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A New Method for Intramolecular Chloroamination of Unfunctionalized Olefins

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Abstract: A new method for the intramolecular chloroamination of unfunctionalized olefins is reported. The reactions were carried out at room temperature for 3 h using hydrated copper(II) chloride as both promoter and chlorine source, and the corresponding vincinal haloamines were obtained in good isolated yields.

Keywords: chloroamination; 2-chloromethylpyrrolidines; 3-chloropiperidines; copper(II) chloride; unfunctionalized olefins

Vincinal haloamines such as 2-chloromethylpyrrolidines or 3-chloropiperidines have shown great potential as mechanism-based anticancer agents (nitrogen mustards),[1] these structures also appear as important subunits of natural products such as benzastatins,[2] cylindricines,[3] or securamines.[4]

Early reports for the preparation of 2-halomethylpyrrolidines used an intramolecular haloamination of an aminoalkene in the presence of dihalogen.[5] Göttlich et al. developed the free radical intramolecular chloroamination of pent-4-en-1-amine compounds. The substrates were first converted to the corresponding N–Cl derivatives, and Cu(I)-catalyzed free radical cyclization of the chloroamines at elevated temperature gave 3-chloropiperidines as the final products.[6] Iodides such as tetrabutylammonium iodide[7] or samarium iodide[8] were also effective to promote the reaction at elevated temperature, again 3-chloropiperidines were obtained as the final products. Göttlich et al. also showed that unsaturated *N*-chloroamines could be cyclized under palladium catalysis, giving 3-chloropiperidines as the final products.[9] Somfai et al. showed that, in the presence of the Lewis acid-$TiCl_3$ system, chloroamines were able to undergo intramolecular free radical cyclizations at low temperature, giving the corresponding 2-chloromethylpyrrolidines in good to excellent yields.[10]

Chemler et al. showed that *N*-tosyl-*o*-allylaniline could be converted to the corresponding bromomethyl heterocyclic compounds using a Pd(II)/Cu(II)/K_2CO_3 catalyst system.[11] The reaction followed a Pd(II)-catalyzed hydroamination mechanism, giving a cyclic palladation intermediate which was cleaved by cupric halides to produce the final haloamination products. Lu et al. showed that the reaction could be carried out using *O*-allylic carbamate as substrate without the use of potassium or cesium carbonate.[12] Muñiz et al. realized the direct synthesis of bicyclic guanidines using a Pd(II)-CuX_2 system.[13] Michael et al. showed that NCS was also able to cleave the Pd–C intermediate, leading to the corresponding *N*-acyl-2-chloromethylpyrrolidine products in good to excellent yields.[14] Very recently Liu et al. realized the chloroamination of C=C double bonds using the $Pd(OAc)_2$-H_2O_2-$CaCl_2$ system.[15]

It is our purpose to develop new method for the preparation of unfunctionalized vincinal haloamines. In this communication we wish to report our preliminary results on Cu(II)-promoted intramolecular chloroamination of unfunctionalized olefins.

The Pd(II)-mediated cyclization reported by Chemler, Lu, Michael or Liu generally followed a hydroamination mechanism in which C=C was first activated upon coordination with palladium, and intramolecular aminopalladation of alkenes was a key step for this type of reaction.[16] Different amination products could be obtained *via* subsequent cleavage of the C–Pd bond with different reagents. In this manner, Chemler et al. realized the cyclization of arenesulfonyl-*o*-allylanilines with $Cu(OAc)_2$ under different conditions.[17] Inspired by these results, and on the basis of Cu-catalyzed C=C bond activation reactions,[18] we assumed that a similar reaction should take place when palladium was replaced by copper: the unfunctionalized C=C double bond would first be activated

upon Cu(I)- or Cu(II)-coordination, and subsequent nucleophilic attack of an amino group on the activated C=C double bond would give an intermediate which might be converted to the corresponding haloamines through intramolecular chlorine transfer or by the action of another molecule of cupric halide, thus enabling the intramolecular haloamination of unfunctionalized olefins.

To test if this assumption was reasonable, a reaction was carried out using 2,2-diphenylpent-4-en-1-amine (**1a**) as model substrate in the presence of commer-

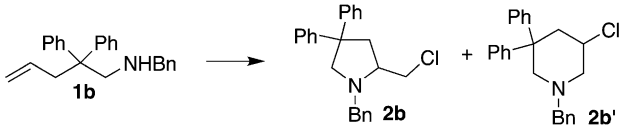
cially available cuprous and cupric halides. This compound was chosen as model substrate due to its ease of preparation and its UV absorption property which made it easy for us to monitor the reaction with TLC. However, no product was detected after the reaction mixtures had been stirred in different solvent systems at different temperatures.

