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$SnCl_2$-mediated carbonyl allylation of aldehydes and ketones in ionic liquid

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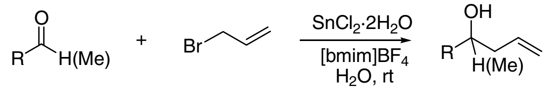
Abstract—In ionic liquid [bmim]BF_4, $SnCl_2·2H_2O$ acts as an inexpensive and efficient metal salt for carbonyl allylation. By applying ionic liquid, some previously reported serious operational problems associated with the $SnCl_2$-mediated allylation reaction are avoided. Furthermore, ketones, which are less reactive than aldehydes, can also be allylated in high yields with this system.

The addition of allyl-metal reagents to carbonyl compounds has been impressively developed in the past few years.[1] In particular, the Barbier type coupling reaction between allyl halide and carbonyl compounds has proven to be an efficient way to prepare homoallylic alcohols by virtue of its synthetic potential and operational simplicity. Among the numerous metals that have been applied in this reaction, tin receives more and more attention due to its suitable activity, low cost and low toxicity of the final inorganic tin derivatives. In the past few years, stannous dichloride, which is even cheaper and easier to obtain, has been considered as a new alternation to mediate carbonyl allylation. It was reported that $SnCl_2$ mediated carbonyl allylation could be activated by Pd(II),[2] Cu(I),[3] Cu(II)[4] and Ti(III).[5] Very recently, Yuan and co-workers[6] and Guo and co-workers[7] found that $SnCl_2$ itself could mediate carbonyl allylation when ultrasonic radiation was employed or when a strictly limited amount of water was used as the solvent. However, ultrasonic radiation is not a popular condition in organic chemistry laboratory and there is one serious operational problem associated with Guo's reaction. As said in Guo's paper, so little amount of water was used in the process as the solvent, that the reaction mixture might become too dense to deal with.[7] On the other hand, as far as we know, there were only two reports concerning the Barbier type $SnCl_2$-mediated allylation of ketones. In these two reports, copper[3b] or ultrasonic radiation[6] was indispensable to accomplish the allylation.

All these previously reported examples of $SnCl_2$ mediated carbonyl allylation occur under aqueous or aqueous-organic biphasic conditions. The aqueous solvent provides good solubility for $SnCl_2$. On the other hand, the polar environment of the aqueous solvent may be necessary to weaken the R–X bond. The ionic liquid [bmim]BF_4 (1-*n*-butyl-3-methylimidazolium tetrafluoroborate) is known as a highly polar and hydrophilic solvent, which is similar to water. By virtue of high polarity and high hydrophilicity, when we applied ionic liquid as the solvent in this process, the carbonyl allylations mediated by $SnCl_2$ transpired as we expected. The reaction mixture became clear and easy to deal with. The ionic liquid could be recycled and reused in the next cycle without any further purification. Furthermore, ketones, which were less reactive than aldehydes, could also be allylated in high yields with our system, which was only mediated by $SnCl_2$ itself without any other auxiliary methods. Herein, we present an efficient and operationally easier alternation for $SnCl_2$-mediated carbonyl allylation (Scheme 1).

The allylation of aldehydes (0.5 mmol) by allyl bromide (0.75 mmol) was carried out with $SnCl_2·2H_2O$ (0.6 mmol) in [bmim]BF_4 (2 mL) and H_2O (0.2 mL) at room temperature for 24 h.[8] The experimental results are summarized in Table 1.



Scheme 1.

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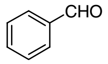
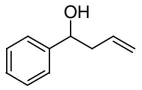
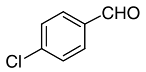
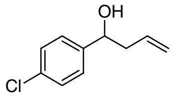
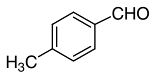
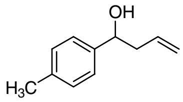
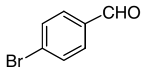
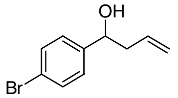
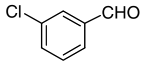
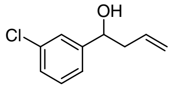
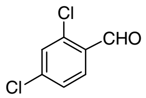
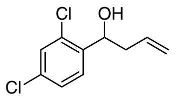
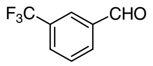
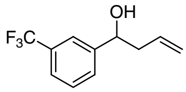
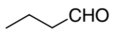
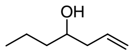
Table 1. The application of $SnCl_2{\cdot}2H_2O$/allyl bromide/[bmim]BF_4 system in carbonyl allylation of aldehydes

