# Geminal Acylation of Ketones Mediated by Boron Trichloride. An Improved Method for the Synthesis of 4,4-Dimethyl-1,3-cyclopentanediones

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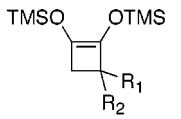
The geminal acylation of acetals and ketones with 1,2-bis[(trimethylsilyl)oxy]cyclobutene (**1**) catalyzed by $BF_3$·$Et_2O$ is a powerful method for the introduction of a 1,3-cyclopentanedione moiety.[1] The process involves an initial aldol reaction that gives an isolable cyclobutanone compound, followed by an acid-induced acyl migration to provide the diketone. Both steps are now normally accomplished in one pot.[1b−d] We showed that methylated analogues **2** and **3** could also undergo the reaction with acyclic and cyclic ketones,[2] but yields with **3** were usually

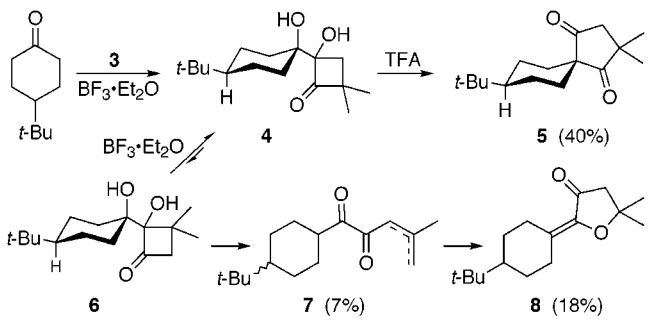



**1** $R_1 = R_2 = H$
**2** $R_1 = Me$, $R_2 = H$
**3** $R_1 = R_2 = Me$

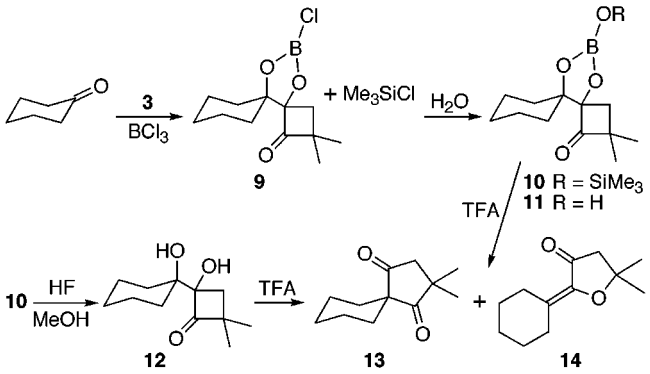
below 50% except with some conjugated[2] and aromatic ketones.[3] As illustrated in Scheme 1 with the reaction of 4-*tert*-butylcyclohexanone, the desired 1,3-cyclopentanedione **5** was formed in only 40% yield by the acid-catalyzed rearrangement of the initially formed, equatorial cyclobutanone **4**. However, it appeared that $BF_3$·$Et_2O$ also facilitated equilibration of **4** to **6**, which led to the production of a significant amount of 3-furanone **8** via ring-opened 1,2-diones **7**.[2] This equilibration certainly makes this methodology less attractive for the synthesis of the many natural products that contain subunits derivable from 4,4-dimethyl-1,3-cyclopentanediones.

To explore the possibility that the Lewis acid might both mediate the initial aldol reaction and inhibit subsequent equilibration of **4**, reactions of **3** with $BCl_3$ were conducted at −78 °C in an NMR tube and on a preparative scale.[4] Scheme 2 presents the salient features of the novel process, which proceeds with the incorporation of boron by the formation of five-membered borate-containing compounds. Addition of cyclohexanone to a solution of $BCl_3$ ($^{11}$B NMR $\delta$ 46.3) in $CD_2Cl_2$ resulted in a signal

