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A Novel Aqueous Barbier-Grignard-Type Allylation of Aldehydes in a Mg / $BiCl_3$ Bimetal System[1]

Makoto Wada*, Tomohiro Fukuma, Mika Morioka, Toshikazu Takahashi, and Norikazu Miyoshi

Department of Chemistry, Faculty of Integrated Arts and Sciences,
The University of Tokushima, Minamijosanjima, Tokushima 770, Japan

Abstract: The allylation of aldehydes with allylic bromides proceeded smoothly in a Mg / $BiCl_3$ bimetal system even in THF-H_2O to afford the corresponding homoallylic alcohols in good yields.

The addition of allylic organometallics to carbonyl compounds is an important synthetic reaction for the preparation of homoallylic alcohols. Numerous methods utilizing allylic organometallics derived from a number of metallic elements have been developed in anhydrous solvents.[2] In general, organometallic compounds usually have to be prepared and treated in anhydrous solvents, owing to rapid protonolysis. In the last decade there has been increasing recognition that organic reactions carried out in aqueous media or protic solvents may offer advantages over those occurring in organic solvents.[3] For example, protection and deprotection processes in organic synthesis can sometimes be simplified. It is therefore important to investigate the reaction of organometallic reagents with substrates which possess unprotected hydroxy groups and carboxyl groups. For this purpose it is desirable to develop a new reagent which is stable in aqueous media or protic solvents and to devise an efficient method using those solvents. Among the many organometallic reagents that have been successfully employed, allylzinc, allyltin, and allylindium reagents comprise a unique group which undergo reactions with aldehydes in aqueous media.[4]

The Grignard (or Barbier) reaction using metallic magnesium (Mg) and an allylic halide in anhydrous solvents is one of the most useful and convenient methods for performing allylation reactions. However, needless to say, there is no report of the Grignard (or Barbier) allylation in aqueous media, and, to our knowledge, a bimetal system containing metallic Mg mediated allylation of aldehydes is hitherto unknown.[5] Herewith, we wish to report a novel aqueous Barbier-Grignard-type allylation of aldehydes with allylic bromides in a Mg / $BiCl_3$ bimetal system.

First, the allylation of 3-phenylpropanal with allyl bromide was examined under various reaction conditions and the results are shown in Table 1. When the Barbier reaction was carried out in the presence of Mg alone (1.5 equimolar amounts) in anhydrous THF, the corresponding homoallylic alcohol was obtained in only 65% yield. The yield decreased to 49% when 2.0 equimolar amounts of Mg were used (Entries 1 and 2). When the reactions were carried out in the presence of Mg-$BiCl_3$ in anhydrous THF, the yields of corresponding homoallylic alcohols increased to 78% and 64% respectively (Entries 3 and 4). To our great surprise, however, when the reaction was tried in THF-H_2O (4 : 1) in the presence of Mg-$BiCl_3$ (1.5 : 1), the desired homoallylic alcohol was obtained in 90% yield. The yield decreased to 78% when 2.0 equimolar amounts of Mg were used (Entries 5 and 6). It is only natural that no homoallylic alcohol was obtained in THF-H_2O by using Mg alone (Entry 7) and the reaction didn't take place at all without Mg (Entry 8).

Thus, the use of $BiCl_3$ and the addition of water are essential for the present Barbier-Grignard-type allylation of aldehydes in aqueous media, and the suitable molar ratio, Mg / $BiCl_3$, is 1.5, viz., the yield of homoallylic alcohol decreased by the use of an excess amount of Mg metal. Although the reaction

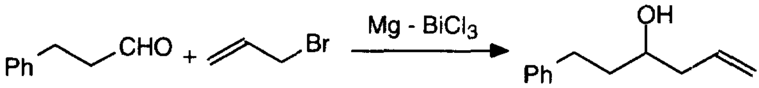


Table 1. Allylation of 3-phenylpropanal with allyl bromide under various reaction conditions[a]