We reasoned that the sterically less hindered primary amino group in substrate **1a** would coordinate to the central metal more tightly, leading to the decrease of nitrogen nucleophilicity and reactivity. This would also lead to the blockage of the essential C=C bond binding site, rendering the substrate less reactive for subsequent reaction. This unproductive binding was also observed in several transition metal-catalyzed hydroamination reactions.[19] We assumed that when a substituent was introduced to the nitrogen atom (such as benzyl group in **1b**), the coordination of the nitrogen atom to the central metal would more or less be hindered due to the steric hindrance caused by the thus introduced benzyl group. Furthermore, an alkyl group substitution on the nitrogen atom would also increase the nucleophilicity of the nitrogen group in some extent, rendering the nitrogen atom more reactive to undergo the subsequent attack on the activated C=C double bond.

On the basis of this rationale, compound **1b** was tested as another substrate in the presence of different copper salts. To our delight, products were detected in two flasks after the reaction mixtures had been stirred at room temperature in acetonitrile for 24 h: one is **1b** with 1 equiv. of anhydrous $CuCl_2$, another is **1b** with 1 equiv. of $CuCl_2{\cdot}2H_2O$. The products were later characterized as the intramolecular chloroamination product *N*-benzyl 2-chloromethyl-4,4-diphenylpyrrolidine (**2b**). The 3-chloropiperidine product (**2b′**) was also detected. This product might be formed through rearrangement of **2b** or be formed as a minor product during the reaction. The amount of **2b′** was increased when concentrating the reaction mixture at elevated temperature, and refluxing **2b** in THF resulted in a complete conversion of **2b** to **2b′**. A clean NMR spectrum was sometimes difficult due to the conversion of **2b** to **2b′** in chlorinated solvents such as $CDCl_3$.[10] A low temperature is advantageous to avoid any unnecessary conversion of **2b** to **2b′** when handling the reaction mixture, and NMR spectra should be recorded immediately after the sample has been prepared in $CDCl_3$.

Encouraged by these preliminary results, reactions in different solvents were then carried out to find suitable conditions for this reaction, and the results are summarized in Table 1.

Table 1. Reaction of **1b** in different solvents.[a]



Entry	Solvent	**1b**[b]	**2b**[b]	**2b′**[b]
1	hexane	>95	–	–
2	CH_3CN	41	49	19
3	CH_3OH	11	54	35
4	acetone	32	45	23
5	$CHCl_3$	>95	–	–
6[c]	THF	<1 (<1)	86 (87)	14 (13)
7	benzene	<1	79	21
8	toluene	<1	78	22
9	dioxane	35	45	20
10	DCE	<1	68	32

[a] *Reagents and conditions:* $CuCl_2{\cdot}2H_2O$: 0.5 equiv, reaction time = 12 h, reaction temperature = room temperature.
[b] Based on crude NMR analysis.
[c] Data in parentheses are results with anhydrous $CuCl_2$.

As shown in Table 1, solvents had a significant effect on the course of the reaction. An alkane solvent such as hexane was unsuitable for the reaction, and the starting material was recovered almost unchanged. Reactions in benzene, toluene or THF gave promising results. Complete conversion of **1b** was observed, and product **2b** could be formed in good yields in these solvents. Anhydrous and $CuCl_2{\cdot}2H_2O$ gave similar results, and the latter was used as reagent due to its lower price, its easy availability and its ease of handling. THF was chosen as reaction medium for further study due to its low toxicity, its good solubility for $CuCl_2{\cdot}2H_2O$ and its ease of removal.

To see if compound **2b′** was formed through rearrangement of product **2b** or formed as a minor product during the reaction, the reaction carried out in the open air was monitored, and the ratios of starting material **1b**, products **2b** and **2b′** were recorded. The results are listed in Table 2.

