SnCl₂/Cu-Mediated Carbonyl Allylation Reaction in Water: Scope, Selectivity and Mechanism

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Copper was found to be able to promote the SnCl₂-mediated carbonyl allylation reactions in water, giving the corresponding homoallylic alcohol products in very high yields. Detailed studies showed that the reaction could be applied to a variety of carbonyl compounds including those with hydroxyl, amino and nitro groups. It was also found that this reaction showed good regioselectivities for some substrates. Furthermore, carefully controled experiments and *in situ* NMR measurements provided important insights into the mechanism of the newly developed reaction.

Keywords　　carbonyl allylation, Barbier reaction, aqueous media, green chemistry, tin dichloride, copper

Introduction

Since 1980s studies on the organic reactions occurring in aqueous media have grown to be a very important field because these reactions are relatively safe, cheap and environmentally benign.[1] In particular, by virtue of its synthetic potential, mechanistic intrigue and operational simplicity, the one-pot Barbier coupling reaction between allyl halide and carbonyl compounds in aqueous media has attracted considerable attention recently.[1] Using this elegant method, homoallylic alcohols can be synthesized in a highly efficient and environmentally benign way.

Up to now many metals have been tried for the aqueous Barbier allylation reaction. Successful examples include indium,[2] antimony,[3] bismuth,[4] lead,[5] manganese,[6] magnesium,[7] zinc,[8] tin[9] and gallium.[10] Although good yields can often be obtained in these reactions, it is worthy to note that not all of the above aqueous Barbier reactions were conducted in fully aqueous media. Organic cosolvents such as ethanol and DMF were occasionally utilized to improve the yields. Moreover, use of ultrasonic irradiation is often indispensable in the above Barbier reactions.

In comparison to the great efforts that have been devoted to the zero-valence metal mediated Barbier reactions, very little attention has been paid to the aqueous Barbier reaction mediated by water-soluble reductive metal salts such as SnCl₂. So far what is known is that SnCl₂ can not efficiently mediate the coupling between allyl halide and carbonyl compounds in water, unless some Pd(II)[11] or copper(I)[12] catalyst is introduced to the reaction. Furthermore, in the above SnCl₂-mediated Barbier reactions, either an organic/water biphasic condition has to be used or certain organic cosolvent must be added to the reaction.

Recently we have tried to find the methods to achieve high-yield SnCl₂-mediated Barbier reactions in fully aqueous media. We found that SnCl₂ in combination with copper could result in great reactivity for the Barbier allylation reactions in tap water (Scheme 1).[13] After the preliminary communication was published,[13] we have conducted further detailed studies trying to expand the scope of the reaction. Good regioselectivities have been observed. Meanwhile we have performed careful NMR studies and obtained a lot of novel and important insights into the mechanism of the reaction. In the present full paper we wish to report all these important results.

Scheme 1
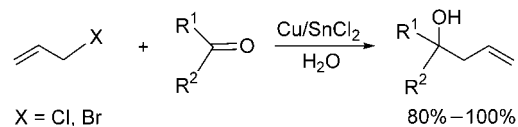
Results and dicussion

Using the SnCl₂/Cu procedure (See the experimental section) we have studied the coupling between a variety of carbonyl compounds and allyl chloride or bromide (Table 1). The yields are usually in the range 80%—100% and therefore, the reaction is very successful. It is worthy mentioning that these yields are much better than those reported before for the Cu(II)/Sn(II)[12] system under a water/dichloromethane biphasic condition.

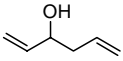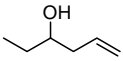As seen from Table 1, both allyl chloride and bro-