Entry	$BiCl_3$[b]	Mg[b]	Solvent	Yield / %[c]
1	–	1.5	THF	65
2	–	2.0	THF	49
3	1	1.5	THF	78
4	1	2.0	THF	64
5	1	1.5	THF - H_2O	90
6	1	2.0	THF - H_2O	78
7	–	2.0	THF - H_2O	0
8	1	–	THF - H_2O	0

a. The molar ratio of allyl bromide to 3-phenylpropanal was 1.5.
b. Molar equivalent to allyl bromide.
c. Isolated yield.

mechanism of the present reaction is not yet clear at the present time, we assumed that the allylating agent prepared *in situ* was stable in aqueous media. Therefore, we next investigated the stability of the allylating agent prepared *in situ* in aqueous environment. After leaving the reaction of allyl bromide with Mg-$BiCl_3$ in THF-H_2O (4 : 1) for a number of hours, 3-phenylpropanal was added to the reaction mixture (the molar ratio of allyl bromide : Mg : $BiCl_3$: 3-phenylpropanal = 1.5 : 2.25 : 1.5 : 1.0). As shown in Table 2, noteworthy is the fact that the reactivity of the allylating agent prepared *in situ* to 3-phenylpropanal did not disappear for several hours in aqueous media.

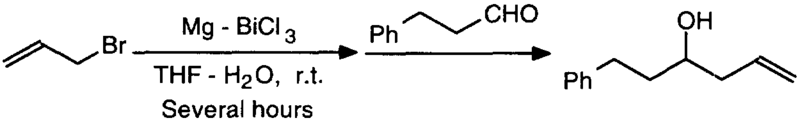


Table 2. Investigation of the stability of the allylating agent in aqueous environment

Entry	Delay Period / h	Yield / %[a]
1	1	84
2	3	79
3	5	63

a. Isolated yield.

Next, the scope and versatility of the present reaction were investigated by using various aldehydes. As shown in Table 3, not only aromatic and aliphatic aldehydes but also cinnamic aldehyde reacted smoothly to afford the corresponding homoallylic alcohols in good yields. Also, nearly equimolar amounts of allyl bromide reacted smoothly with carbonyl compounds containing a carboxyl group such as pyruvic acid, 2-oxobutyric acid, and phthalaldehydic acid, which are usually unusable substrates owing to rapid protonolysis of an allylating agent. Thus, the present reaction takes place smoothly without the protection of the carboxyl group.

Furthermore, we examined the reaction using commercially available aqueous aldehydes. Aqueous α-chloroacetaldehyde reacted with nearly equimolar amounts of *(E)*-1-bromo-2-hexene to afford the corresponding homoallylic alcohol in 75% yield (Eq. 1). The allylation of aqueous formaldehyde (formalin) with *(E)*-1-bromo-2-hexene also proceeded smoothly to give the adduct in 89% yield (Eq. 2). In a similar fashion, succinaldehydic acid (15% solution in water) also reacted with allyl bromide without the protection of the carboxyl group to obtain the corresponding lactone in 65% yield (Eq. 3).

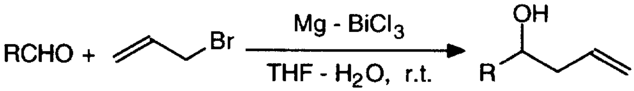
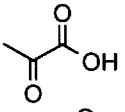
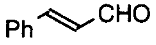
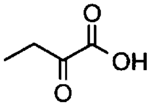
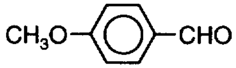
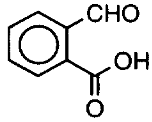


Table 3. Allylation of various aldehydes with allyl bromide[a]

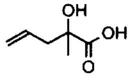
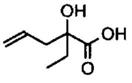
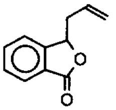
Entry	Aldehyde	Yield / %[b]	Entry	Aldehyde	Yield / %[b]
1	$PhCH_2CH_2CHO$	90			
2	$PhCH_2CHO$	90			
3	$CH_3(CH_2)_7CHO$	81	9		80[d]
4	c-Hexyl-CHO	64			
5	$CH_2{=}CH(CH_2)_8CHO$	84			
6		83[c]	10		76[d]
7	PhCHO	73			
8		83	11		85[d]

a. All the products gave satisfactory IR and ^{1}H NMR spectra, and some products were also identified by elemental analyses or by comparison with authentic samples.