As shown in Table 2, in the presence of 0.5 equiv. of $CuCl_2{\cdot}2H_2O$, the reaction carried out at room tem-

Table 2. Reaction mixture compositions at different reaction times.[a]

Entry	Reaction time [h]	**1b**[b]	**2b**[b]	**2b′**[b]
1	1	44	47	9
2[c]	3	29 (33)	68 (58)	11 (9)
3[c]	6	12 (16)	77 (73)	11 (11)
4	9	6	79	15
5	12	<1	86	14
6	18	<1	86	14
7	24	<1	83	17
8	48	<1	85	15

[a] *Reaction conditions:* 0.5 equiv. of $CuCl_2 \cdot 2H_2O$, solvent = THF, reaction temperature: room temperature.
[b] Determined by crude NMR analysis.
[c] Data in parentheses were results from 0.5 equiv. of $CuCl_2$.

perature was completed in 12 h. Considering the experimental error, the ratio of **2b** to **2b′** essentially remained unchanged during the reaction, possibly indicating that the 3-chloropiperidine product **2b′** was formed during the reaction as a minor product (anti-Markovnikov product) rather than from the isomerization of the kinetic product **2b**. Again, both $CuCl_2$ and $CuCl_2 \cdot 2H_2O$ gave similar results (entries 2 and 3, data in parentheses).

Experiments were then carried out to test the thermostability of product **2b**. Somfai et al. indicated that chloromethylpyrrolidine compounds tended to isomerize to the corresponding 3-chloropiperidine compounds in chlorine-containing solvents.[10] However, it took around 18 h for compound **2b** to completely isomerize to compound **2b′** when the original reaction mixture was refluxed in THF. Another control experiment was also carried out by refluxing isolated **2b** in THF. The ratio of **2b** to **2b′** was monitored by NMR analysis, and the results are summarized in Table 3.

The results in Table 3 also showed that compound **2b** was stable enough in ethereal solvents such as THF, possibly indicating that product **2b′** appearing in reaction mixture was mainly formed as a result of a chemoselective reaction.

Table 3. Isomerization of **2b** in refluxing THF.

Entry	Time [h]	**2b**[a]	**2b′**[a]
1	1	70	30
2	3	56	44
3	6	41	59
4	9	21	79
5	12	11	88
6	15	7	93
7	18	0	> 99

[a] Determined by NMR analysis of crude reaction mixture.

To test if CuCl was also able to promote the reaction, and to study the effect of air on the course of the reaction, substrate **1b** was allowed to react with 1 equiv. of CuCl. Reactions in the presence of 0.5 equiv. of $CuCl_2 \cdot 2H_2O$ were carried out for comparison, and the results are shown in Table 4.

Table 4. Reaction of **1b** under different conditions.[a]

Entry	Cu salt (equiv.)	Conditions	**1b**[b]	**2b**[b]	**2b′**[b]
1	$CuCl_2 \cdot 2H_2O$ (0.5)	open air	<1	86	14
2	$CuCl_2 \cdot 2H_2O$ (0.5)	Ar	51	36	13
3	CuCl (1.0)	open air	52	38	10
4	CuCl (1.0)	Ar	>99	–	–
5[c]	$CuCl_2 \cdot 2H_2O$ (1.0)	Ar	<1	86	14
6[d]	$CuCl_2 \cdot 2H_2O$ (0.5)	open air	42	35	23

[a] *Reagents and conditions:* solvent = THF, reaction time = 12 h, reaction temperature = room temperature.
[b] Determined by NMR analysis of the crude reaction mixture.
[c] Reaction time = 3 h.
[d] Reaction was carried out in DMF, reaction time = 12 h.

As these results indicate, air had a drastic effect on the course of the reaction. When 0.5 equiv. of $CuCl_2 \cdot 2H_2O$ was used and the reaction was carried out in the open air, complete conversion of **1b** was observed after 12 h (entry 1), but only half of the substrate was converted when the reaction was carried out under argon (entry 2). Similarly, when 1 equiv. of CuCl was used, some substrate could be converted to products when the reaction was carried out in the open air (entry 3), and almost no reaction was observed when the reaction was carried out under argon (entry 4). This possibly indicated that Cu(I) itself was inactive for the chloroamination of **1b**, but could promote the reaction when it was oxidized to Cu(II) upon exposure to air. Cu(I) may be formed during the reaction, and the thus formed Cu(I) would have to be re-oxidized to Cu(II) in order for the reaction to proceed to completion. Air has less effect on the course of the reaction when 1 equiv. of Cu(II) was used (entry 5).