mide can be used for the allylation. Nonetheless, allyl bromide is slightly more reactive than allyl chloride. On the other hand, allyl alcohol is completely inert in the reactions.
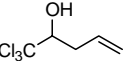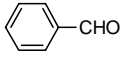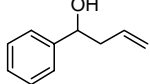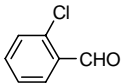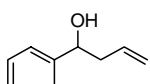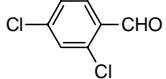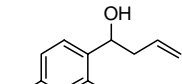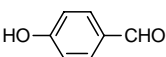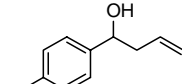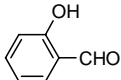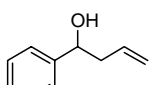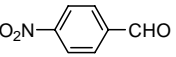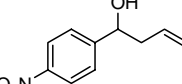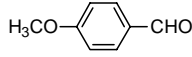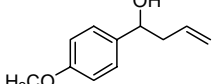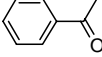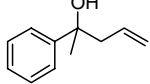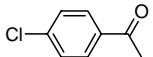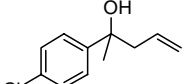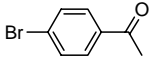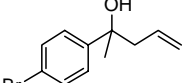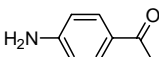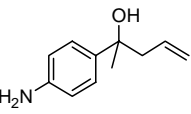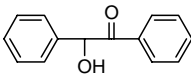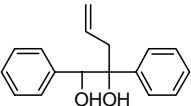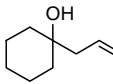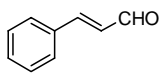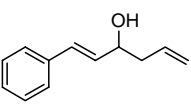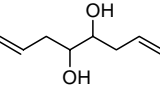
Table 1 Carbonyl allylation mediated by Cu/SnCl$_2$ in water

Entry	Substrate	Product	X	Yield[a] (%) /time (h)
1	CH$_2$=CHCHO		Cl	88/3
			Br	94/3
2	CH$_3$CH$_2$CHO		Cl	98/3
			Br	98/3
3	CCl$_3$CHO		Cl	95/3
			Br	96/3
4	C$_6$H$_5$CHO		Cl	100/8
			Br	100/8
5	o-Cl-C$_6$H$_4$CHO		Cl	100/3
			Br	100/3
6	2,4-Cl$_2$-C$_6$H$_3$CHO		Cl	100/8
			Br	100/8
7	p-HO-C$_6$H$_4$CHO		Cl	92/8
			Br	94/8
8	o-HO-C$_6$H$_4$CHO		Cl	92/6
			Br	94/3
9	p-O$_2$N-C$_6$H$_4$CHO		Cl	85/8
			Br	92/8
10	p-H$_3$CO-C$_6$H$_4$CHO		Cl	88/3
			Br	92/3
11	(CH$_3$)$_2$CO		Cl	91/3
			Br	95/3
12	C$_6$H$_5$COCH$_3$		Cl	20/24
			Br	91/8
13	p-Cl-C$_6$H$_4$COCH$_3$		Br	100/8
14	p-Br-C$_6$H$_4$COCH$_3$		Br	80/12

Continued

Entry	Substrate	Product	X	Yield[a] (%) /time (h)
15	p-H$_2$N-C$_6$H$_4$COCH$_3$		Br	80/3
16	CH$_3$CH(OH)COCH$_3$		Br	95/8
17	C$_6$H$_5$CH(OH)COC$_6$H$_5$		Br	100/8
18	cyclohexanone		Br	90/8
19	C$_6$H$_5$CH=CHCHO		Br	85/3
20	(CHO)$_2$		Br	91/3

[a] Isolated yield.

Mediated by SnCl$_2$/Cu, both aliphatic (Entries 1—3, 19 and 20) and aromatic (Entries 4—10) aldehydes can be allylated smoothly. In comparison, most zero-valence metals show problems for the allylation of aliphatic aldehydes. For a dialdehyde (Entry 20), dialcohol is found to be the major product. For α,β-unsaturated aldehydes (Entries 1 and 19), only 1,2-addition products are observed.

Both allyl chloride and bromide show good reactivities for aliphatic ketone (Entry 11). However, in the allylation of aromatic ketones (Entries 12—15), use of allyl bromide gives much better yields than the use of allyl chloride.

Interestingly, it is found that carbonyl compounds containing hydroxyl or amino groups (Entries 7, 8, 15—17) can be efficiently allylated without any O- or N-protection. This is clearly advantageous compared to the traditional allylation methods using the organometallic reagents. Also, carbonyl compounds containing the NO$_2$ group (Entry 9) can also be smoothly allylated giving the corresponding homoallylic alcohol. Compared to this result, it has been reported that the NO$_2$-containing carbonyl compounds were often reductively destroyed in many zero-valence metal mediated allylation reactions.[6-9]

Reaction selectivity

In order to study the regioselectivity and stereoselectivity of the SnCl$_2$/Cu-mediated allylation reactions, simple allyl halides are replaced by *trans*-cinnamyl hal-

ides (Scheme 2). The results are summarized in Table 2.

