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Direct Barbier-type allylation of aromatic acetals and dioxolanes in the presence of β-cyclodextrin in water☆

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Abstract—A new and convenient procedure for the synthesis of homoallylic alcohols directly from aromatic acetals and dioxolanes has been developed with very good yields under biomimetic conditions using a Zn-mediated Barbier-type allylation in the presence of β-cyclodextrin in water.

Allylation of carbonyl compounds is an important carbon–carbon bond forming reaction in organic chemistry for the preparation of homoallylic alcohols,[1] which are useful tools for the construction of complex molecules and are important building blocks for the synthesis of natural products.[2] Amongst the various methods for protecting carbonyl compounds, acetals are the most commonly used protecting groups in the course of total syntheses.[3] However, methodologies involving direct allylation of acetals are highly advantageous over two-step procedures, which include converting acetals to carbonyl compounds and then allylating later. Most of the reported methods utilize different metals and acid catalysts for the conversion of acetals to homoallyl ethers.[4] Only a few methods have been reported for the direct conversion of acetals to homoallyl alcohols.[5] These methods have various disadvantages such as the use of hazardous organic solvents, expensive, and moisture sensitive reagents, etc. To date, there has been no report on the conversion of acetals to homoallyl alcohols in aqueous medium although water is safe, economical, and environmentally benign.

Organic reactions in water have been widely studied in order to minimize the use of organic solvents, most of which are flammable, toxic, or carcinogenic.[6] Thus, there is a need to develop organic reactions in water with a recyclable catalyst and without the use of any harmful organic solvents. To achieve these ideal conditions, the best choice appeared to be through supramolecular catalysis.[7]

In order to develop an environmentally benign process for C–C bond formation, we have applied supramolecular catalysis to the zinc-mediated allylation reaction in water. Zinc is commonly accepted as being non-toxic and is usually activated in aqueous Barbier reactions.[8] We report herein, for the first time, a practical and efficient method for the direct synthesis of homoallylic alcohols from aromatic acetals in the presence of β-cyclodextrin and Zn/allyl bromide in water.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which selectively bind substrates and catalyze chemical reactions with high selectivity. Supramolecular catalysis involves reversible formation of host–guest complexes vice non-covalent bonding as is seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus mimicking of biochemical selectivity, which is due to the orientation of the substrate by complex formation, positions only certain regions for favorable attack and is therefore superior to chemical selectivity, which typically involves random attack due to the intrinsic reactivity of the substrate at different positions. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins[9] prompted us to attempt the allylation of acetals and dioxolanes using Zn/allyl bromide/NH_4Cl and β-cyclodextrin in water as the solvent (Schemes 1 and 2).

Keywords: Acetals; Allylation; Allyl bromide; Zinc; β-Cyclodextrin; Water.
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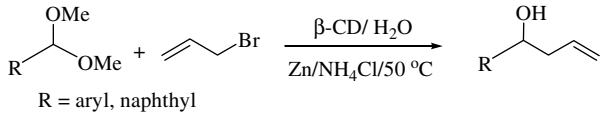
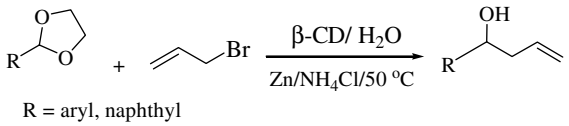


R = aryl, naphthyl

Scheme 1.

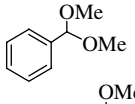
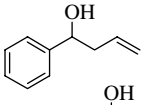
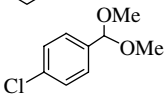
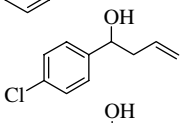
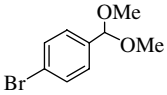
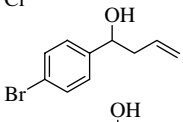
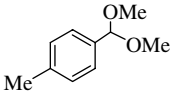
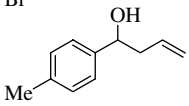
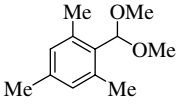
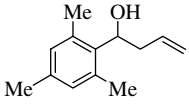
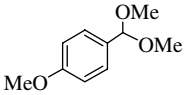
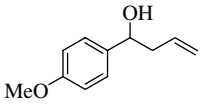
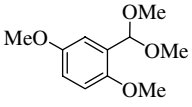
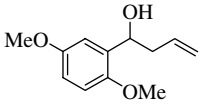
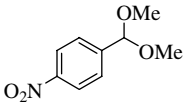
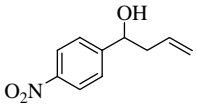
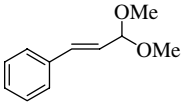
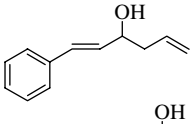
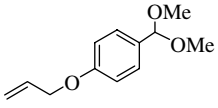
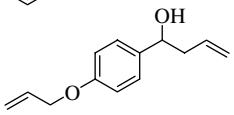
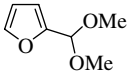
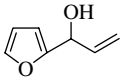
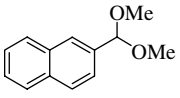
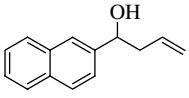


R = aryl, naphthyl

Scheme 2.