Oxygen is rather soluble in DMF.[20] To see if the oxygen concentration would have some positive effect on the course of the reaction, a reaction with 0.5 equiv. of $CuCl_2$ was carried out in DMF in the open air. However, no significant rate enhancement was observed, and the chemoselectivity could not exceed the result from THF (entry 6). Reactions carried out in DMF were not further pursued due to the difficulty of solvent removal.

After establishing a general method for intramolecular chloroamination of pent-4-en-1-amine compounds, several experiments were carried out to find optimal conditions for the reaction, and the results

are listed in Table 5. TLC analysis in an early study indicated that, in the presence of 1 equiv. of $CuCl_2 \cdot 2H_2O$, most of the starting material was consumed in 2 h, and the starting material was not detectable after 2.5 h. Lowering the amount of $CuCl_2 \cdot 2H_2O$ led to a drop of reaction rate (Table 5, entries 1 to 3), and further increasing the amount of $CuCl_2 \cdot 2H_2O$ did not show significant rate enhancement (Table 5, entries 4 to 9).

Table 5. Effect of the amount of $CuCl_2 \cdot 2H_2O$ on the course of the reaction.[a]

Entry	Equiv. of $CuCl_2 \cdot 2H_2O$	**1b**[b]	**2b**[b]	**2b′**[b]
1	0.25	42	50	8
2	0.50	27	61	12
3	0.75	12	78	10
4	1.0	<1	91	9
5	2.0	<1	92	8
6	3.0	<1	90	10
7[c]	1.0	26	66	8
8[c]	2.0	24	68	8
9[c]	3.0	27	66	7

[a] *Reagents and conditions:* reaction time = 3 h, solvent = THF, reaction temperature: room temperature.
[b] Determined by NMR analysis of the crude reaction mixture.
[c] Reaction time = 1 hour.

Different substrates were then tested in Cu(II)-promoted intramolecular chloroamination. The reaction was carried out using 1 equiv. of $CuCl_2 \cdot 2H_2O$ as both reaction promoter and chlorine source, and the reaction time was fixed at 3 h to ensure complete conversion of other substrates. The results are listed in Table 6.

As shown in Table 6, both Thorpe–Ingold (**1b**–**1h**, entries 1-7, **1l**, **1p**–**1t**, entries 11, 15-19) and non-Thorpe–Ingold substrates (**1m**–**1o**, entries 12 to 14) were able to undergo the intramolecular chloroamination reaction. The reactions proceeded readily at room temperature, providing the corresponding products in good isolated yields. *N*-Phenyl substrate **1o** gave a lower yield possibly due to the lower reactivity of the nitrogen atom (entry 14), *N*-acylated or *N*-tosylated substrates (**1i** to **1k**, entries 8 to 10) failed to react, possibly due to the lack of sufficient nucleophilicity of the nitrogen atom. Reaction of hex-5-en-1-amine substrates **1q**–**1s** gave the corresponding 2-chloromethylpiperidine products **2q**–**2s** in good to excellent yields, and seven-membered ring products **2q′**–**2s′** were not detected (entries 16–18). More than a 90% isolated yield for the 2-chloromethylpyrrolidine compounds was generally difficult because of the formation of 3-chloropiperidine compounds.

In addition to terminal olefins, di- and trisubstituted substrates **1t** and **1u** were also tested, and these substrates were generally less reactive than terminal olefins. While product **2t** was isolated in 52% yield (entry 19), only a trace amount of **2u** was detected (entry 20). This may be attributed to the weaker coordination of the substituted C=C double bonds to the central metal caused by the steric hindrance of these substrates, indicating that the steric effect was one of the governing factors for the successful cyclization of a substrate.

To further prove the 2-chloromethylpyrrolidine skeleton, compound **2g** was crystallized from hexane, and the single crystal was subjected to X-ray diffraction experiment. The ORTEP drawing of **2g** indicated that the compound had a typical envelope conformation, with one phenyl group at the equatorial position and another at the axial position. The benzyl group was also placed at the equatorial position (Figure 1).

