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Allylation of acetals and ketals with allyltrimethylsilane catalyzed by the mixed Lewis acid system AlBr3/CuBr ☆

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Abstract—The synthesis of homoallyl ethers from various acetals and a cyclic ketal with allyltrimethylsilane catalyzed by aluminum bromide in the presence of trimethylaluminum as a desiccant is described. We found that the addition of a catalytic amount of copper(I) bromide accelerates the allylation reactions to afford the homoallyl ether derivatives in good to excellent yield.
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The synthesis of homoallyl ethers by the allylation of acetals and ketals with allylsilanes is a valuable C–C bond formation and is commonly applied in organic synthesis.[1] Usually, these reactions require the presence of a Lewis acid promoter or catalyst, such as TiCl4,[2] TMSOTf,[3] and others.[4] We have recently reported the use of a 10:1 mixture of AlBr3/AlMe3 as an efficient Lewis acid promoter system for the synthesis of a sterically demanding Diels–Alder adduct, which served as an advanced intermediate in the synthesis of a tricyclic BCD analogue of ouabain.[5] We proposed that a small amount of AlMe3 eliminated any HX formed during the reaction. This paper describes a new application of the mixed Lewis acid system AlBr3/AlMe3, namely the synthesis of homoallyl ethers by the reaction of acetals and ketals with allyltrimethylsilane.

The ability of the AlBr3/AlMe3 mixture to act as a Lewis acid promoter or catalyst was studied on the allylation of benzaldehyde dimethyl acetal with allyltrimethylsilane, which we used as a model reaction (Scheme 1).

Table 1 describes the yields of the product as a function of the mole-equivalents of Lewis acid used, the
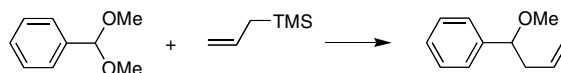
Scheme 1.

Table 1. Reaction conditions for the allylation of benzaldehyde dimethyl acetal with allyltrimethylsilane

Entry[a]	AlBr3/AlMe3[b] (mol %)	Temp (°C)	Time (h)	Yield[c] (%)
1	100	−78	2	98
2	50	−78	2	94
3	10	−78	7	28
4	10	−78 → RT	48	92
5	6	−78 → RT	48	83
6	3	−78 → RT	148	82
7	1	−78 → RT	148	56
8	0	RT	48	0

[a] In a typical experiment, a solution of 2 mmol acetal and 2 mmol silane in 7 mL anhydrous DCM was cooled to −78 °C with stirring under argon. Then, AlMe3 (2 M solution in toluene) was added, followed by the addition of AlBr3 (1 M/CH2Br2). The reaction mixture was allowed to warm to room temperature and was stirred for the time indicated.
[b] All experiments were performed with a 6:1 ratio of AlBr3/AlMe3.
[c] GC conversion.

temperature and the reaction time. If stoichiometric or sub-stoichiometric amounts of a 6:1 mixture of AlBr3/AlMe3 are used (entries 1 and 2), the reaction is complete after 2 h of stirring at −78 °C with a high yield of product. If 10 mol % of the Lewis acid mixture is used (entries 3 and 4), the reaction needs to be warmed to

Table 2. Product formation as a function of the $AlBr_3/AlMe_3$ ratio with a constant overall catalyst loading of 6%

Entry[a]	$AlBr_3/AlMe_3$	Yield (%)[b]
1	100:0	45[c]
2	90:10	85
3	85:15	83
4	75:25	62
5	50:50	42
6	25:75	17
7	0:100	3

[a] The reaction conditions are the same as those described under footnote a of Table 1, with a constant overall catalyst loading of 6% and 48 h stirring at room temperature.
[b] GC conversion, except entry 1.
[c] Isolated yield.

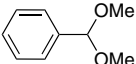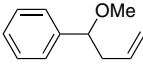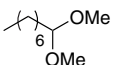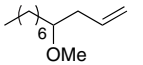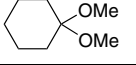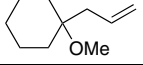room temperature and stirred for 48 h to go to completion.

The amount of catalyst can be lowered to 6, 3, and 1 mol% (entries 5, 6, and 7) but the reaction takes longer and the yields start to decrease. In a control experiment (entry 8, Table 1), the starting materials were stirred without the presence of the Lewis acid; no product formation was observed.

We next examined the influence of the ratio of $AlBr_3/AlMe_3$ on the reaction outcome. For this purpose we conducted the allylation of our model reaction under the same reaction conditions with a constant overall catalyst loading of 6%, but with different $AlBr_3/AlMe_3$ ratios. The results are listed in Table 2.