**Scheme 1**




**Scheme 2**




for the complexed $BCl_3$ at $\delta$ 8.3 in the $^{11}$B NMR.[5a] Introduction of **3** ($^{29}$Si NMR[5b] $\delta$ 18.4 and 18.0) initiated the disappearance, over several hours, of the $BCl_3$−cyclohexanone complex and the emergence of a $^{11}$B NMR signal at $\delta$ 27.6, which was ascribed to a very labile compound **9**, and a $^{29}$Si NMR signal at $\delta$ 29.9, which was identified as $Me_3SiCl$ by admixture with genuine $Me_3SiCl$ (in a separate experiment). Addition of water to the reaction medium caused the immediate disappearance of the $^{11}$B NMR signal at $\delta$ 27.6 and the emergence of a signal at $\delta$ 20.3. At the same time, the $Me_3SiCl$ signal was replaced by a $^{29}$Si NMR signal at $\delta$ 16.5. Aqueous workup gave a mixture of **10**, the hydrolyzed product **11**, and the known diol **12**[2] (2.4:1.2:1, respectively). (Introduction of a large amount of $Me_3SiCl$ before workup afforded only **10** and **12**, in a 6.5:1 ratio.) Spectral data supporting the structure of **10** included IR peaks at 1785 (C═O) and 1456 (B−O) $cm^{-1}$, a 9-proton singlet at $\delta$ 0.19 in its $^1$H NMR, $^{13}$C NMR signals at $\delta$ 215.5 (C═O), 99.3 and 88.1 (quaternary C−O's), and 0.97 ($SiMe_3$), and the $^{11}$B and $^{29}$Si signals noted above. The $^{11}$B NMR signal for **11** was at $\delta$ 21.9, and its IR spectrum included absorption at 3214 $cm^{-1}$ (BO−H). Thus, it appears that the labile nature of the B−Cl bond, relative to the B−F bonds of $BF_3$, allowed the initial aldol to take place by an association of the boron with both the carbonyl oxygen and an oxygen on **3**.

Rearrangement of **4** in TFA gave only diketone **5**, but stirring a 6.5:1 mixture of the borates **10** and **11** in TFA

(1) (a) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759−1773. (b) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804−811. (c) Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311−1318. (d) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485−1491.

(2) Crane, S. N., Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722−8729.

(3) Crane, S. N., Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352−1355.

(4) $TiCl_4$ and $SnCl_4$, although commonly used in Mukaiyama aldol reactions, produced complex mixtures of products.

(5) (a) Nöth, H.; Wrackmeyer, B. In *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; *NMR, Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; Springer-Verlag: Berlin, 1978; Vol. 14. (b) Marsmann, H. In *Oxygen-17 and Silicon-29; NMR, Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; Springer-Verlag: Berlin, 1981; Vol. 17.

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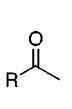
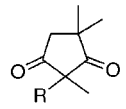
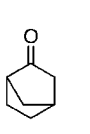
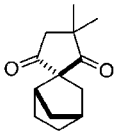
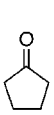
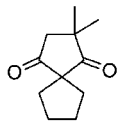
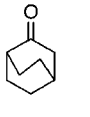
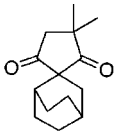
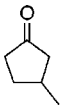
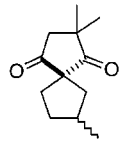
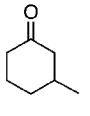
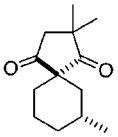
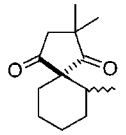
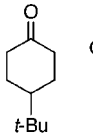
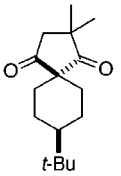
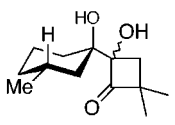
**Table 1. Reactions of 3 with Various Ketones**

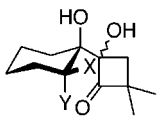
| substrate | product | yield (%) | substrate | product | yield (%) |
|---|---|---|---|---|---|
|  |  **15** R = $CH_3$ 83<br>**16** R = $CH_2CH_3$ 75<br>**17** R = $CH_2C_6H_5$ 51<br>**18** R = $C_6H_5$ 47 | |  |  **22** | 82 |
|  |  **19** | 81 |  |  **23** | 97 |
|  |  **20a,b** (2:1) | 46 |  |  **24** | 85 |
|  |  **21a,b** (2:1) | 29 |  |  **5** | 98 |

at room temperature overnight gave both **13** and 3-furanone **14** (1.2:1). Nevertheless, HF in methanol smoothly converted **10** and **11** to a mixture of **12** and **13** (7.4:1), and the rearrangement to **13** was completed in 87% yield from cyclohexanone by the addition of TFA without the production of any 3-furanone **14**.

