# An Improved *gem*-Dimethylcyclopropanation Procedure Using Triisopropylsulfoxonium Tetrafluoroborate

Michael G. Edwards, Richard J. Paxton, David S. Pugh, Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

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**Abstract:** A new procedure for the cyclopropanation of α,β-unsaturated carbonyl compounds and related systems is described which employs triisopropylsulfoxonium tetrafluoroborate and sodium hydride in dimethylformamide. Using this reagent, a range of α,β-unsaturated ketones (and an ester and a vinyl nitro example) has been converted into the corresponding *gem*-dimethylcyclopropyl carbonyl compounds; in addition, a preliminary result is described in which an activated alcohol is converted directly into a *gem*-dimethylcyclopropyl ketone by a one-pot tandem oxidation–cyclopropanation sequence, albeit in low yield.

**Key words:** cyclopropanes, cyclopropanation, tandem oxidation procedures, sulfoxonium salts, ruthenium tetroxide

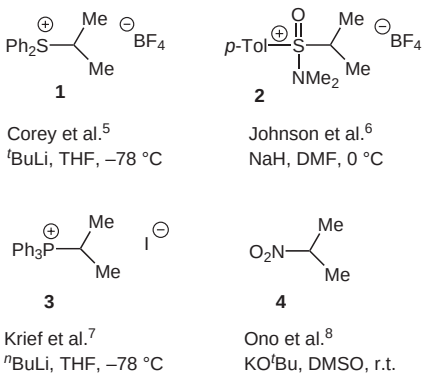


**Figure 1**

In recent years there has been a revival of interest in cyclopropanation chemistry with the development of efficient carbenoid sources and the application of organocatalysis to provide several elegant enantioselective syntheses.[1,2] This is a testament to both the prevalence of the cyclopropane unit in nature[1] and the utility of functionalised cyclopropanes as synthetic building blocks.[2] Although the parent methylene cyclopropane is present in numerous natural products, the *gem*-dimethylcyclopropane group is a more common structural motif.[3] There are numerous procedures available to prepare *gem*-dimethylcyclopropanes,[4] but it is noteworthy that only a limited number involve isopropyl transfer to electron-deficient alkenes (Figure 1).[5–8] The first such procedure was reported by Corey and Jautelat and utilised diphenylsulfonium isopropylide (**1**).[5] This reagent efficiently produces *gem*-dimethylcyclopropanes from unsaturated esters and amides but with α,β-unsaturated ketones, epoxide formation can compete (for example, 3-methyl-2-cyclohexenone gives mainly the unsaturated epoxide[5a]). In addition, the use of a strong base and low temperatures is required. In 1973, Johnson's group disclosed the use of (dimethylamino)isopropyl-*p*-tolyloxosulfonium tetrafluoroborate (**2**) for the *gem*-dimethylcyclopropanation of *trans*-1,2-dibenzoylethene and *trans*-chalcone.[6] However the synthesis of salt **2** was difficult and low-yielding and the scope of the procedure has not been demonstrated. More recently, it has been shown that the cyclopropanation of unsaturated esters can be achieved using the isopropyl phosphorane **3**[7] and the nitro compound **4**,[8] but again the scope of these reagents has not been determined (e.g. there are no examples of the use with α,β-unsaturated ketones).

As part of our continuing programme in telescoped processes and tandem oxidation processes (TOP),[9] we have recently become interested in developing improved routes to functionalised cyclopropanes.[10,11] First, a tandem procedure was designed for the one-pot oxidation–cyclopropanation of allylic alcohols using $MnO_2$ in conjunction with stabilised sulfuranes such as (carbethoxymethylene)dimethylsulfurane.[10] We went on to develop an improved procedure for the dimethylsulfoxonium methylide cyclopropanation of α,β-unsaturated ketones using trimethylsulfoxonium iodide and 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (MTBD).[11]