The data show that $AlBr_3$ alone (entry 1) gave the product in only 45% isolated yield. We also observed an unidentified precipitate, which was formed early on during the reaction. If the catalyst mixture contained 10–15% $AlMe_3$, no precipitate in the reaction mixture was formed and the product yields were the highest (entries 2 and 3). Upon further lowering of the $AlBr_3/AlMe_3$ ratio the yields decreased (entries 4, 5, and 6). $AlMe_3$ without $AlBr_3$ did not give the product in noteworthy yield (entry 7). These results indicate that a small amount of $AlMe_3$ added to $AlBr_3$ is of significant benefit for the catalytic process, presumably due to scavenging any HBr, which is present or is formed in the reaction mixture. However, if the content of $AlMe_3$ is further increased, the product yields decrease. We generally found that $AlBr_3/AlMe_3$ ratios between 6:1 and 10:1 gave the best catalytic results.

With this information in hand, we investigated the allylation of other acetals and ketals. In case of alkyl derivatives (Table 3, entries 2 and 3), we observed a conspicuously reduced product yield compared to our model reaction. Upon screening of various additives for enhanced catalytic activity, we were surprised to find that CuBr significantly increases the formation of the allylated products. Table 3 compares the yields of the product of our model system (entry 1) and two alkyl derivatives (entries 2 and 3) with and without the addition of 10 mol% CuBr to the $AlBr_3/AlMe_3$ catalytic mixture (10 mol%, 10:1 ratio). The reaction mixtures

Table 3. Comparison of product yields after 1 h of reaction time with and without the addition of CuBr

Entry[a]	Substrate	Product	Yield (%)[b] no CuBr	Yield (%)[b,c] CuBr added
1			52	77
2			36	93
3			16	81

[a] Reactions were carried out as described in footnote a of Table 1, using 10 mol% of a 10:1 mixture of $AlBr_3/AlMe_3$. The reactions were stirred for 1 h at room temperature and then analyzed by GC. All reactions were still incomplete.
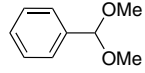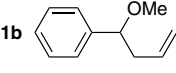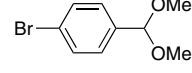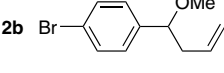[b] GC conversion.
[c] 10 mol% of CuBr was suspended in anhydrous DCM prior to the addition of the substrates and the catalyst mixture.
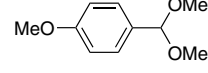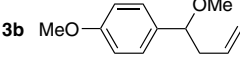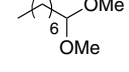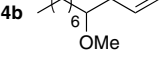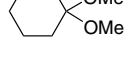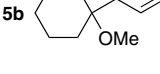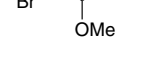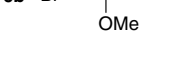
were analyzed by GC after 1 h of stirring at room temperature. The results impressively demonstrate the ability of CuBr to enhance the performance of the catalytic mixture, which is most evident in the case of the alkyl-substituted derivatives (entries 2 and 3).

As we have demonstrated earlier, the catalytic allylation of benzaldehyde dimethyl acetal does not require the presence of CuBr, and the corresponding aromatic homoallyl ether can be isolated in 92% yield after 24 h stirring at room temperature using 10 mol% of $AlBr_3/AlMe_3$ (Table 1, entry 4). However, in the presence of CuBr the same reaction is faster and is complete after only 3 h at room temperature. In the case of the less reactive alkyl derivatives, longer reaction times with 10% $AlBr_3/AlMe_3$ alone did not significantly improve the yields shown in Table 3 and the presence of CuBr was necessary to obtain high yield of the product. At present, we cannot give a detailed explanation on how CuBr acts as a catalytic promoter. Presumably, the catalytically active system is a mixed aluminum–copper species.
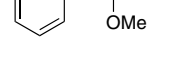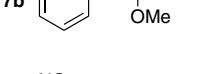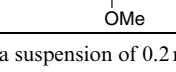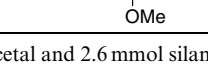
In Table 4 are listed the results for the allylation of various substrates. For all reactions, CuBr was used as a cocatalyst. The comparison of entries 1 and 2 reveals that the bromo substituent in acetal **2a** leads to a decreased reaction rate, compared to that of the unsubstituted acetal **1a**. The allylation of the *para*-methoxy-substituted acetal **3a** was unsuccessful and only the formation of higher molecular weight species was indicated by GC analysis, presumably due to polymerization of an alkylated *para*-quinone methide cation. The alkyl-substituted derivatives **4a** and **5a** (entries 4 and 5) gave the corresponding homoallyl ethers in comparatively short reaction times, with a lower yield for the cyclic ketal **5a**. For the bromo substituted acetal **6a**, the use of 20 mol% CuBr and 20 mol% $AlBr_3/AlMe_3$ was necessary to obtain an adequate yield of **6b**,[6] reflecting the

