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Addition of water to arylidenecyclopropanes: a highly efficient method for the preparation of *gem*-aryl disubstituted homoallylic alcohols

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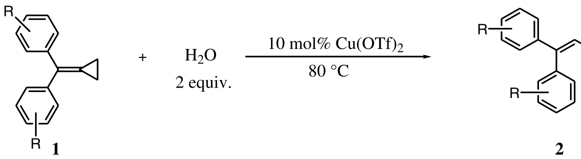
Abstract—Arylidenecyclopropanes react with water in the presence of a catalytic amount of $Cu(OTf)_2$ to afford the corresponding *gem*-aryl disubstituted homoallylic alcohols in good to excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

Synthesis of *gem*-aryl disubstituted homoallylic alcohols has been the subject of increasing interest in recent years because these structural units are useful, not only for the synthesis of Ca^{2+} channel antagonists,[1] but also for the synthesis of numerous biologically active natural products.[2a–d] Hence, the development of an efficient procedure for the synthesis of *gem*-aryl disubstituted homoallylic alcohols under mild conditions has remained an important subject.[3] While the synthesis of unsubstituted homoallylic alcohols has been studied to a wider extent,[4] there have been few practical methods for the efficient preparation of *gem*-disubstituted homoallylic alcohols. The first practical synthesis of *gem*-aryl disubstituted homoallylic alcohols was performed by the reaction of triphenylphosphine with cyclic ethers in the presence of a stoichiometric amount of strong acids, such as trifluoromethanesulfonic acid and trifluoroacetic acid, followed by treatment of the resulting hydroxyl alkylphosphonium salts with bases and subsequent reaction of the corresponding phosphonium inner salts with carbonyl compounds.[5] The homoallylic alcohols were obtained in the range of 38–90% yields. Afterward, the synthesis of *gem*-aryl disubstituted homoallylic alcohols was carried out in a catalytic way.[6a] Rhodium-catalyzed synthesis of *gem*-aryl disubstituted homoallylic alcohols using diaryldiazomethanes and allylic alcohols is not generally applicable due to the lack of efficiency and narrow scope.[6a] Recently, Onaka et al. reported the synthesis of *gem*-aryl disubstituted homoallylic alcohols via the carbonyl-ene reaction of α-methylstyrenes with paraformaldehyde in the presence of $BF_3{\cdot}OEt_2$ and molecular sieves 4 Å.[6b]

During the last decade, methylenecyclopropanes (MCPs) have become readily available and found application in organic synthesis as versatile building blocks. Their chemical reactivity is due to a high level of ring strain, although they are surprisingly stable and easy to handle.[7] Recently, we reported the convenient synthesis of homoallylic halides from methylenecyclopropanes and hydrogen halides.[8] This result, in turn, prompted us to investigate a possibility of the synthesis of homoallylic alcohols through MCPs. During our investigation, Min Shi and Bo Xu reported that the reaction of diphenylidenecyclopropane with water in the presence of $Sn(OTf)_2$ (10 mol%) at 80°C gave the corresponding homoallylic alcohol in 25% yield after 48 h.[9] Encouraged by the observation of Min Shi's group, we carried out a systematic investigation on the reaction of MCPs with water in order to obtain higher and practically useful chemical yields. We found that, in the presence of 10 mol% $Cu(OTf)_2$ and 2 equiv. of water at 80°C, MCPs **1** underwent smooth ring opening to give the corresponding homoallylic alcohols **2** in good to excellent yields (Eq. (1)).