As an extension for our natural product programme, we also required a method for the nucleophilic *gem*-dimethylcyclopropanation of α,β-unsaturated ketones that would eliminate competitive epoxide formation (via reaction of the ketone), proceed under mild reaction conditions, and be applicable to a range of Michael acceptors. It is well established that the ylide derived from treatment of a sulfoxium salt with base can undergo nucleophilic cyclopropanation of α,β-unsaturated alkenes (the Corey–Chaykovsky reaction) via alkylidene transfer.[12] We therefore explored the preparation and reactions of a triisopropylsulfoxonium salt. As the S-alkylation of sulfoxides is successful only in the case of methylation,[13] it was necessary to synthesise such a salt by oxidation of the triisopropylsulfonium salt[14] (itself derived from diisopropyl sulfide). Unfortunately, the literature contains few reports on the oxidation of sulfonium salts to sulfoxonium salts. The best method, aqueous sodium *m*-chloroperbenzoate,[15]

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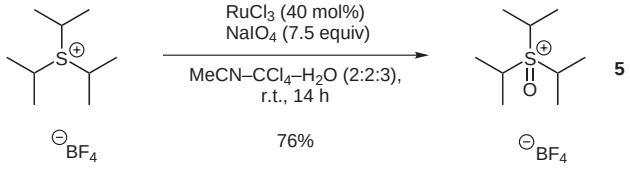
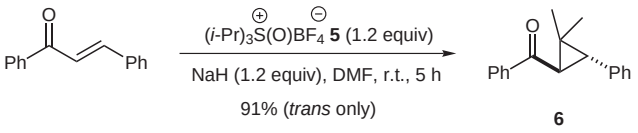
was not useful for this substrate because the oxidation could not be driven to completion. We reasoned that the use of a more powerful oxidant could overcome the slow oxidation of the sterically encumbered sulfonium salt. Ruthenium tetroxide[16] has been applied to the oxidation of many organic functionalities and, after optimisation of the classical Sharpless conditions ($RuCl_3$, MeCN–$CCl_4$–$H_2O$),[17] we found that with 40 mol% of $RuCl_3$ and 7.5 equivalents of $NaIO_4$, triisopropylsulfoxonium could be prepared, after recrystallisation from MeOH–$Et_2O$, in 76% yield[18] (Scheme 1).




**Scheme 1**

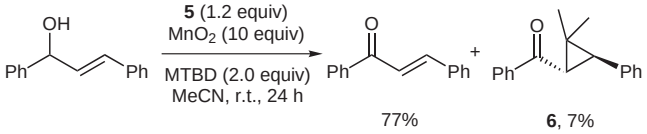
With the sulfoxonium salt in hand, the cyclopropanation of α,β-unsaturated ketones was explored; the initial experiments were conducted under literature conditions for dimethylsulfoxonium methylide cyclopropanation (NaH in DMF).[12d] We were delighted to observe that, after five hours at room temperature, the *gem*-dimethylcyclopropane adduct of chalcone[6] was obtained in 91% yield (Scheme 2). Most notably, only a single diastereomer, the *trans*-product, was obtained. Following this success, a range of α,β-unsaturated ketones was examined as cyclopropanation substrates (Table 1).




**Scheme 2**

The results illustrated in Table 1 indicate that cyclopropanation of a wide range of α,β-unsaturated ketones proceeds readily in 33–93% yield.[19,20] The results demonstrate a tolerance for both cyclic and acyclic substrates; high yields being obtained in both series. Even in the cases where moderate yields were obtained, there was no evidence for any of the epoxide (1,2-addition products). Moreover, in all examples studied, only a single diastereomer of product, the *trans*-cyclopropane, was obtained. Most notably, (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (entry 3) afforded only the 1,4-mono-addition product **8** in 85% yield. Electron-poor and electron-rich α,β-unsaturated ketones both seem to participate reasonably well as evidenced by the successful use of both (*E*)-1,4-diphenylbut-2-ene-1,4-dione (entry 7) and chromone (entry 9). Even a terminal vinyl group could be successfully cyclopropanated (entry 4). The reaction appears to tolerate heterocyclic functionality (entry 2) and the use of (*E*)-2-nitrostyrene illustrates the use of electron-withdrawing groups other than carbonyls. In contrast to the use of dimethylsulfoxonium methylide,[12] enolisable substrates can be problematic leading to alternative condensation byproducts and a lower yield (entries 5 and 6). Furthermore, the use of cyclohexenone led to only 4% of the desired product. Presumably, the slower rate of cyclopropanation, due to the steric encumberance of an ylide bearing three isopropyl groups, renders deprotonation a competitive alternative for the basic ylide.