Table 4. Allylation of various substrates using optimized reaction conditions

Entry[a]	Substrate	Product	Time (h)	Yield (%)[b]
1	**1a**	**1b**	3	100
2	**2a**	**2b**	24	100
3	**3a**	**3b**	25	0
4	**4a**	**4b**	2	98
5	**5a**	**5b**	1	81
6	**6a**	**6b**	24	84[c]
7	**7a**	**7b**	46	83
8	**8a**	**8b**	48	76[d]

[a] In a typical experiment, a suspension of 0.2 mmol CuBr, 2.0 mmol acetal and 2.6 mmol silane in 5.0 mL anhydrous DCM was cooled to −78 °C with stirring under argon. Then, 20.0 μmol AlMe$_3$ (2 M solution in toluene) was added, followed by the addition of 0.2 mmol AlBr$_3$ (1 M/CH$_2$Br$_2$). The reaction mixture was allowed to warm to room temperature and was stirred for the time indicated. All reaction mixtures were quenched with aq NaHCO$_3$ prior to work-up, except for **6b** and **8b** where NEt$_3$ was used instead. All reactions were monitored by GC and stopped after the complete disappearance of the starting materials. The products were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy.
[b] Isolated yield.
[c] 20 mol % CuBr and 20 mol % AlBr$_3$/AlMe$_3$ were used.
[d] The product is 90% clean by GC and NMR. CAUTION: The product has a strong unpleasant odor!

decreased reactivity of the acetal function in **6a** due to the electron-withdrawing bromine substituent. With 10 mol % of CuBr and 10 mol % AlBr$_3$/AlMe$_3$, only 50% of **6b** was obtained (data not shown). An interesting case is the cyano-substituted acetal **8a** in which both the nitrile group and the acetal function can competitively coordinate to the Lewis acid catalyst during the reaction. We observed that the reaction has an induction period of several hours in which no product formation could be detected. This might point toward a preferred initial binding of the catalyst to the nitrile group, with subsequent binding to the acetal and allylation. For the purification of **6b** and **8b**[7] it is necessary to quench the reaction mixtures with triethylamine prior to the aqueous work-up. To the best of our knowledge, the described example (entry 8) is the first example of a successful Lewis acid-catalyzed allylation of an acetal having a peripheral functionality present in the molecule, emphasizing the potential value of our new method in synthetic chemistry.

In summary, we have disclosed a new and potent Lewis acid catalyst for the synthesis of homoallyl ethers from acetals, ketals, and allyltrimethylsilane, namely a system comprised of AlBr$_3$, AlMe$_3$, and CuBr. The exact catalytically active component is unknown, but is believed to be a mixed Al–Cu species. AlMe$_3$ acts as a desiccant scavenging unwanted HBr from the reaction mixture.

Acknowledgements

References and notes

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6. Spectroscopic data for **6b**: ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.7 (m, 1H, C*H*=C), 5.1 (m, 2H, C*H$_2$*=C), 3.4 (m, 6H, C*H$_3$*, C*H$_2$*Br, C*H*–O), 2.4 (m, 2H, C*H$_2$*–allyl); ^{13}C NMR (126 MHz, CDCl$_3$): δ 133.3 (*C*H=C), 118.2 (*C*H$_2$=C), 79.5 (*C*H–O), 57.3 (*C*H$_3$), 36.8 (*C*H$_2$–allyl), 33.9 (*C*–Br); IR (neat): v 3077, 2979, 2930, 2825, 1641, 1433, 1339, 1095, 994, 919 cm^{-1}.

7. Spectroscopic data for **8b**: ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.7 (m, 1H, C*H*=C), 5.0 (m, 2H, C*H$_2$*=C), 3.3 (m, 4H), 2.4 (m, 2H), 2.3 (m, 1H), 2.2 (m, 1H), 1.8 (m, 1H), 1.7 (m, 1H); ^{13}C NMR (126 MHz, CDCl$_3$): δ 133.3 (*C*H=C), 119.7 (*C*N), 117.9 (*C*H$_2$=C), 78.0 (*C*H–O), 56.9 (*C*H$_3$), 37.0 (*C*H$_2$–allyl), 29.3 (*C*–CN), 13.2 (*C*–CCN); IR (neat): v 3078, 2979, 2934, 2828, 2246, 1641, 1441, 1358, 1094, 997, 918 cm^{-1}.