So far, all the reactions were carried out using a stoichiometric amount of $CuCl_2 \cdot 2H_2O$ as both reaction promoter and chlorine source. The fact that reactions proceeded differently in an inert atmosphere and in the open air possibly indicated an aerobic reoxidation of Cu(I) to Cu(II). After establishing a general procedure for Cu(II)-promoted intramolecular chloroamination of unfunctionalized olefins, reactions in the presence of 10 mol% of $CuCl_2 \cdot 2H_2O$ and a chlorine source were carried out to test for the possible aerobic reoxidation of Cu(I) and to establish a catalytic protocol. The results are summarized in Table 7. The chlorine source was chosen such that HCl was gently released to regenerate the $CuCl_2$ needed for the reaction. TMS or chloramine-T was not suitable for the reaction, and only small amounts of the substrate

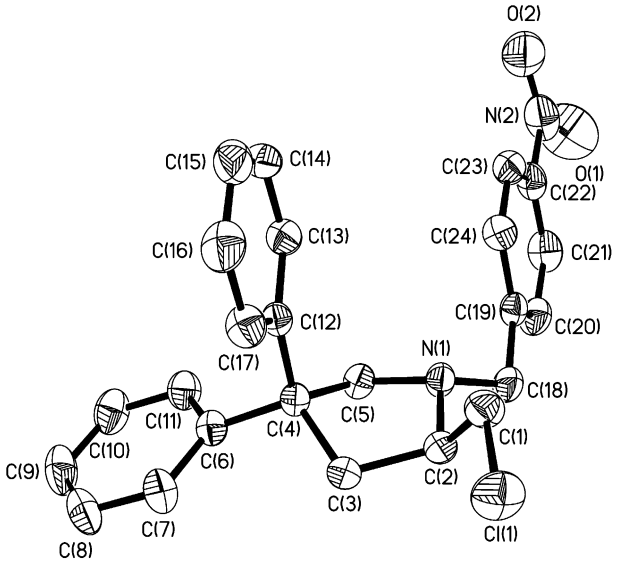
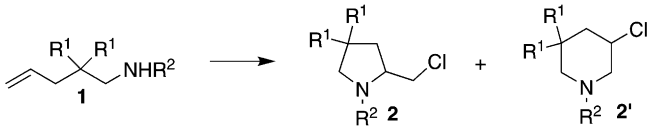
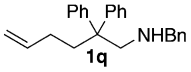
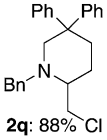
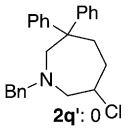
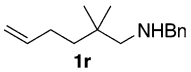
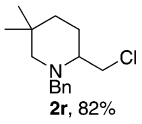
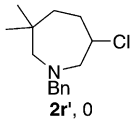
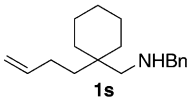
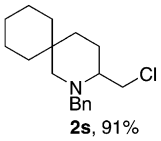
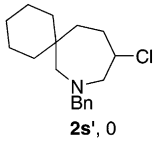
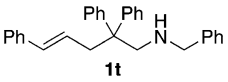
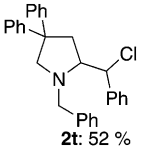
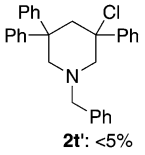
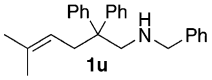
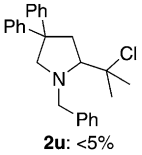


Figure 1. Crystal structure of **2g**. Hydrogen atoms are omitted for clarity.

Table 6. Cu(II)-promoted intramolecular chloroamination.[a]



Entry	Substrate	R^1	R^2	**2**[b]	**2′**[b]
1	**1b**	Ph	$PhCH_2$	74	11
2	**1c**	Ph	4-Me-$C_6H_4CH_2$	83	9
3	**1d**	Ph	4-MeO-$C_6H_4CH_2$	84	8
4	**1e**	Ph	4-F-$C_6H_4CH_2$	77	9
5	**1f**	Ph	4-Br-$C_6H_4CH_2$	80	10
6	**1g**	Ph	4-O_2N-$C_6H_4CH_2$	74	13
7	**1h**	Ph	*i*-Bu	78	0
8	**1i**	Ph	Ac	0	0
9	**1j**	Ph	Ts	0	0
10	**1k**	Ph	Boc	0	0
11	**1l**	Me	Bn	63	18
12	**1m**	H	Bn	56	19
13	**1n**	H	Bu	67	<5
14	**1o**	H	Ph	48	0
15	**1p**	-$(CH_2)_5$-	Bn	68	14
16				 **2q**: 88%	 **2q'**: 0
17				 **2r**, 82%	 **2r'**, 0
18				 **2s**, 91%	 **2s'**, 0
19				 **2t**: 52 %	 **2t'**: <5%
20				 **2u**: <5%	–

[a] *Reagents and conditions:* substrate 0.5 mmol, $CuCl_2 \cdot 2H_2O$: 0.5 mmol, solvent = THF (20 mL), reaction time = 3 h, reaction temperature = room temperature.
[b] Isolated yields.

were converted (entries 1 and 2). Ammonium chlorides such as Bu_4NCl or NH_4Cl failed to react (entries 3 and 4). It appeared that an ideal chlorine source should not only be able to release HCl, but should not undergo any reaction with the substrates or coordinate to copper. Keeping these points in mind, our attention was turned to some inorganic salts with weak Lewis acidity.