After developing a successful method for cyclopropanation via isopropyl transfer we briefly investigated a one-pot $MnO_2$ oxidation–cyclopropanation reaction[11] (Scheme 3). This procedure produced chalcone in 77% yield along with a 7% yield of the oxidized/cyclopropanated adduct **6**. We are currently optimising these conditions.




**Scheme 3**

## Acknowledgment

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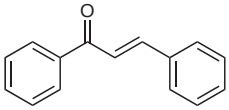
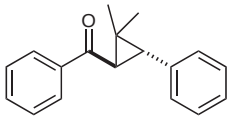
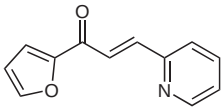
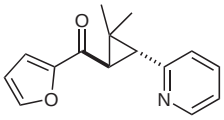
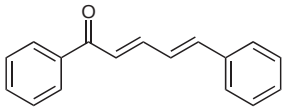
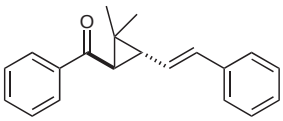
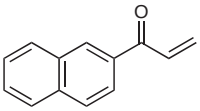
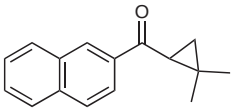
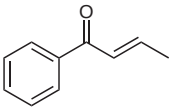
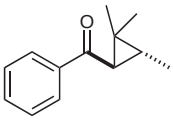
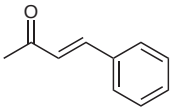
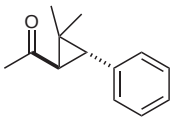
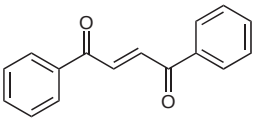
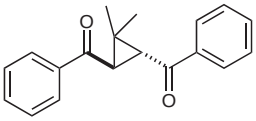
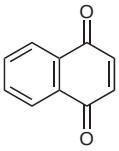
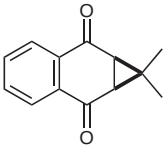
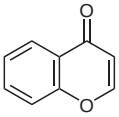
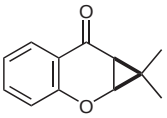
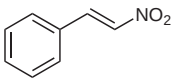
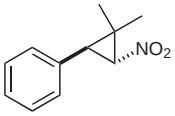
**Table 1** Cyclopropanation Using Triisopropylsulfoxonium Tetrafluoroborate **5** and NaH in DMF[a]

| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  **6** | 5 | 91 |
| 2 |  |  **7** | 2 | 71 |
| 3 |  |  **8** | 4 | 85 |
| 4 |  |  **9** | 24 | 53 |
| 5 |  |  **10** | 1.5 | 53 |
| 6 |  |  **11** | 2 | 33 |
| 7 |  |  **12** | 23 | 68 |
| 8 |  |  **13** | 3 | 92 |
| 9 |  |  **14** | 3 | 95 |
| 10 |  |  **15** | 17 | 93 |

[a] Using 1.2 equiv *i*-$Pr_3S(O)BF_4$ in DMF at r.t.
[b] Isolated yield of chromatographically homogeneous material; >95% *trans*-isomers by $^1H$ NMR spectroscopy.