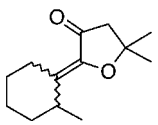
A three-step, one-pot procedure was developed on the basis of the above findings. Geminal acylations were carried out on a variety of ketones (Table 1).[6] There was a very pronounced improvement in the overall yields of the diketones over the previous procedure with $BF_3$·$Et_2O$.[2] The relative stereochemistry of diketones **5** and **22** was the same as from that the $BF_3$·$Et_2O$ procedure, and the stereoselectivity in their production was at least as good as with $BF_3$·$Et_2O$. The relative stereochemistry of **24**, the only product from 3-methylcyclohexanone, was established by comparison with the $^{13}C$ NMR data for **5**, **13**, and the 2,4-DNP derivative of the former.[2] Diketone **24** was derived from two cyclobutanone−diol compounds **25a,b**. Comparison of their $^{13}C$ NMR shifts with those



**25a,b**



**26** X = H, Y = Me
**27** X = Me, Y = H



**28a,b**

of **4** and other similar compounds indicated that they differed only in the face of **3** that had been attacked. However, 2-methylcyclohexanone was an exceptional substrate with regard to both yield and stereoselectivity. It appeared that the initial aldol step with this substrate took place in a reasonable yield, but six of the eight possible diols were produced, in a ratio of 8.4:1.9:1.9:1.1:1:1. Two of these, the major diol **26** and one of the minor diols **27**, were obtained in an enriched form by chromatography. The structures of these were evident from the NMR data, although the relative configurations at C-2 could not be determined. Whereas **27** rearranged cleanly to **21a** in TFA, the major diol **26** gave only small amounts of diketone **21b** and 3-furanones **28a,b** along with intractable material. Except with acetophenone, starting materials were largely returned when conjugated ketones (isophorone, 1-indanone, and α-tetralone) were subjected to the one-pot procedure with **3** and $BCl_3$. Acetophenone gave only a modest yield of dione **18**.

In summary, the mechanism of action of $BCl_3$ appears to differ in an important way from that of $BF_3$·$Et_2O$ because $BCl_3$ not only induces the initial aldol reaction but it is incorporated into a cyclic borate that inhibits subsequent equilibration of the aldol product. The use of $BCl_3$ now makes the formation of 4,4-dimethyl-1,3-cyclopentanediones by geminal acylation a very attractive synthetic methodology.

## Experimental Section

**General.** Compound **3** was prepared using the method for the preparation of **1**.[7] $CH_2Cl_2$ was distilled from $CaH_2$. All reactions were performed under $N_2$. $^1H$ NMR spectra were obtained at 300 MHz in $CDCl_3$ unless specified otherwise. Chemical shifts are relative to internal TMS. Ratios of products were determined by integration of corresponding signals in the $^1H$ NMR spectra of mixtures. $^{13}C$ NMR spectra were recorded at 75 MHz; chemical shifts are relative to solvent. Each $^{13}C$ chemical shift is followed in parentheses by the number of attached protons as determined by APT and heteronuclear correlation spectra. For spectral data obtained from mixtures, only clearly distinguished signals are reported. $^{11}B$ NMR spectra were recorded at 96.3 MHz; chemical shifts are relative to an external $BF_3$·$Et_2O$ standard. $^{29}Si$ NMR spectra were recorded at 59.6 MHz; shifts are relative to external chlorotrimethylsilane reference.

**General Procedure.** $BCl_3$ (3.2 mL) and then **3** (0.84 g, 3.2 mmol) were added to a solution of the ketone (2.0 mmol) in $CH_2Cl_2$ (5.0 mL) at −78 °C. This was stirred at −78 °C for 24−37 h, or at −22 °C for 6−8 h, or warmed to room temperature overnight. The mixture was recooled to −78 °C before a solution of 50% HF (1.6 mL) in MeOH (3.4 mL) was added and the mixture was stirred for 10 min. The mixture was warmed to room temperature and stirred for 1 h. The mixture was concentrated under reduced pressure. The residue was stirred in TFA (6.0 mL) for 24 h. $CH_2Cl_2$ was added, and the solution was washed with $H_2O$, to which $NaHCO_3$ was added to give pH 7, and then the solution was dried over anhydrous granular $Na_2SO_4$. Concentration under vacuum gave a brown material to which hexanes (50 mL) were added. The resulting solution was passed through Florisil (3 cm × 1.5 cm), flushing with additional hexanes (100 mL). Solvent evaporation from the combined filtrates gave the diketone product. Further purification, when necessary, was accomplished by flash chromatography. Spectral data for **5**, **13**, **15**, **16**, **18**, **19**, **20a,b**, **21a,b**, **22**, **23**, and **28a**,**b** have been reported.[2,3]