Among several metal chlorides tested (entries 5 to 9), $MgCl_2$ was superior to other chlorides regarding the conversion of the substrate and the chemoselectivity for compound **2b**. In the presence of 5 mol% of $CuCl_2 \cdot 2H_2O$ as catalyst and 1.1 equiv. of $MgCl_2$ as chlorine source, 47% of the substrate could be converted after 12 h, yielding 38% of **2b** plus 9% of 3-chloropiperidine compound **2b′**. No product was de-

Table 7. Reaction of **1b** catalyzed by 5 mol% of $CuCl_2 \cdot 2H_2O$ in the presence of different chlorine sources.[a]

Entry	Chlorine Source	(**2b**+**2b′**)[b]
1	chloramine-T	13 (10+3)
2	TMS-Cl	12 (8+4)
3	Bu_4NCl	NR[c]
4	NH_4Cl	NR
5	$ZnCl_2$	27 (17+10)
6	$MgCl_2$	47 (38+9)
7	$CaCl_2$	33 (20+13)
8	$FeCl_3$	30 (17+13)
9	LiCl	35 (19+16)
10[d]	$MgCl_2$	NR
11[e]	$MgCl_2$	76 (65+11)
12[f]	$MgCl_2$	>99 (79+21)

[a] *Reaction conditions:* $CuCl_2 \cdot 2H_2O$ loading = 5 mol%, reaction time = 24 h, solvent = THF, temperature = room temperature. Reaction carried out in open air with 1.1 equiv. of chlorine source.
[b] Determined by NMR analysis of the crude reaction mixture.
[c] NR = no reaction.
[d] In the absence of $CuCl_2 \cdot 2H_2O$.
[e] 10 mol% $CuCl_2 \cdot 2H_2O$, 12 h, oxygen atmosphere.
[f] 10 mol% $CuCl_2 \cdot 2H_2O$, 18 h, oxygen atmosphere.

tected when $MgCl_2$ alone was used (entry 10), indicating that $MgCl_2$ itself could not promote the reaction but simply acted as a chlorine source. An enhanced reaction rate was observed when the reaction was carried out in an oxygen atmosphere (entries 11 and 12).

To check the validity of these conditions, representative substrates **1b**, **1d**, **1g**, **1i**, **1j**, **1l**, **1m** and **1p** were subjected to the Cu(II)-catalyzed intramolecular chloroamination using $MgCl_2$ as chlorine source. 10 mol% of Cu(II) was finally used to reduce the reaction time, and 1.1 equiv. of $MgCl_2$ was used as chlorine source. The results are summarized in Table 8. Reactions in an oxygen atmosphere were also carried out. The data in parentheses show that reactions carried out in an oxygen atmosphere proceeded faster than those in the open air, thus opening a way for the catalytic intramolecular chloroamination of unfunctionalized olefins. Conventional ligands were unable to speed up the reactions, and a search for efficient ligands to accelerate the reaction is underway.

Table 8. Cu(II)-catalyzed intramolecular chloroamination of unfunctionalized olefins.

Entry	Substrate	**2**[a]	**2′**[a]
1	**1b**	70 (75)	15 (13)
2	**1d**	75 (80)	12 (11)
3	**1g**	68 (74)	10 (13)
4	**1i**	NR[b]	
5	**1j**	NR	
6	**1l**	65 (69)	12 (19)
7	**1m**	59 (65)	17 (20)
8	**1p**	60 (72)	19 (16)

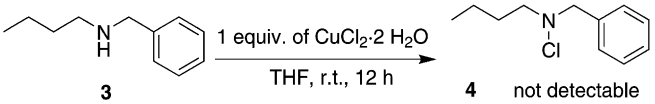
[a] Isolated yields. Data in parentheses are results in an oxygen atmosphere. *Reaction conditions:* 10 mol% of $CuCl_2 \cdot 2H_2O$, 1.1 equiv. of $MgCl_2$, room temperature, 18 h.
[b] NR = no reaction.