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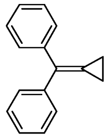
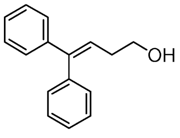
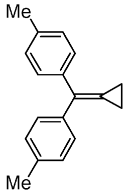
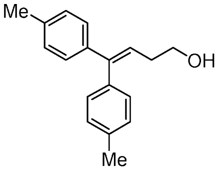
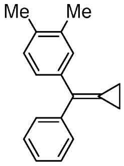
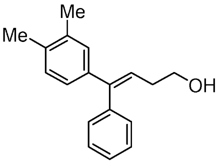
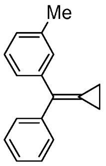
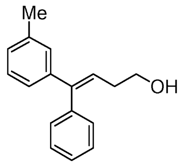
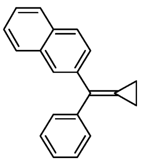
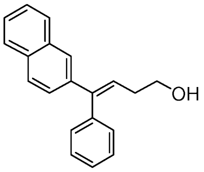
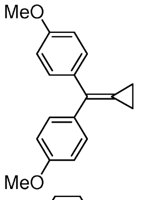
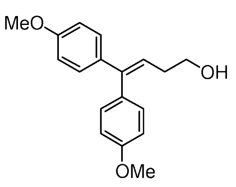
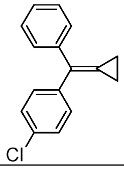
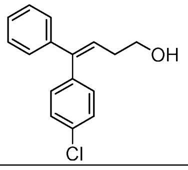
The results are summarized in Table 2. All the reactions, which were carried out in a sealed pressure vial, were monitored by GC and the reactions completed in 3–4 days at 80°C. Normally, the reaction was carried out on 0.5 mmol scale using 1.0 mmol of water, but the use of water on a larger scale (>3 mmol) diminished the chemical yield of the product dramatically (Table 1).

Table 1. Equivalents of water versus the chemical yield of **2a**

Entry	Equiv. of H_2O	Yield of **2a** (%)
1	1	68
2	2	86
3	5	54
4	45	Trace

Table 2. Addition of water to alkylidenecyclopropane **1**[a]

entry		1		2	yield / %[c]
1		**1a**		**2a**	86
2		**1b**		**2b**	87
3		**1c**		**2c**[b]	(84)[d]
4		**1d**		**2d**[b]	81
5		**1e**		**2e**[b]	(85)[d]
6		**1f**		**2f**	92
7		**1g**		**2g**[b]	72

[a] The reaction of **1** (0.5 mmol) with water (1.0 mmol) was carried out at 80°C.

[b] The products were obtained as a mixture of *E*/*Z* isomers, which were unseparable.

[c] Isolated yield based on **1**.

[d] The number in parenthesis indicates that the reaction of **1** with water was carried out in benzene (0.1–0.15 ml) as solvent at 80°C.

We investigated the effect of the amount of water on the chemical yield of **2a** in the reaction of **1a** using 10 mol% $Cu(OTf)_2$. As shown in Table 1, the use of 2 equiv. of H_2O gave the highest chemical yield. Lower chemical yields were obtained when one or three equivalents of water were used. Interestingly, the yield dropped dramatically upon the use of a larger amount of water (entry 4). This is perhaps a reason why Min Shi and Bo Xu obtained only 25% yield when they carried out the reaction of **1a** with water in the presence of 10 mol% of $Sn(OTf)_2$.

The reaction was sensitive to air and should be performed under an inert-gas atmosphere; if the reaction was carried out under air, the chemical yield decreased.[10] In entries 1–2, 4, and 6–7, when a mixture of the MCPs (0.5 mmol) and water (1 mmol) was heated at 80°C, if the MCPs became liquid although they were solid at room temperature or even at 60°C. If an MCP became liquid at 80°C, we obtained the corresponding homoallylic alcohol in excellent or good yield. However, in entries 3 and 5, **1c** and **1e** did not became liquid at 80°C and the mixture of the MCPs and water consisted of solid and liquid.[11] In these cases, addition of very small amounts (0.1–0.15 ml) of benzene changed the solid MCPs into liquids, and the desired **2c** and **2e** could be obtained in high chemical yields. Except for entries 3 and 5, no organic solvents were used in the other entries; if THF, 1,4-dioxane, CH_3CN, or DMSO were used as the solvent in the reaction of **1a**, **2a** was not obtained at all. If small amounts (0.1–0.15 ml) of benzene were used as the solvent, **2a** was produced in 69% yield (cf. entry 1). The use of cyclohexane and hexane gave a similar result as benzene. Accordingly, the reaction of **1** with water was very sensitive to reaction conditions: (1) the use of a sealed pressure vial under an inert gas atmosphere: (2) 2 equiv. of H_2O; (3) 80°C without organic solvents (very small amounts of benzene or hydrocarbon solvent are acceptable if needed). In the absence of Lewis acid catalysts, no reaction occurred. Among the Lewis acids examined, $Cu(OTf)_2$ gave the best result. $Sn(OTf)_2$ was less reactive than $Cu(OTf)_2$, and no reaction occurred in the presence of $Yb(OTf)_3$, $Sc(OTf)_3$ and $Zn(OTf)_3$. It should be mentioned that the protic acid, TfOH (10 mol%), can catalyze the addition of water to **1a** under similar conditions, but the yield of **2a** (46%) was lower than that of the $Cu(OTf)_2$ catalyzed reaction. Increasing the mol% of TfOH did not change the yield of the desired homoallylic alcohol and decreasing the mol% TfOH gave **2a** in much lower yield.