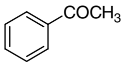
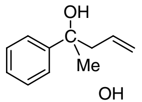
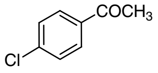
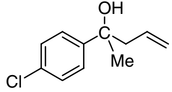
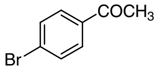
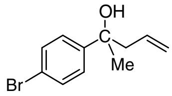
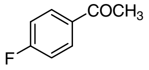
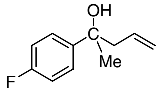
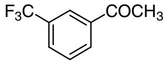
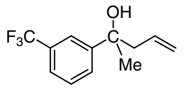
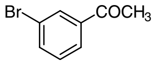
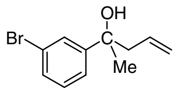
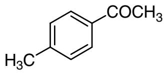
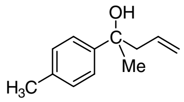
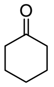
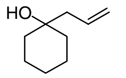
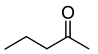
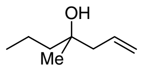
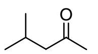
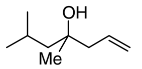
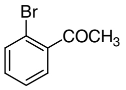
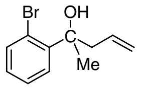
Entry	Substrate	Product	Yield (%)[a]
1			88
2			55
3			81
4			77
5			93
6			83
7			95
8			20

[a] Isolated yields. Products were confirmed by 400 MHz ^1H NMR and 100 MHz ^{13}C NMR.

It was shown that aromatic aldehydes gave moderate to high allylation yields. Aromatic aldehydes with different substituents could be allylated efficiently. *m*-Trifluoromethylbenzaldehyde had the highest yield due to the strong electron-withdrawing effect. But *p*-nitrobenzaldehyde did not offer the desired product because the nitro group could be reduced in this Barbier-type allylation when low valence metal or its salt was used. Due to the strong electron-donating effect, the allylation of anisaldehyde (*p*-methoxybenzaldehyde) failed. *n*-Butyl aldehyde exhibited a low activity because of the electron-donating effect of the aliphatic chain (entry 8).

Ketones, due to the lower electrophilicity of the carbonyl carbon, are not so active in Barbier type allylation as aldehydes. The successful examples for allylation of ketones were much less than those for aldehydes. However, after some optimization,[9] when 2.0 M equiv of $SnCl_2{\cdot}2H_2O$ was used instead of 1.2 M equiv for aldehydes, the allylation yields of ketones increased significantly. The new allylation system proved to be an efficient and mild allylation system for ketones. The experimental results are summarized in Table 2. According to Wu's calculation,[10] we believed that the ionic liquid, as a high polar solvent, played an important role in this process. The parallel experiments gave their evidence. In parallel experiments using DCM and THF instead of [bmim]BF_4, no allylation occurred. Furthermore, when H_2O was employed as solvent instead of ionic liquid, even in a strictly limited amount, no allylation for ketones occurred.[7]

Table 2. The application of $SnCl_2{\cdot}2H_2O$/allyl bromide/[bmim]BF_4 system in carbonyl allylation of ketones

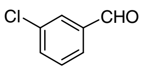
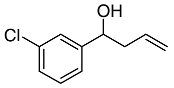
Entry	Substrate	Product	Yield (%)[a]
1			73
2			65
3			83
4			85
5			94
6			91
7			43
8			65
9			42
10			32
11			7[b]

[a] Isolated yields.

[b] 83% of the substrate was recovered.

As shown in Table 2, both aliphatic and aromatic ketones could be allylated in good to excellent yields (entries 1–10). Aromatic ketones with EWG on the aromatic ring (entries 2–6) gave higher yields than those with EDG (entry 7). Because of the strong electron-withdrawing effect caused by the trifluoromethyl group, 3′-trifluoromethyl acetophenone had the highest yield in all the substrates we examined (entry 5). The aliphatic ketone cyclohexanone gave a moderate yield (entry 8), but the isolated yields of acyclic aliphatic ketones were low (entries 9 and 10). The bromo group in 2′-bromoacetophenone is so large that it makes 2′-bromoacetophenone inert by steric hindrance (entry

Table 3. Recycling and reuse of ionic liquid [bmim]BF_4 in carbonyl allylation of *m*-chlorobenzaldehyde

Substrate	Product	Cycle	Yield (%)[a]
		1	91
		2	88
		3	87
		4	87
		5	85

[a] Isolated yields.

