# Cyclopropanation of Allylic Alcohols using Substituted Haloalkylzinc Reagents: Synthesis of *gem*-Dimethylcyclopropanes

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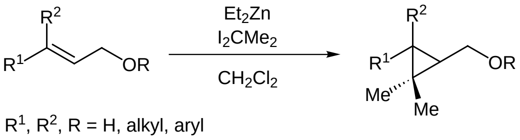
**Abstract:** *gem*-Dimethylcyclopropanes were obtained by a cyclopropanation of allylic alcohols and ethers using a mixture of diethylzinc and 2,2-diiodopropane in 53–96% yields. Enantioenriched *gem*-dimethylcyclopropanes were also synthesized using a glucose-derived auxiliary.

**Key words:** cyclopropanation, *gem*-dimethylcyclopropanes, carbenoids, chiral auxiliaries, stereoselective synthesis

The synthesis of *gem*-dimethylcyclopropanes have attracted great attention due to their presence in pyrethroid esters, which are remarkable insecticides derived from chrysanthemic acid[1] and in a number of natural products.[2] Several methods have therefore been developed to introduce the dimethylcarbene unit on an alkene through a cyclopropanation reaction. One of the oldest method involving a 1,3-dipolar addition of 2-diazopropane to activated double bonds, afforded a mixture of pyrazolines that could then be decomposed into the *gem*-dimethylcyclopropane through thermal or photolytic extrusion of nitrogen.[3] Another efficient method for the generation of *gem*-dimethylcyclopropane derivatives involves the addition-elimination sequence starting from an α,β-unsaturated carbonyl. Several reagents such as diphenyl sulfonium isopropylidene,[4] the related phosphonium isopropylidene,[5] or 2-methyl-1-propenylmagnesium bromide[6] have been developed to achieve this transformation. Even though these procedures usually give high yields of the corresponding cyclopropane, the geometry of the double bond is sometimes not preserved.[4a,5d] A variety of methods involving carbenes or radicals generated from 2,2-dihalopropane, chromous sulfate,[7] lithium cyclotetraene dianion,[8] or Co(0)- or Ni(0)-complex and zinc also allow the introduction of the dimethylcarbene fragment.[9] However, in these cases, the yields are usually poor. Finally, electrosynthesis provides another route for generation of *gem*-dimethylcyclopropanes. Sibille's group succeeded in cyclopropanating allylic alcohols using this process.[10] However, an excess of 2,2-dibromopropane and a sacrificial zinc anode were necessary. A zinc carbenoid as proposed for the classical Simmons–Smith reaction[11] is thought to be formed in solution, in contradiction to the results obtained by Léonel's group, using in this electrochemical process activated olefins, 2,2-dibromopropane and an aluminium rod as anode.[12] To the best of our knowledge, the only examples of Simmons–Smith cyclopropanation under Furukawa's conditions[13] using 2,2-diiodopropane and diethylzinc were reported by Musso's group for cyclopentene and cyclohexene. Moderate yields (45% and 59% respectively) of the corresponding *gem*-dimethylcyclopropane were observed after 5 days.[14] Herein, we report an efficient cyclopropanation of allylic alcohols and ethers to generate *gem*-dimethylcyclopropanes using modified conditions involving an equimolar amount of diethylzinc and 2,2-diiodopropane[15] (Equation).

The carbenoids can usually be prepared efficiently from diethylzinc and a dihalocompound,[13] and are more reactive in non-complexing solvents such as dichloromethane.[16] Furthermore, the stability of the carbenoid can be greatly improved by addition of an equimolar quantity of dimethoxyethane to the diethylzinc.[17] Also previous studies in our laboratory showed that the stoichiometry of the diiodoalkane and diethylzinc is very important for optimizing the yields and the diastereomeric ratios when zinc reagents are used.[18]