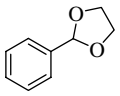
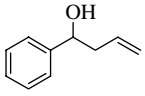
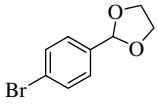
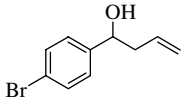
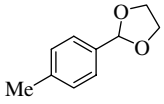
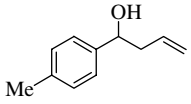
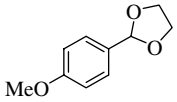
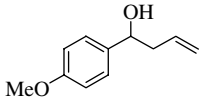
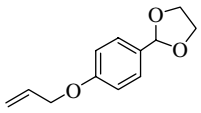
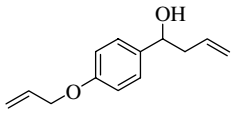
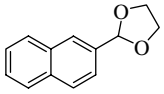
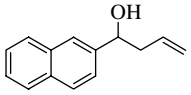
The reactions were carried out by dissolving β-cyclodextrin in water at 50 °C followed by the addition of the acetal and Zn/allyl bromide/NH_4Cl and stirring at that temperature until the reaction was complete.[10] The results are summarized in Tables 1 and 2 and the yields were very good (80–86%). This methodology is compatible with bromo, chloro, methyl, methoxy, and nitro groups. Acetals and dioxolanes possessing allyloxy and double bonds were neatly converted to the corresponding homoallylic alcohols in good yields without the formation of any by-product in reaction times ranging from 8 to 10 h. All the products were characterized by mass, ^1H NMR and IR spectroscopy and compared

Table 1. β-Cyclodextrin catalyzed allylation of acetals using Zn/allyl bromide in aqueous media

Entry	Substrate (**1**)	Product (**3**)[a]	Time (h)	Yield[b] (%)
a			8	86
b			8	88
c			8	88
d			8	84
e			10	80
f			10	80
g			10	80
h			10	88
i			10	82
j			8	85
k			10	82
l			8	86

[a] All the products were characterized by MS, ^1H NMR, and IR spectroscopy.
[b] Isolated yields.

Table 2. β-Cyclodextrin catalyzed allylation of dioxolanes using Zn/allyl bromide in aqueous media

Entry	Substrate (**2**)	Product (**3**)[a]	Time (h)	Yield[b] (%)
a			8	82
b			8	84
c			8	80
d			10	80
e			10	82
f			10	82

[a] All the products were characterized by MS, ^{1}H NMR, and IR spectroscopy.
[b] Isolated yields.

with the known compounds.[9b] These reactions could be effectively carried out at 50 °C and did not proceed in the absence of CD. The β-cyclodextrin can also be recovered and reused. These reactions also occur with aliphatic acetals and dioxolanes, however, the yields are less than satisfactory (15–20%). Here, the role of CD appears to activate the acetal or dioxolane group by hydrogen bonding, thereby facilitating its cleavage[11] in situ and enhancing the reactivity of the carbonyl oxygen for Barbier-type allylation reaction. Hence, the rates of CD catalyzed acetal hydrolysis and allylation reactions are nearly the same as the aldehyde formed in these reactions is simultaneously converted to the homoallylic alcohol.

In conclusion, this work demonstrates a new, mild, and efficient procedure for the synthesis of homoallylic alcohols directly from aromatic acetals and dioxolanes using a zinc-mediated Barbier reaction in the presence of β-cyclodextrin as the catalyst in water as solvent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.125.

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10. *General procedure*: β-Cyclodextrin (0.1 mmol) was dissolved in 20 mL of water by heating at 50 °C, then the acetal/dioxolane (1 mmol) was added slowly with stirring. After 15 min at this temperature, zinc powder (1.2 mmol), allyl bromide (1.2 mmol), and NH_4Cl (2.0 mmol) were added sequentially and the mixture was stirred at 50 °C until the reaction was complete (Tables 1 and 2). The organic material was extracted with ethyl acetate, dried, and concentrated under reduced pressure. The resulting product, although evident as a single compound by TLC, was purified by passing through a column of silica gel using ethyl acetate/*n*-hexane (2:8) as an eluent.
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