**12-Bora-2,2-dimethyl-11,13-dioxa-12-[trimethylsilyl(oxy)]-dispiro[3.0.5.3]tridecan-1-one (10) and 12-Bora-12-hydroxy-2,2-dimethyl-11,13-dioxadispiro[3.0.5.3]tridecan-1-one (11).** Compound **3** (0.86 g, 3.3 mmol) was added over 5 min to a solution of cyclohexanone (0.20 g, 2.1 mmol) and $BCl_3$ (3.3 mL) in $CH_2Cl_2$ (5.0 mL) at −78 °C. The resulting solution was stirred at −78 °C for 11 h. Aqueous workup, drying of the solution over

(6) One experiment in which the substrate was the ethylene glycol acetal of *tert*-butylcyclohexanone gave a mixture of **5**, **8**, and *tert*-butylcyclohexanone in a ratio of roughly 2:1:4, respectively.

(7) Bloomfield, J. J.; Nelke, J. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 167−172.

anhydrous $Na_2SO_4$, and evaporation of the solvent gave a mixture of a white solid (**12**, 127 mg) and a yellow oil (**10** and **11** in a 2:1 ratio, 459 mg). The sample consisting of just **10** and **11** was obtained by washing the oil off the solid with hexanes. For **10**: $^1$H NMR $\delta$ 2.29 (1H, d, $J$ = 13.2 Hz), 2.07 (1H, d, $J$ = 13.2 Hz), 1.29 (3H, s), 1.16 (3H, s), 0.19 (9H, s); $^{11}$B NMR ($CD_2Cl_2$) $\delta$ 20.3; $^{13}$C NMR ($CD_2Cl_2$) (selected signals) $\delta$ 215.5, 99.3, 88.1, 82.3, 39.6, 34.8, 34.5, 26.0, 24.1, 22.6, 22.3, 22.1, 0.97; $^{29}$Si NMR ($CD_2Cl_2$) $\delta$ 16.5. For **11**: $^1$H NMR $\delta$ 2.32 (1H, d, $J$ = 13.5 Hz), 2.12 (1H, d, $J$ = 13.5 Hz), 1.30 (3H, s), 1.18 (3H, s); $^{11}$B NMR ($CD_2Cl_2$) $\delta$ 21.9. The mixture of **10** and **11** (0.584 g) was stirred in TFA (3.0 mL) at room temperature for 20 h. Workup provided a brown oil (0.408 g). $^1$H NMR analysis showed the presence of **13** and **14** (1.5:1).

**2-Benzyl-2,4,4-trimethyl-1,3-cyclopentanedione (17):** yellow oil; $^1$H NMR $\delta$ 7.27−7.14 (3H, m), 7.08−6.98 (2H, m), 2.99 (1H, d, $J$ = 12.8 Hz), 2.92 (1H, d, $J$ = 12.8 Hz), 2.43 (1H, d, $J$ = 18.4 Hz), 1.74 (1H, d, $J$ = 18.3 Hz), 1.27 (3H, s), 1.12 (3H, s), 0.62 (3H, s); $^{13}$C NMR $\delta$ 221.3 (0), 216.9 (0), 136.3 (0), 130.0 (2C, 1), 128.4 (2C,1), 127.1 (1), 58.6 (0), 51.8 (2), 46.1 (0), 42.5 (2), 26.7 (3), 23.0 (3), 22.4 (3).

**(5*R**,7*S**)-2,2,7-Trimethylspiro[4.5]decane-1,4-dione (24):** very pale yellow crystals from EtOAc−hexane; mp 59.5−61 °C; $^1$H NMR $\delta$ 2.61 (2H, s), 1.93 (1H, br m), 1.81 (1H, m), 1.72 (1H, m), 1.68−1.55 (2H, m), 1.53 (1H, m), 1.48 (1H, apparent dq, $J$ = 3.9, 12.9 Hz), 1.222 (3H, s), 1.215 (3H, s), 1.15 (1H, d, $J$ = 13.2 Hz), 0.92 (1H, apparent dt, $J$ = 4.8, 14.1 Hz), 0.86 (3H, d, $J$ = 6.9 Hz); $^{13}$C NMR $\delta$ 220.1 (0), 216.3 (0), 56.0 (0), 50.4 (2), 46.4 (0), 38.3 (2), 33.7 (2), 30.5 (2), 26.7 (1), 25.5 (3), 25.3 (3), 22.4 (3), 21.1 (2). For the 4-(2,4-dinitrophenylhydrazone) derivative: orange crystals from MeCN−$CH_2Cl_2$−hexane, mp 231−233 °C; $^1$H NMR $\delta$ 11.11 (1H, br s), 9.14 (1H, d, $J$ = 2.6 Hz), 8.39 (1H, dd, $J$ = 2.5, 9.5 Hz), 7.88 (1H, d, $J$ = 9.5 Hz), 2.77 (2H, s), 2.18−1.88 (2H, m), 1.82 (1H, m), 1.75−1.50 (4H, m), 1.33 (1H, apparent triplet, $J$ = 12.8 Hz), 1.25 (3H, s), 1.24 (3H, s), 1.01 (1H, apparent dq, $J$ = 3.4, 12.9 Hz), 0.92 (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR $\delta$ 220.3 (0), 164.7 (0), 145.0 (0), 138.0 (0), 130.3 (1), 129.3 (0), 123.4 (1), 116.4 (1), 53.8 (0), 46.0 (0), 40.3 (2), 38.8 (2), 33.8 (2), 32.1 (2), 26.7 (1), 25.8 (2C, 3), 22.6 (3), 21.3 (2).