**Equation**

The initial optimization of the reaction conditions for generation of *gem*-dimethylcyclopropanes from allylic alcohols was done on cinnamyl alcohol using diethylzinc and 2,2-diiodopropane. The results are presented in Table 1. The first conditions that employed 2 equivalents of diethylzinc, 2 equivalents of DME and 4 equivalents of 2,2-diiodopropane resulted in poor conversions (entry 1). $^1$H NMR of the crude reaction mixture indicated that a large quantity of 2,2-diiodopropane was left unreacted. Furthermore, an NMR study showed that diethylzinc reacted within a few minutes with one equivalent of diiodopropane to generate $EtZnCMe_2I$, and that the second equivalent remained untouched.[19] This carbenoid is probably too bulky to allow for the approach of the second equivalent of diiodopropane to the zinc center. However, the reaction of this species was very efficient and very clean when an equimolar amount of diethylzinc and diiodopropane were

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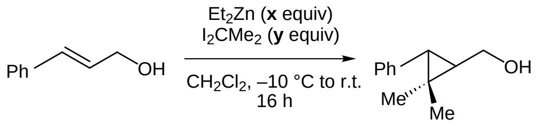
used (entries 2–4). High conversions were observed with only 2 equivalents of the reagents but the optimal yields were obtained when 4 equivalents of this reagent were used.[20] The addition of DME was found to reduce the conversion to the cyclopropane product (entry 5 vs. 4). The use of carbenoids bearing a trifluoroacetate or a phenolate group instead of the ethyl group[21] resulted in the complete decomposition of the starting material (entries 6–7).

**Table 1** Optimization of Reaction Conditions



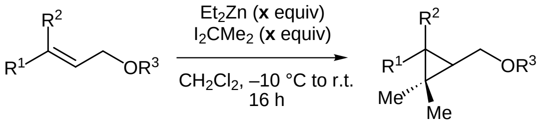
| Entry | x | y | Additive (equiv) | Conversion[a] |
|---|---|---|---|---|
| 1 | 2 | 4 | DME (2) | 17% |
| 2 | 2 | 2 | none | 76% |
| 3 | 3 | 3 | none | 94% |
| 4 | 4 | 4 | none | 95% |
| 5 | 4 | 4 | DME (4) | 78% |
| 6 | 4 | 4 | $F_3CCO_2H$ (4) | < 5%[b] |
| 7 | 4 | 4 | 2,4,6-trichlorophenol (4) | < 5%[b] |

[a] Determined by $^1$H NMR of the crude reaction mixture.
[b] Decomposition of the starting material was observed.

The optimized reaction conditions were then applied to a variety of allylic alcohols (Table 2, entries 1–8). The conversions were generally greater than 90% for a variety of olefins bearing a mono-, di- or trisubstitution pattern, independently of the (*Z*)- or (*E*)-configuration (entries 1–8). The lesser reactive 4-benzyloxy-2-buten-1-ol gave lower conversions (entries 5–6).

Ethers derived from cinnamyl alcohol were also converted in very high yields to the corresponding cyclopropane using 3 equivalents of the zinc carbenoid (Table 2, entries 9–13). No residual alkene could be observed by NMR in the cases of methyl-, benzyl- or *p*-methoxybenzylether (entries 9–11). Allylic ethers bearing protecting groups such as *tert*-butyldimethylsilyl and triisopropylsilyl were not as reactive probably for steric reasons. Accordingly, low conversions were obtained with the ether bearing a *tert*-butyldimethylsilyl group (entry 12), and only starting material was recovered in the case of the tri-isopropylsilylether (entry 13).

**Table 2** Cyclopropanation of Allylic Alcohols and Ethers using Diethylzinc and 2,2-Diiodopropane



| Entry | x | R$^1$ | R$^2$ | R$^3$ | Conversion[a] | Yield[b] |
|---|---|---|---|---|---|---|
| 1 | 4 | H | H | H | 91% | 71% |
| 2 | 4 | Ph | H | H | > 95% | 96% |
| 3 | 4 | Pr | H | H | 90% | 58% |
| 4 | 4 | H | Et | H | 94% | 64% |
| 5 | 4 | H | $BnOCH_2$ | H | 66% | 44% |
| 6 | 5 | H | $BnOCH_2$ | H | 73% | 53% |
| 7 | 4 | Me | Me | H | 94% | 62% |
| 8 | 4 | Ph | Me | H | > 95% | 75% |
| 9 | 3 | Ph | H | Me | > 95% | 66% |
| 10 | 3 | Ph | H | Bn | > 95% | 80% |
| 11 | 3 | Ph | H | PMB | > 95% | 77% |
| 12 | 3 | Ph | H | TBDMS | 39% | n.d. |
| 13 | 3 | Ph | H | TIPS | < 5% | n.d. |

[a] Determined by $^1$H NMR of the crude reaction mixture.
[b] Isolated yield of analytically pure product ($^1$H, $^{13}$C, IR, HRMS).

