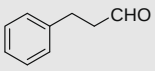
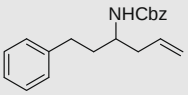
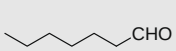
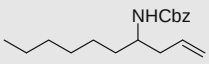
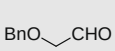
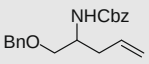
Table 2
Synthesis of various substituted homoallyl amines[a]

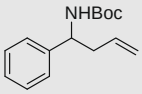
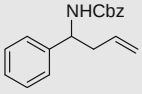
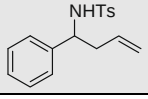
Entry	Aldehyde **1**	Time (h)	Homoallyl amine	**2**[b]	Yield (%)
1		10		**2a**	92
2		8		**2b**	90
3		8		**2c**	88
4[18]		6		**2d**	95
5		8		**2e**	85
6[19]		8		**2f**	85
7		8		**2g**	75
8[20]		12		**2h**	76
9		6		**2i**	85
10[21]		12		**2j**	78
11		6		**2k**	88
12		8		**2l**	82
13[22]		8		**2m**	92

[a] Conditions: $Cu(OTf)_2$ (5 mol %), acetonitrile, rt.
[b] All products (except products **2d**, **2f**, **2h**, **2j**, and **2m**) have been previously reported.[8,10–12]

the yield significantly to 40% (entry 5). When 20 mol % of the copper catalyst was used, the yield dropped considerably to 70% (entry 6).

The substrate scope for the three-component reaction of various aldehydes, benzyl carbamate ($CbzNH_2$), and allyltrimethylsilane was found to be general (Table 2). In the presence of 5 mol % of

Table 3
Synthesis of protected homoallyl amines from benzaldehyde

Entry	Amine	Time (h)	Homoallyl amine	Yield (%)
1	Boc-NH_2	8		82
2	Cbz-NH_2	10		92
3	Ts-NH_2	6		80

Conditions: $Cu(OTf)_2$ (5 mol %), acetonitrile, rt.

copper(II) triflate, a variety of aldehydes were successfully transformed into the corresponding Cbz-protected homoallyl amines at room temperature. Moreover, the conditions were mild and the reactions were rapid, and no side products were formed. First, we chose 4-substituted aromatic aldehydes to carry out the allylation reaction. As is evident from Table 2, besides benzaldehyde (entry 1), other substituted aromatic aldehydes also served as good substrates for this reaction. For example, mono-substituted benzaldehydes (methyl, bromo, and methylthiol) gave the desired homoallyl amines in excellent yields (>88%) (entries 2–4). Interestingly, aldehydes with electron-donating groups on the phenyl ring (entries 5 and 6) gave the expected products in good yields. On the other hand, aromatic aldehydes possessing electron-withdrawing groups on the phenyl ring and α,β-unsaturated aldehydes (entries 7–9) gave the corresponding protected homoallyl amines only in moderate yields. This methodology could be extended to a variety of functional groups such as a long-chain aliphatic and phenyl propionaldehyde. Interestingly, benzyl-protected glycolaldehyde gave the desired product in excellent yield, which allows an easy access to aminoalcohols (92%, entry 13, Table 2).

To further study the scope of the reaction, we also examined the reaction of benzaldehyde and allyl trimethylsilane with benzyl carbamate, *tert*-butyl carbamate, and *para*-toluene sulfonamide in the presence of 5 mol % $Cu(OTf)_2$. The results are summarized in Table 3. The reaction with *tert*-butyl carbamate went to completion to provide the Boc-protected homoallyl amine in 82% yield. Similarly, the benzyl carbamate and *para*-toluene sulfonamide reactions afforded homoallyl amines in excellent yields (92% and 80%, respectively).

In summary, we have demonstrated a highly efficient synthesis of homoallylamines via a copper-catalyzed, one-pot, three-component reaction of aldehydes, carbamates, and allyltrimethylsilane. This method offers several advantages including mild reaction conditions, a low quantity of the catalyst (5 mol %), and no formation of by-products. The current method can be applied to numerous functionalized substrates. Extension of this work by employing chiral ligands is underway.