Scheme 2

X = Cl	minor	major
X = Br, R = phenyl	minor	major
X = Br, R = alkyl	major	minor
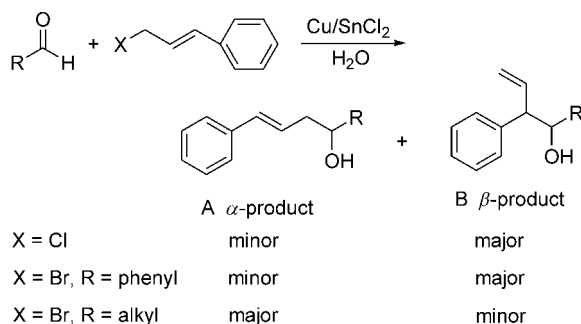
It is found that when reacting with aliphatic aldehydes, cinnamyl chloride and bromide show completely different regioselectivity in the allylation reactions. For cinnamyl chloride (Entries 1—3), the *anti-γ*-products are the major products. However, when cinnamyl bromide is used, the *α*-products are the major products. In comparison with these results, when aromatic aldehydes are used both cinnamyl chloride and bromide provide the *anti-γ*-products as the major products (Entries 4—6).

Table 2 Regio- and stereo-selectivities in the SnCl$_2$/Cu-mediated allylation reactions between aldehydes and cinnamyl halides

Entry	Substrate	X	Yield^a/% A	Yield^a/% B	*anti* ： *syn*^{b} B
21	⌇CHO	Cl	trace	90%	98 ： 2
		Br	92%	trace	—
22	⌇CHO	Cl	9%	85%	92 ： 8
		Br	91%	trace	—
23	⌇CHO	Cl	trace	88%	97 ： 3
		Br	92%	trace	—
24	⌇CHO	Cl	7%	88%	82 ： 18
		Br	35%	61%	87 ： 13
25	O$_2$N—⌇CHO	Cl	trace	95%	98 ： 2
		Br	trace	95%	99 ： 1
26	H$_3$CO—⌇CHO	Cl	trace	88%	71 ： 29
		Br	trace	90%	82 ： 18

^{a} Isolated yields. ^{b} Detected by ^{1}H NMR and GC-MS, determined by GC-MS.

The pheny-substituent of cinnamyl halides should affect the regioselectivity. According to Li's report,[14] The carbon-carbon bond is easily formed at the less substituted carbon when the *γ*-substituents of allyl halides are large. However, catalyzed by Cu/SnCl$_2$, the allylation could often provide high proportion of *γ*-addut even when *γ*-substiuent of allyl halide was phenyl.

Currently the mechanism for the *α*-adduct formation has not been totally clarified. Nevertheless, it was proposed recently by Loh *et al.* that the metal salts formed from the metal-mediated allylation can catalyze the *γ*-adduct to undergo a bond cleavage to generate the parent aldehyde *in situ* followed by a concerted rearrangement, perhaps a retro-ene reaction followed by a 2-oxonia[3,3]sigmatropic rearrangement to furnish the *α*-adduct.[14] If Loh's proposal is correct, then in our study the *α*-adduct formation from cinnamyl bromide but not from cinnamyl chloride should be caused by the different Lewis acidities of SnCl$_4$ and SnBr$_4$. These different Lewis acidities should result in different catalytic effects on the rearrangement of the *γ*-adduct, and therefore, different yields of *α*-adducts.

Reaction mechanism

In order to understand the reaction mechanism, we have tried a variety of reaction conditions (Table 3). From the study a lot of interesting behaviors are observed.