**(1′*R**,3′*R**)-2-Hydroxy-4,4-dimethyl-2-(1-hydroxy-3-methylcyclohexyl)cyclobutanone (25a,b).** A 1:1 mixture of epimers (at C-2) was obtained by aqueous workup after the HF/MeOH treatment. For this mixture: $^1$H NMR $\delta$ 3.44 (OH), 2.18 (1H, d, $J$ = 12.8 Hz), 2.17 (1H, d, $J$ = 12.9 Hz), 1.91 (2H, d, $J$ = 12.8 Hz), 1.87−1.84 (2H, m), 1.36 (6H, s), 1.155 (3H, s), 1.153 (3H, s), 0.90 (6H, d, $J$ = 6.4 Hz); $^{13}$C NMR $\delta$ 220.0 (0), 92.6 (0), 92.5 (0), 74.0 (0), 55.2 (0), 38.6 (2), 38.0 (2), 34.4 (2), 31.7 (2), 29.2 (2), 27.3 (1), 27.0 (1), 20.9 (2), 20.6 (2), 24.7 (3), 22.5 (3), 20.9 (3).

**(1′*R**,2′*R**)-2-Hydroxy-4,4-dimethyl-2-(1-hydroxy-2-methylcyclohexyl)cyclobutanone (26):** yellow solid; mp 113.5−116 °C; $^1$H NMR $\delta$ 3.60 (OH), 2.15 (1H, dd, $J$ = 0.6, 12.8 Hz), 2.00 (1H, d, $J$ = 12.8 Hz), 1.66 (1H, br m), 1.36−1.17 (8H, m), 1.37 (3H, s), 1.16 (3H, s), 1.00 (3H, d, $J$ = 6.8 Hz); $^{13}$C NMR $\delta$ 218.9 (0), 94.4 (0), 74.1 (0), 55.3 (0), 39.0 (2), 36.3 (1), 34.0 (2), 30.9 (2), 25.7 (2), 24.8 (3), 21.5 (3), 21.0 (2), 17.5 (3). Stirring **26** (9 mg) in TFA (1 mL) at room temperature for 7 h provided only 2 mg of a brown oil, which consisted of a 1:1 mixture of **21b** and **28a**,**b** (1:1).

**(1′*R**,2′*S**)-2-Hydroxy-4,4-dimethyl-2-(1-hydroxy-2-methylcyclohexyl)cyclobutanone (27):** white solid; mp 139−141.5 °C; $^1$H NMR $\delta$ 2.45 (OH), 2.44 (1H, d, $J$ = 12.3 Hz), 1.84 (1H, d, $J$ = 12.3 Hz), 1.91 (1H, br m), 1.73−1.63 (2H, m), 1.63−1.47 (2H, m), 1.47−1.36 (4H, m), 1.35 (3H, s), 1.20 (3H, s), 1.03 (3H, d, $J$ = 7.5 Hz); $^{13}$C NMR $\delta$ 218.5 (0), 94.3 (0), 74.7 (0), 55.4 (0), 38.4 (2), 34.7 (1), 29.2 (2), 27.1 (2), 25.1 (3), 21.3 (3), 20.9 (2), 19.6 (2), 15.8 (3). Diol **27** (11 mg) was dissolved in trifluoroacetic acid-*d* at room temperature. $^1$H NMR after only 5 min revealed rearrangement to **21a** was complete. Aqueous workup provided **21a** as a yellow oil (10 mg).

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**Supporting Information Available:** Experimental details, additional characterization data, and NMR spectra for new compounds and for byproducts (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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