We then applied this methodology to an asymmetric version of the reaction using a known glucose derivative as a chiral auxiliary.[22] The 1-*O*-cinnamyl-3,4,6-tri-*O*-benzyl-β-D-glucose was prepared using the Schmidt's trichloroacetimidate glycosylation method, as previously described in the group.[23] The results for the asymmetric cyclopropanation reaction are given in Table 3. Our results indicate that the conversions are sensitive to the reaction temperature and can be favorably influenced by the initial addition of 1 equivalent of zinc iodide.[24] Lower reaction temperatures were found to decrease the conversions of the reaction, and did not significantly increase the diastereomeric ratio (entry 1 vs. 4). Also, increasing the equivalents of the reagent from 4 to 10 did not improve the diastereomeric ratio (entries 3 and 7 vs. 1 and 4). Even though the pretreatment with $ZnI_2$ did slightly increase the conversions, no improvement in diastereomeric ratio was noted (entry 2 and 5 vs. 1 and 4). The best results, 84% conversion with 82:18 dr, were obtained with 4 equivalents of reagent and overnight reaction at room temperature. The chiral auxiliary could be efficiently cleaved using a method previously developed in the group,[25] yielding the 3,3-dimethyl-2-phenylcyclopropylmethanol in 65%, without any loss of selectivity.

In conclusion, we have reported a new and effective procedure for the synthesis of *gem*-dimethylcyclopropanes, employing diethylzinc, 2,2-diiodopropane. This method should found extensive use in the synthesis of biologically important products containing *gem*-dimethylcyclopropanes. Extension of this methodology to an enantioselective version of the reaction will be reported in due course.

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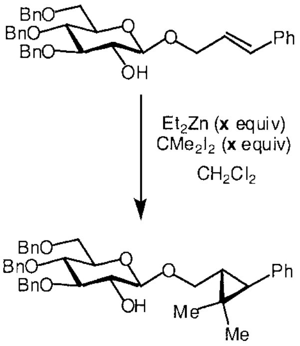
**Table 3** Diastereoselective Cyclopropanation using the Glucose-derived Chiral Auxiliary



| Entry | x | Temp. (°C) | Time (h) | Conversion[a] | dr[b] |
|---|---|---|---|---|---|
| 1 | 4 | –10 to r.t. | 16 | 84% | 82:18 |
| 2 | 4[c] | –10 to r.t. | 18 | 88% | 78:22 |
| 3 | 10 | –10 to r.t. | 18 | 75% | 80:20 |
| 4 | 4 | –20 | 16 | 43% | 86:14 |
| 5 | 4[c] | –20 | 16 | 67% | 84:16 |
| 6 | 4 | –20 | 69 | 89% | 84:16 |
| 7 | 10 | –20 | 16 | 59% | 79:31 |

[a] Determined by $^1$H NMR of the crude reaction mixture.

[b] Determined by quantitative $^{13}$C NMR of the crude reaction mixture.

[c] One equiv of $ZnI_2$ was added.

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(20) Typical Experimental Procedure: To a solution of the alkene (0.4 mmol) in anhyd $CH_2Cl_2$ (16 mL) at –10 °C was added dropwise $Et_2Zn$ (1.6 mmol, 1.2 mmol in the case of the ethers). After 10 min of stirring at that temperature, 2,2-diiodopropane (1.6 mmol, 1.2 mmol in the case of the ethers) was added dropwise over 2 min and the solution was stirred overnight at r.t. The formation of a precipitate (probably $ZnI_2$) was rapidly observed. The solution was then diluted with ether (10 mL) and washed with 10% aq HCl (10 mL), sat. aq $Na_2SO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure.The crude cyclopropanes were purified by flash chromatography on silica gel.

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