Table 3 Allylations of benzaldehyde under different reaction conditions

Entry	Condition	Yield/%
1	SnCl$_2$, H$_2$O	0
2	Cu (crude), H$_2$O	0
3	Cu (crude), SnCl$_2$, DCM	51
4	Cu (crude), SnCl$_2$, DCM ： H$_2$O (20 ： 1)	100
5	Cu (crude), SnCl$_2$, DCM ： H$_2$O (1 ： 1)	100
6	Cu (crude), SnCl$_2$, tap water	100
7	Protection (N$_2$), Cu (treated with HCl), SnCl$_2$, boiled water	100
8	CuO, SnCl$_2$, tap water	57
9	CuCl, SnCl$_2$, tap water	82
10	CuCl, SnCl$_2$, water ： DCM (1 ： 1)	93

(1) Trace products (<5%) can be observed when only copper or tin dichloride is used in the allylation (Entries 1 and 2). Therefore, a combination of SnCl$_2$ and Cu is necessary.

(2) The reaction in full DCM medium gives a fairly low yield (51%) while addition of even 5% water increases the yield to nearly 100% (Entries 3—6). Therefore, water is beneficial to the allylation reaction.

(3) Cu is pre-treated with HCl solution in order to remove any oxide on the surface. This "clean" Cu is then used in the allylation reaction where N$_2$ protection is utilized (Entry 7). Almost the same yield is obtained in the reaction. Therefore, it is Cu but not copper oxide that plays the key role in the reaction.

(4) When CuO (Entry 8) is used to replace Cu in the allylation reaction, a fairly low yield (57%) is observed. When CuCl (Entries 9 and 10) is used to replace Cu in the allylation reaction, the yield rises to 82% which is still lower than the yield with Cu. Therefore, it is Cu(0) but not Cu(I) or Cu(II) that is crucial.

Further investigations on the allylation reaction are performed using the *in situ* ^{1}H NMR technique (Figure 1). Using this method we can monitor the reaction intermediates at every stage of the reaction. The details

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about the NMR experiment can be found in the experimental section. In the following we only describe the observations.
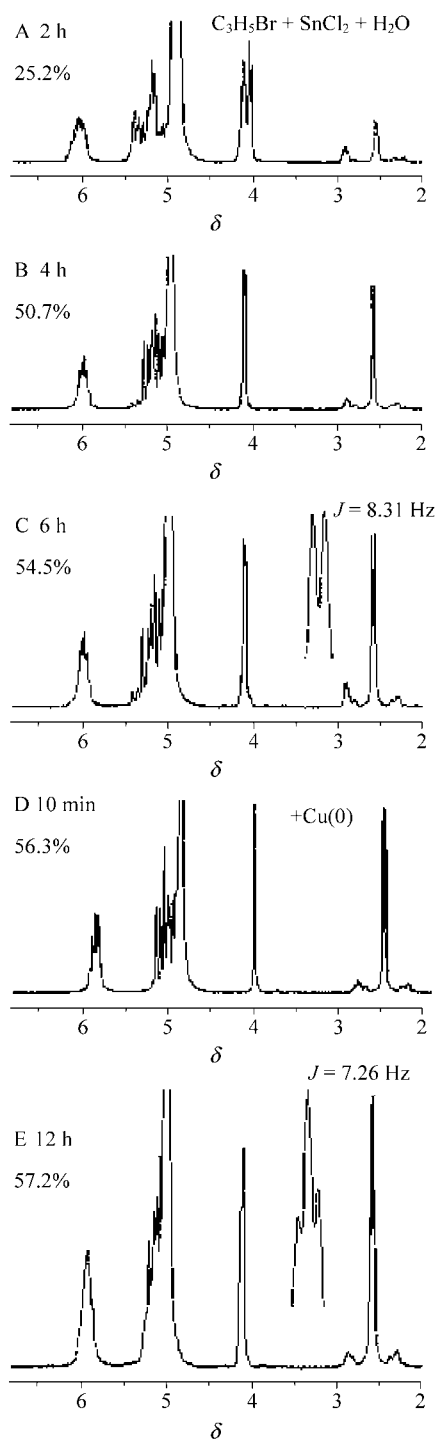
Figure 1 *In situ* ^{1}H NMR spectra of (A) D_2O solution of $SnCl_2$/allyl bromide after 2 h, (B) the same solution as A after 4 h, (C) the same solution as A after 6 h, (D) copper was added in the solution as C after 10 min, (E) the same solution as C after 12 h.