11). *p*-Nitroacetophenone, as well as *p*-nitrobenzaldehyde, did not offer the corresponding homoallylic alcohol either.

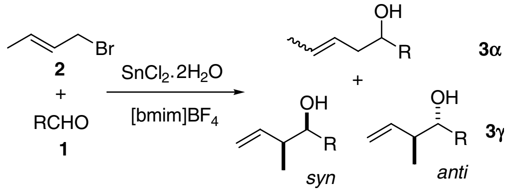
Effort to recycle and reuse ionic liquid was also attempted. The recycle process was investigated starting with fresh [bmim]BF_4. After the reaction was complete, Et_2O was used to extract the products. Then the ionic liquid was used directly in the next cycle without any purification. Because of its high allylation yield, *m*-chlorobenzaldehyde was chosen as the substrate to investigate the recycle process (Table 3).

As shown in Table 3, the ionic liquid could be recycled and reused for 5 cycles without a notable reduction in yields. This made our allylation system more environmentally benign.

Detailed investigation on regio- and diastereoselectivity is in progress in our laboratory, some primary results showed that it was a γ-addition reaction and the *anti*-isomer was the major product. Those results are summarized in Table 4.

A plausible mechanism is shown in Scheme 2.[7,11] The carbonyl allylation proceeded via the intermediate of allylbromodichlorotin, which was formed by oxidative addition of allyl bromide to $SnCl_2$. This mechanism provided an explanation for the γ-selectivity by the chair-like transition state. In contrast to the 88% yield shown in Table 1, entry 1, the yield of allylation of benzaldehyde without H_2O was only 45%. The small amount of water seemed to cause the hydrolysis of the Sn(IV)–Cl bonds to activate the allylic tin intermediate.[12] When we mixed $SnCl_2{\cdot}2H_2O$ (0.6 mmol), allyl bromide (0.75 mmol) in 2 mL [bmim]BF_4 with 0.2 mL H_2O, ^1H NMR analysis showed some new peaks at $\delta = 2.4$ and $\delta = 1.8$, which were considered to be the signals of the allyltin species[13,7] mentioned above or its hydrolysis product. Detailed investigation on the mechanism is still in progress.

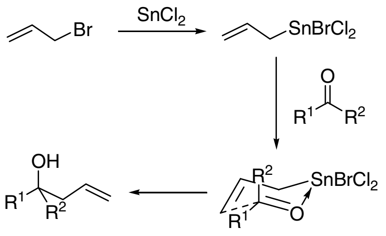
Table 4. Primary results for investigation of regio- and diastereoselectivity



Entry	Substrate	Yield (%)[a]	3α3γ (*anti*:*syn*)[b]
1	R = Ph	96	10:90 (78:22)
2	R = *p*-BrPh	97	8:92 (75:25)
3	R = *p*-CH_3Ph	93	9:91 (69:31)

[a] Isolated yields.

[b] The ratio was determined by 400 MHz ^1H NMR.



Scheme 2.

In conclusion, the present study demonstrated an efficient $SnCl_2$-mediated carbonyl allylation of allyl bromide to aldehydes and ketones in ionic liquid. The reaction is easy to perform and environmentally benign. Detailed investigation on the mechanism, regio- and diastereoselectivity of this allylation is in progress in our laboratory.

Acknowledgement

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8. Typical procedures for allylation of aldehydes using $SnCl_2{\cdot}2H_2O$/allyl bromide/[bmim]BF_4 system are as follows. The allylation of carbonyl compounds (0.5 mmol) by allyl bromide (0.75 mmol) was carried out with $SnCl_2{\cdot}2H_2O$ (0.6 mmol) in [bmim]BF_4 (2 mL) and H_2O (0.2 mL) at room temperature for 24 h. Then the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. Purification was performed by column chromatography over silica gel.

9. The allylation of ketone (0.5 mmol) by allyl bromide (1 mmol) was carried out with $SnCl_2{\cdot}2H_2O$ (1 mmol) in [bmim]BF_4 (2 mL) and H_2O (0.2 mL) at room temperature for 24 h.
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