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(18) **Preparation of Triisopropylsulfoxonium Tetrafluoroborate**
A 250 mL round-bottomed flask with stirrer bar was charged with triisopropylsulfonium tetrafluoroborate[14] (6.20 g, 25.0 mmol, 1.0 equiv), and then MeCN (36 mL), $CCl_4$ (36 mL), and $H_2O$ (54 mL) were added via syringe. The resulting biphasic solution was stirred vigorously and ruthenium(III) chloride (2.07 g, 10.0 mmol, 0.40 equiv) added in a single portion. The mixture was stirred for 10 min and then $NaIO_4$ (40.10 g, 187.5 mmol, 7.5 equiv) was added in 5 portions over ca. 5 min to the brown-coloured solution. The flask was loosely stoppered with a cork and the mixture vigorously stirred overnight at r.t. (14 h). The resulting grey-brown heterogeneous suspension was filtered through a Celite® pad (3 cm × 70 mm Ø) and washed with $H_2O$ (400 mL). The yellow filtrate was stirred vigorously and MeOH (50 mL) added to quench the residual $RuO_4$. The green suspension was concentrated under reduced pressure to remove the water present (60 °C) and the grey solid residue suspended in acetone (400 mL). The reaction mixture was stirred for a further 10 min and filtered to remove the residual inorganic solids. Concentration of the filtrate under reduced pressure afforded a yellow-orange powder that was recrystallised from MeOH–$Et_2O$. The crude solid was dissolved in 10 mL of boiling MeOH and $Et_2O$ added until the solution remained turbid. The mixture was then re-heated until homogeneous and allowed to cool, to afford the title compound as colourless plates (5.06 g, 76%); mp 108–109 °C. IR (acetone): $\nu_{max}$ = 3427, 1699, 1642, 1462, 1369, 1235, 1198, 1049 $cm^{-1}$. $^1H$ NMR (400 MHz, acetone-$d_6$): δ = 1.79 (d, *J* = 7.0 Hz, 18 H, $CH_3$), 4.73 (sept, *J* = 7.0 Hz, 3 H, CH). $^{13}C$ NMR (100 MHz, acetone-$d_6$): δ = 15.7 ($CH_3$), 53.0 (CH). $^{19}F$ NMR (254 MHz, acetone-$d_6$): δ = –151.6. $^{11}B$ NMR (87 MHz, acetone-$d_6$): δ = –1.9. ESI-MS: *m/z* (%) = 177 (100) [$M^+$]. HRMS–FAB: *m/z* calcd for $C_9H_{21}OS$: 177.1308 (0.4 ppm error); found: 177.1308 [$M^+$]. Anal. Calcd for $C_9H_{21}BF_4OS$: C, 40.93; H, 8.01. Found: C, 40.76; H, 7.85.
(19) All known products were characterised by NMR spectroscopy and comparison of key data with those published; novel products were fully characterised.
(20) **Representative Procedure for Cyclopropanation of α,β-Unsaturated Carbonyl Compounds (Table 1, Entry 1)**
A 25 mL round-bottomed flask with stirrer bar was charged with NaH (60% dispersion in mineral oil, 23 mg, 0.57 mmol, 1.2 equiv), sealed with a rubber septum and purged with argon. The flask was maintained under argon and anhyd DMF (4 mL) was added. The vigorously stirred suspension was cooled to 0 °C, the septum briefly removed and triisopropylsulfoxonium tetrafluoroborate (152 mg, 0.57 mmol, 1.2 equiv) added in a single portion. The mixture was stirred for 5 min before the addition of a solution of (*E*)-chalcone (100 mg, 0.48 mmol) in DMF (1 mL) dropwise by cannula. The cooling bath was removed and the brown-coloured solution allowed to stir at r.t. until the reaction was deemed to be complete by TLC (5 h). The reaction was quenched by the addition of sat. aq $NH_4Cl$ (5 mL), diluted with $H_2O$ (20 mL) and extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were dried ($Na_2SO_4$) and the solvent removed in vacuo. The residue was purified by column chromatography (PE–$Et_2O$, 19:1 ) to afford *trans*-(2,2-dimethyl-3-phenylcyclopropyl)-phenylmethanone (**6**) as a cream-coloured solid (109 mg, 91%); mp 63–64 °C. $R_f$ = 0.29 (PE–$Et_2O$, 19:1). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, $CH_3$), 1.27 (s, 3 H, $CH_3$), 2.91 (d, *J* = 6.0 Hz, 1 H, CH), 3.12 (d, *J* = 6.0 Hz, 1 H, CH), 7.20–7.24 (m, 3 H, ArH), 7.28–7.32 (m, 2 H, ArH), 7.49–7.53 (m, 2 H, ArH), 7.57–7.61 (m, 1 H, ArH),7.99–8.02 (m, 2 H, ArH). Data consistent with those reported in the literature.[6]