After $SnCl_2$ (2 mmol) and allyl bromide (1.5 mmol) are mixed in D_2O (3 mL) for 2 h, a new peak corresponding to an allyltin species appears [δ 2.5, J (^{119}Sn-H) $=155$ Hz)] (Figure 1A). Since this peak is a doublet, it

may correspond to CH_2=$CHCH_2SnBr_3$. Using this new peak and the peak for un-reacted allyl bromide (δ 4.1), the yield of the allyltin species is calculated to be 25.2%.

After 4 h, the peak at δ 2.5 increases and the yield of allyltin is calculated to be 50.7% (Figure 1B). After 6 h, the yield of allyltin becomes 54.5% (Figure 1C). Therefore, it seems that after 6 h the mixture has reached equilibrium at which about 55% allyl bromide has been converted to allyltin.

Cu is added into the above mixture which has stayed for 6 h. After 10 min, NMR measurement indicates that the yield of allyltin increases to 56.3% (Figure 1D). After 12 h, NMR measurement indicates that the yield of allyltin increases to 57.2% (Figure 1E). These experiments suggest that Cu addition should not significantly change the allyl halide-vs.-allyltin equilibrium.

However, it is clear from Figure 1 that after the addition of Cu, the peak at δ 2.5 changes from a doublet (J $=8.31$ Hz) to a triplet ($J=7.26$ Hz). A possible explanation for this change is that without Cu the two allylic protons in the allyltin species are magnetically equivalent, but in the presence of Cu these two allylic protons are not magnetically equivalent any more.

It is not hard to understand why the two allylic protons in the allyltin species are magnetically equivalent in the absence of Cu. On the other hand, the fact that the two allylic protons in the allyltin species are not magnetically equivalent in the presence of Cu strongly suggests that Cu interacts with allyltin forming a complex.

Although it remains unclear what kind of structure this allyltin-Cu complex could have, it is clear that this complex formation promotes the carbonyl allylation reaction. One possible reason is that the carbonyl compound can also bind to the Cu surface and therefore, the reaction is catalyzed by the local enrichment effect (Scheme 3). Of course it is possible that the allyltin-Cu complex alters the electronic structure of the allyltin species making the allyltin species more reactive as a nucleophile.

Scheme 3
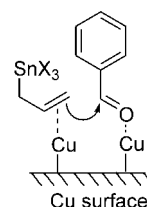
Conclusion

Detailed studies on the scope, selectivity and mechanism of the newly discovered $SnCl_2$/Cu-mediated carbonyl allylation reaction in full aqueous media have been performed. The results demonstrate that the $SnCl_2$/Cu system, being mild, cheap, and environmentally benign, is very successful for the aqueous allylation of a variety of carbonyl compounds. Very good re-

gioselectivities have been observed, and detailed control and NMR experiments have been conducted which offer us important insights into the mechanism of the reaction.

Experimental

All the reactions were carried out in air. ^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 MHz) instrument using TMS as internal standard and CDCl$_3$ (or D$_2$O) as solvents. IR spectra were recorded on an FT/IR/410 JASCO instrument. GC-MS was recorded on a TRACE GC-MS instrument.

Typical procedure

To a mixture of carbonyl compound (10 mmol) and allyl halide (15 mmol) in water (20 mL), copper powder (20 mmol) and SnCl$_2$ (20 mmol) were added. The mixture was vigorously stirred at room temperature for approximately 3 h. The mixture was extracted with ether (3×30 mL). The combined organic layers were washed by water (2×20 mL). Then the organic layer was dried over anhydrous MgSO$_4$ and was filtered and evaporated. The residue, for most cases, afforded the corresponding homoallylic alcohols of sufficient purity as judged by TLC (TLC monitoring on silica gel; eluent, ether acetate-petroleum, 1/3 *V/V*) and 300 MHz ^{1}H NMR without the need for further purification. If necessary, purification was performed by flash column chromatography (silica gel 60—120 mesh; eluent, ether acetate-petroleum, 1/5 *V/V*). All products in Table 1 and Table 2 are known compounds.

NMR experiments

Tin dichloride (2 mmol) and allyl bromide (1.5 mmol) were mixed with D$_2$O (3 mL). After the first three spectra were obtained, copper (1 mmol) was added to the mixture before recording the next two spectra.

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