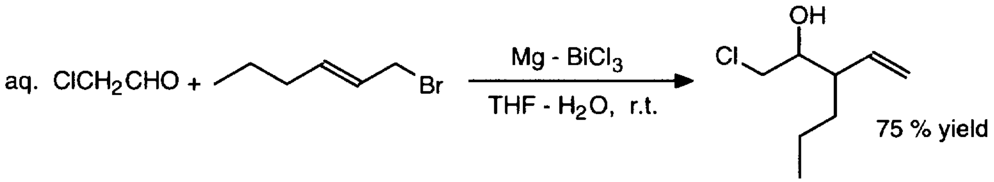
b. Isolated yield.

c. 1,2-Addition product was obtained.

d. In Entries 9, 10, and 11, the products were as follows:

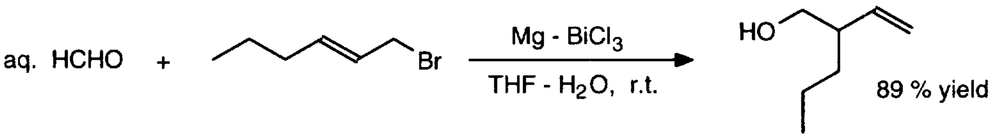
Entry 9;  Entry 10;  Entry 11; 

Although we have already reported the allylation of aldehydes by using Bi, $BiCl_3$-Zn, $BiCl_3$-Fe, or $BiCl_3$-Al,[6] the Mg / $BiCl_3$ system should be of particularly high scientific and commercial interest because Barbier and Grignard reactions[7] are widely used not only in the academic world but also in the industrial field. Therefore, further investigations are needed for the elucidation of the precise mechanism of the present reaction and are now in progress.

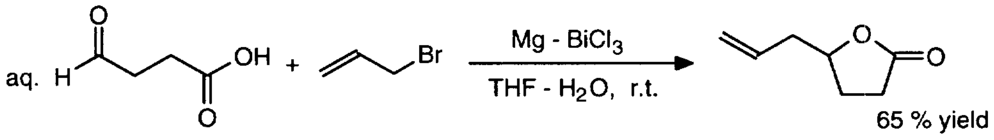


(1)

The diastereomeric ratio was not determined.



(2)



(3)

Finally, it was found that the Barbier-Grignard-type allylation of an aldehyde with an allylic bromide proceeded in aqueous media in a Mg / $BiCl_3$ bimetal system to afford the corresponding homoallylic alcohol in good yield. It is noteworthy that the use of $BiCl_3$ and the addition of water are essential in the present reaction, viz., needless to say, no desired product was obtained when Mg alone was used in THF-H_2O, which signify that some water-tolerant allylating agent prepared *in situ* is stable in aqueous media. Further investigations of the reaction mechanism and an application of the present reaction are now in progress and will be published elsewhere.

A typical procedure for the synthesis of 1-phenyl-5-hexen-3-ol is described as follows: Under an argon atmosphere, allyl bromide (174 mg, 1.44 mmol) was added to a suspension of bismuth trichloride (467 mg, 1.48 mmol) and metallic magnesium (54 mg, 2.20 mmol) in THF (8 ml) and water (2 ml) at room temperature. After stirring for 20 min, 3-phenylpropanal (125 mg, 0.932 mmol) was added to the reaction mixture at room temperature. The resulting reaction mixture was stirred for 18 h at that temperature and quenched with aqueous 1 M hydrochloric acid (10 ml, M = mol dm^{-3}). The organic materials were extracted with diethyl ether (30 ml × 3), and the combined organic layer was washed successively with water and brine, and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by thin layer chromatography on silica gel (hexane : diethyl ether = 4 : 1) to give the corresponding homoallylic alcohol, 1-phenyl-5-hexen-3-ol (148 mg, 90% yield).

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