At higher temperatures (100–140°C) decomposition of MCPs competed with formation of homoallylic alcohols and the desired products were obtained in lower yields. At a lower temperature (60°C) the reaction did not proceed well even after 4–5 days because MCPs were solid at this temperature. The symmetrical MCPs, (1-phenylbenzylidene)cyclopropane **1a**, [1-(4-methylbenzyl)-*p*-toludene]cyclopropane **1b** and [1-(4-methoxyphenyl)-4-methoxybenzylidene]cyclopropane **1f**, underwent facile ring opening of the cyclopropane ring at 80°C with water to afford **2a**, **2b** and **2f** in 86, 87 and 92% yields, respectively (entries 1, 2 and 6). Likewise, the addition of water to the unsymmetrical MCPs, (1-phenyl-3,4-dimethylbenzylidene)cyclopropane **1c**, (1-phenyl-*m*-toludene)cyclopropane **1d**, (1-phenylnaphthyledene)cyclopropane **1e** and [(1-phenyl)-4-chlorobenzylidene]cyclopropane **1g**, proceeded smoothly to afford **2c**, **2d**, **2e** and **2g** as *E*/*Z* isomers, respectively. We attempted to determine the ratio and stereochemistry of the stereoisomers, but all the isomers were unseparable.

The reaction of **1f** bearing an electron-donating group gave **2f** in 92% yield (entry 6). On the other hand, the reaction of **1g** bearing an electron-withdrawing group gave the corresponding homoallylic alcohol **2g** in a moderate yield (entry 7).

We are now in a position to synthesize symmetrical and unsymmetrical *gem*-diaryl substituted homoallylic alcohols in good to high yields. The starting materials, diarylidenecyclopropanes, are readily available, and the other substrates are 2 equiv. of water and catalytic amounts of $Cu(OTf)_2$. Accordingly, this new procedure seems to provide a useful protocol for the synthesis of homoallylic alcohols, although at the present stage the reaction is limited to diarylsubstituted MCPs. The related reaction of di- or mono-alkylsubstituted MCPs is under active investigation in our laboratories.

The preparation of 3-bromopropyltriphenylphosphonium bromide.[12] A mixture of an equimolar amount of trimethylene bromide and triphenylphosphine was heated in xylene at 130°C for 16 h. Repeated recrystallization of the crude product using ethanol gave the desired product in 90% yield.

The preparation of 1a as a representative procedure for the synthesis of MCPs.[13] To a suspension of 3-bromopropyltriphenylphosphonium bromide (10.212 g, 22 mmol) in THF (100 ml) were added three portions of *t*-BuOK (4.937 g, 44 mmol) at intervals of 15 min at room temperature under an Ar atmosphere. After refluxing for 2 h, benzophenone (3.699 g, 20.3 mmol) was added into the yellow–brown suspension at 65°C. The reaction was monitored by TLC. After 2 h, the reaction mixture was cooled to ambient temperature and 100 ml of water was added. The mixture was extracted with hexane twice. The combined organic layer was washed with brine and dried over sodium sulphate. The solvent was evaporated and the residue was filtered through a plug of Celite. Purification by silica gel column chromatography using hexane as eluent gave **1a** in 75% yield.

The preparation of 2a as a representative procedure for the synthesis of homoallylic alcohols. To **1a** (103.1 mg, 0.5 mmol) in a pressure vial under an Ar atmosphere was added water (18 μl, 1.0 mmol) and the mixture was stirred at 80°C for 3 days. After completion of the reaction, which was monitored by GC, the mixture was then filtered through a short silica column with ethyl acetate as eluent. Purification of the product by silica column chromatography (hexane:EtOAc = 30:1) afforded the homoallylic alcohol **2a** in 86% yield.

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