After getting a general idea about the Cu(II)-promoted and Cu(II)-catalyzed intramolecular chloroamination, several experiments were carried out to gain mechanistic insights into the reaction. In Göttlich's studies, substrates were first converted to N–Cl compounds, and subsequent metal-catalyzed cyclization produced the corresponding chloroamination products. To see if the current reaction followed the similar N–Cl pathway or proceeded *via* a Cu(II)-catalyzed pathway, a saturated model substrate **3** was allowed to react with 1 equiv. of $CuCl_2 \cdot 2H_2O$ under typical chloroamination conditions (Scheme 1).[21] However, both TLC and NMR analysis indicated that the corresponding N–Cl compound **4** was not detectable, thus ruling out the possibility of a reaction involving an N–Cl species.

In their series reports, Chemler et al. showed that Cu(II) was able to promote several C=C functionalization reactions. The key step involved a homolysis of the C–Cu bond, and the capture of the thus formed free radical intermediate with different reagents resulted in the diamination or aminooxygenation of the substrates.

Göttlich et al. also proposed a free radical process for the formation of the 2-chloromethylpyrrolidine skeleton from chloramine-T and related chloroamides. They treated *N*-chloro-*N*-(4-pentenyl)amines with a catalytic amount of cupric chloride, and obtained 2-chloropiperidines as their final products. Several control experiments were carried out to study the effect of free radical initiator and scavenger on the course of the reaction, and the results are summarized in Table 9.

The results in Table 9 indicate that light has little effect on the course of the reaction (entries 1 and 2). Moreover, addition of a free radical initiator (AIBN, entry 3), inhibitor (phenol, entry 4) or scavenger (TEMPO, entry 5) also had little impact on the yield of the reaction. These preliminary studies suggest that a free radical mechanism is unlikely for the current reaction.



3 4 not detectable

Scheme 1. Reaction of saturated substrate **3** with $CuCl_2 \cdot 2H_2O$.

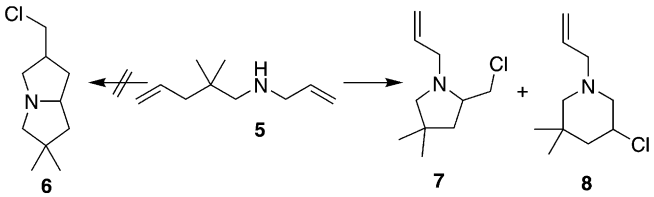
Table 9. Reaction of **1b** in the presence of different additives.[a]

Entry	Additive	**1b**[b]	**2b**[b]	**2b′**[b]
1	none (ambient light)	<1	86	14
2	none (dark)	<1	87	13
3	AIBN	<1	91	9
4	phenol	<1	90	10
5	TEMPO	<1	89	11

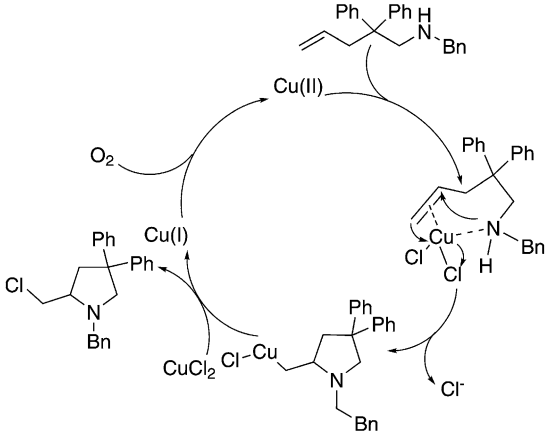
[a] *Reagents and conditions:* $CuCl_2 \cdot 2H_2O$: 1 equiv., reaction time = 3 h, reaction temperature = room temperature.
[b] Determined by NMR analysis of the crude reaction mixture.

Surzur et al. reported a free radical cascade bicyclization of substrate **5** in the presence of $TiCl_3$.[22] They obtained bicyclic compound **6** as a result of free radical cyclization. To test if a similar free radical mechanism is applicable to our reaction system, the reaction of substrate **5** was carried out in the presence of 1 equiv. of $CuCl_2 \cdot 2H_2O$. However, no cascade product **6** could be detected. In contrast, compound **7** was obtained in 51% isolated yield, plus 20% of compound **8** which may be formed through rearrangement of **7** or as a minor product in a chemoselective reaction (Scheme 2). This also supports a non-free radical mechanism of the reaction.