Acknowledgments

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17. *General experimental procedure for the synthesis of homoallyl amines:* To a stirred solution of aldehyde (1 mmol), benzyl carbamate (1.2 mmol), and allyltrimethylsilane (1.5 mmol) in dry acetonitrile (2 mL, 0.5 M) under a nitrogen atmosphere was added $Cu(OTf)_2$ (5 mol %) at room temperature. The mixture was stirred until the reaction was complete as indicated by TLC. The reaction mixture was quenched with saturated NH_4Cl solution and diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc, and the combined organic extract was washed with water and brine. Drying over anhydrous sodium sulfate and subsequent removal of the solvent under vacuum resulted in a colorless oily residue which was purified by column chromatography on silica gel to give the desired product.
18. *Entry 4,* Table 2*: Benzyl 1-[4-(methylthio)phenyl]but-3-enylcarbamate* (**2d**): ^1H NMR (400 MHz, $CDCl_3$): δ in ppm 7.34 (br s, 4H), 7.23–7.17 (m, 5H), 5.71–5.61 (m, 1H), 5.13–5.03 (m, 5H), 4.76 (d, J = 5.6 Hz, 1H), 2.51 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ in ppm = 155.6, 137.3, 136.3, 133.6, 128.5, 128.1, 126.8, 118.6, 66.8, 54.1, 40.9, 15.9. IR ($CHCl_3$): ν_{max} = 3016, 1716, 1500, 1215 cm^{-1}. HRMS (ESI): m/z: calcd for $C_{19}H_{22}NO_2S$: 328.1371 $[M+H]^+$; found: 328.1377.
19. *Entry 6,* Table 2*: Benzyl 1-[4-(trifluoromethoxy)phenyl] but-3-enylcarbamate* (**2f**): ^1H NMR (400 MHz, $CDCl_3$): δ in ppm 7.34–7.32 (m, 7H), 7.17 (d, J = 8.2 Hz, 2H), 5.70–5.60 (m, 1H), 5.14–5.03 (m, 5H), 4.81 (br s, 1H), 2.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ in ppm 155.6, 148.3, 136.2, 133.1, 128.5, 128.2, 127.6, 121.7, 119.1, 119.0, 66.9, 53.8, 40.9. IR ($CHCl_3$): ν_{max} = 3020, 1708, 1508, 1261, 1215 cm^{-1}. HRMS (ESI): m/z: calcd for $C_{19}H_{19}NO_3F_3$: 366.1317 $[M+H]^+$; found: 366.1324.
20. *Entry 8,* Table 2*: Methyl 4-[1-(benzyloxycarbonylamino)but-3-enyl] benzoate* (**2h**): ^1H NMR (400 MHz, $CDCl_3$): δ in ppm 8.00 (d, J = 8.2 Hz, 2H), 7.34–7.32 (m, 7H), 5.68–5.58 (m, 1H), 5.23 (br s, 1H), 5.13–5.02 (m, 4H), 4.85 (d, J = 5.5 Hz, 1H), 3.90 (s, 3H), 2.52 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ in ppm 166.8, 155.6, 147.2, 136.2, 133.1, 129.9, 129.2, 128.5, 128.2, 126.2, 119.0, 66.9, 54.3, 52.1, 40.8. IR ($CHCl_3$): ν_{max} = 3433, 3020, 1701, 1504, 1280 cm^{-1}. HRMS (ESI): m/z: calcd for $C_{20}H_{22}NO_4$: 340.1549 $[M+H]^+$; found: 340.1552.
21. *Entry 10,* Table 2*: Benzyl 1-(furan-3-yl)but-3-enylcarbamate* (**2j**): ^1H NMR (500 MHz, $CDCl_3$): δ in ppm 7.37–7.35 (m, 5H), 7.33–7.31 (m, 2H), 6.33 (m, 1H), 5.78–5.70 (m, 1H), 5.14–5.09 (m, 4H), 4.83 (br s, 1H), 4.83 (d, J = 6.2 Hz, 1H), 2.52 (d, J = 4.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ in ppm 155.7, 143.3, 139.1, 136.4, 133.6, 128.1, 126.4, 118.5, 109.0, 66.8, 46.8, 39.7. IR ($CHCl_3$): ν_{max} = 3016, 1708, 1504, 1334, 1219 cm^{-1}. HRMS (ESI): m/z: calcd for $C_{13}H_{20}NO_3$: 238.1443 $[M+H]^+$; found: 238.1441.
22. *Entry 13,* Table 2*: Benzyl 1-(benzyloxy)pent-4-en-2-ylcarbamate* (**2m**): ^1H NMR (500 MHz, $CDCl_3$): δ in ppm 7.41–7.40 (m, 5H), 7.38–7.33 (m, 5H), 5.86–5.78 (m, 1H), 5.15–5.10 (m, 5H), 4.55 (dd, J = 12.0, 24.0 Hz, 2H), 3.95 (s, 1H), 3.55–3.53 (m, 2H), 2.46–2.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ in ppm 156.0, 138.0, 136.6, 134.3, 128.5, 128.4, 128.1, 127.7, 127.6, 117.9, 73.2, 70.9, 66.6, 50.4, 36.4. IR ($CHCl_3$): ν_{max} = 3437, 3016, 1712, 1508, 1215 cm^{-1}. HRMS (ESI): m/z: calcd for $C_{20}H_{24}NO_3$: 326.1756 $[M+H]^+$; found: 326.1751.