Based on these preliminary results, a tentative reaction path is proposed in Scheme 3. The first step was



Scheme 2. Cyclization of substrate **5** in the presence of $CuCl_2 \cdot 2H_2O$.



Scheme 3. A tentative reaction mechanism.

the activation of the unfunctionalized C=C bond upon substrate coordination to Cu(II). Nucleophilic attack of the amino group on the activated C=C double bond took place, giving an aminocupration intermediate $-N-C-CH_2CuCl$ which yielded the chloromethylpyrrolidine product by the action of another molecule of $CuCl_2$.[23] Copper was released as Cu(I) and was re-oxidized to Cu(II), and completed the reaction cycle.

In summary, we have reported a new method for intramolecular chloroamination of unfunctionalized olefins. In the presence of 1 equiv. of $CuCl_2 \cdot 2H_2O$, *N*-substituted pent-4-en-1-amines or *N*-substituted hex-5-en-1-amine are converted to 2-chloromethylpyrrolidines or 2-chloromethylpiperidine in good isolated yields. $MgCl_2$ can be used as chlorine source, and reactions can be carried out in the presence of a catalytic amount of Cu(II). Cu(I) itself is ineffective in the absence of air, but can promote the reaction in open-air systems. The reaction is easy to carry out and the reagents are inexpensive and are easily available. The reaction can also be carried out in a catalytic manner when a suitable chlorine source such as $MgCl_2$ is used. Using pure oxygen instead of air leads to an accelerated conversion of the substrates. As 2-chloromethylpyrrolidine compounds can be easily converted to 3-chloropiperidines, this work essentially provides access to both 2-chloromethylpyrrolidine and 3-chloropiperidine compounds.

Experimental Section

For experimental details and spectral data for all new compounds, see the Supporting Information. The crystal information file for **2g** has been deposited with the CCDC as CCDC 877716. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Intramolecular Chloroamination Reactions

To a 50-mL round-bottom flask were added 0.5 mmol substrate **1b**, 1 equiv. $CuCl_2 \cdot 2H_2O$ and 20 mL THF. The reaction mixture was stirred for 3 h in an open air system at room temperature. The reaction mixture was washed with water (25 mL × 3), dried over $MgSO_4$ and was concentrated to give an oil. Flash column chromatography (petroleum ether:ethyl acetate = 100:1) gave 2-chloromethylpyrrolidine **2b** in 74% yield, and 3-chloropiperidine product **2b′** in 11% yield.

1-Benzyl-2-(chloromethyl)-4,4-diphenylpyrrolidine (2b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.27 (m, 15H), 4.20 (d, J = 13.2 Hz, 1H), 4.01 (d, J = 9.8 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 3.50 (dd, J = 10.4, 4.2 Hz, 1H), 3.38 (ddd, J = 13.1, 8.8, 4.2 Hz, 1H), 3.17–3.07 (m, 3H), 2.79 (dd, J = 13.1, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.38, 128.74, 128.62, 128.54, 128.32, 127.91, 127.41, 127.32, 126.97, 126.59, 126.31, 126.04, 65.29, 64.38, 59.71, 53.03, 47.32, 42.46;

HR-MS (ESI): $m/z = 362.1760$ $[M+H]^+$, calcd. for $C_{24}H_{24}ClN$: 362.1670.

1-Benzyl-3-chloro-5,5-diphenylpiperidine (2b′): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–7.17 (m, 15H), 3.94 (ddd, $J =$ 14.9, 8.1, 3.9 Hz, 1H), 3.73–3.64 (m, 3H), 3.30 (dd, $J = 10.2$, 3.8 Hz, 1H), 3.08 (d, $J = 12.5$ Hz, 1H), 2.40 (dd, $J = 26.3$, 12.4 Hz, 2H), 2.29 (t, $J = 10.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.23$, 143.79, 136.50, 128.21, 127.47, 127.28, 127.00, 126.36, 125.33, 125.30, 124.88, 61.44, 60.90, 60.29, 52.53, 47.14, 44.85; HR-MS (ESI): $m/z = 362.1669$ $[M+H]^+$, calcd. for $C_{24}H_{24}ClN$: 362.1670.

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