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Stereocontrol in ene-dimerisation and trimerisation of 1-trimethylsilyl-3-phenylcyclopropene

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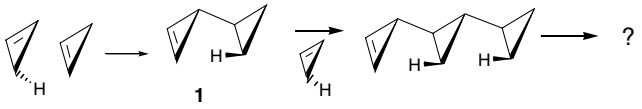
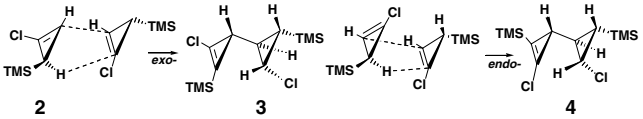
Abstract—1-Trimethylsilyl-3-phenylcyclopropene undergoes a highly stereocontrolled ene-reaction to give a dimer and further reaction leads to one or more trimers derived through two ene-reactions.

There has been considerable recent interest in biologically active compounds containing an array of contiguous cyclopropanes.[1] The synthesis of such molecules in a stereocontrolled manner has generally been achieved by stepwise introduction of each ring.[2] The ene-dimerisation of cyclopropenes leads initially to a cyclopropylcyclopropene. Formally this reaction could be repeated with further molecules of cyclopropene leading to the formation of a single polycyclopropane. In practice, to achieve such a series of reactions would require an extremely high degree of stereo- (*exo*- or *endo*-transition state) and regio-control in each step and in addition would require the rate of reaction of the dimer **1** (Scheme 1) with cyclopropene (only one possible regio- and stereochemistry is shown) to be considerably faster than the dimerisation of this species itself. The known examples of such reactions for substituted cyclopropenes suggest that, although the regiochemistry in dimerisations can be largely controlled by appropriate introduction of substituents, the stereochemistry (and particularly the absolute stereochemistry) is more difficult to control.[3–10]



Scheme 1.

1,3-Diphenylcyclopropene is known to undergo a rapid ene-reaction to give a single dimer, though the stereochemistry of the process is not clear.[11] In the case of 1-chloro-3-trimethylsilylcyclopropene **2**, a single dimer **3** is formed apparently, though not explicitly stated, by the reaction of two enantiomeric molecules through an *exo*-transition state, rather than two identical molecules, which would require an *endo*-transition state and lead to **4**[12a] (Scheme 2). However, during the course of this work, 1-phenylcyclopropene was reported to undergo ene-dimerisation and trimerisation, in each case through an *endo*-transition state.[12b]



Scheme 2.

We have recently reported the preparation and studies of the chemistry of 3-phenylcyclopropene,[13] and some of its derivatives including 1-trimethylsilyl-3-phenylcyclopropene **6**. We now report the ene-dimerisation

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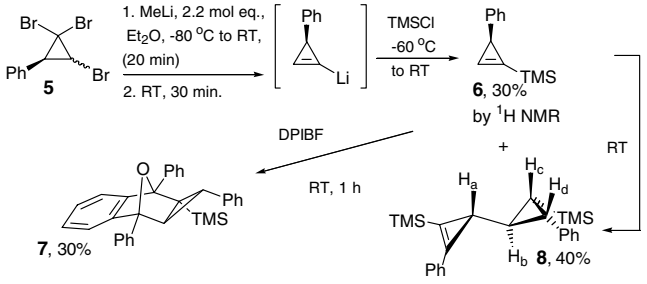
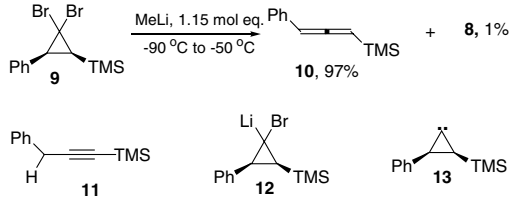
and trimerisation of **6**. The tribromide **5** was treated with 2.2 mol equiv of MeLi at −80 °C, allowed to reach room temperature for 30 min to form the 1-lithio-3-phenylcyclopropene by lithium–halogen exchange,[14] and then quenched with trimethylsilyl chloride to give cyclopropene **6**[15] that could be trapped in 30% yield (from **5**) as **7** by reaction with diphenylisobenzofuran (DPIBF).[16] This reaction also produced a single dimer **8** of the cyclopropene; this could be isolated in 40% yield in the absence of the trap (Scheme 3).[17] The regio- and stereochemistry of **8** is established later (only one enantiomeric series is shown).



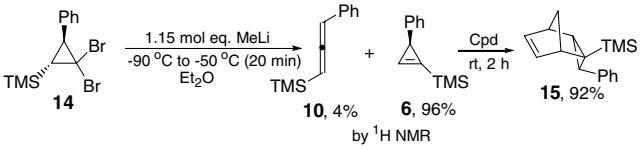
Scheme 3.

In order to better understand this process, a route to the cyclopropene **6** was required which could be carried out at low temperature to minimize dimer formation. Reaction of **9**[18] with methyllithium was expected to lead to a 1,2-silyl shift in an intermediate cyclopropylidene to give cyclopropene **6**.[19] However, when the reaction was carried out at −90 °C and quenched with water at −50 °C, an essentially quantitative yield of allene **10** (Scheme 4) was obtained. At room temperature, the major product was the acetylene **11**, together with allene **10** and a small amount of the dimer **8**.



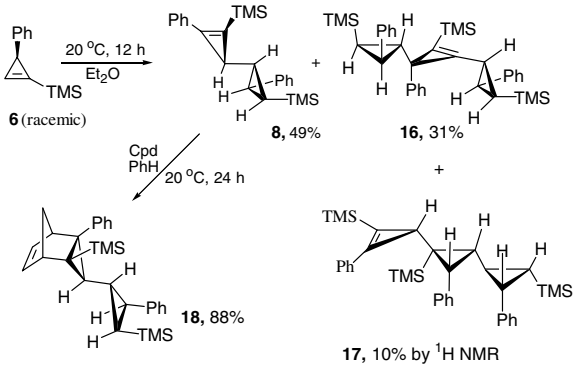
Scheme 4.

In contrast, the *trans*-isomer **14** reacted with methyllithium at −90 °C followed by quenching with water at −60 °C to give the cyclopropene **6** as the major product (Scheme 5), together with ca. 4% of the allene **10**. The cyclopropene **6** was again unstable but could be detected directly by NMR at −40 °C.[20] The cyclopropene could be trapped as a single (4+2)-cycloadduct **15** with cyclopentadiene (CPD) in 92% yield based on **6**. The formation of **6** presumably occurs through intermediates **12** and **13** by a lithium–bromine exchange followed by a formal loss of lithium bromide to give a cyclopropylidene which rearranges by a 1,2-trimethylsilyl shift. The different outcomes from the *cis*- and *trans*-isomers may simply reflect a steric effect slowing the migration of the trimethylsilyl group in the *cis*-case and allowing the normal cyclopropylidene–allene rearrangement[21] to compete; clearly, however, the intermediate cannot be a symmetrical free carbene or both isomers would give the same product. Moreover, a more subtle effect based on the stereochemistry of the lithium–bromine exchange or on the formation of a more complex intermediate is also possible.



Scheme 5.

If the cyclopropene was worked up at 20 °C in the absence of a trap, the dimer **8** was again obtained, in this case accompanied by two trimers, **16** and **17**[22] (Scheme 6). The dimer was efficiently trapped by reaction with cyclopentadiene to give a crystalline adduct **18**.[22] Under these conditions neither of the trimers reacted with the diene.



Scheme 6.

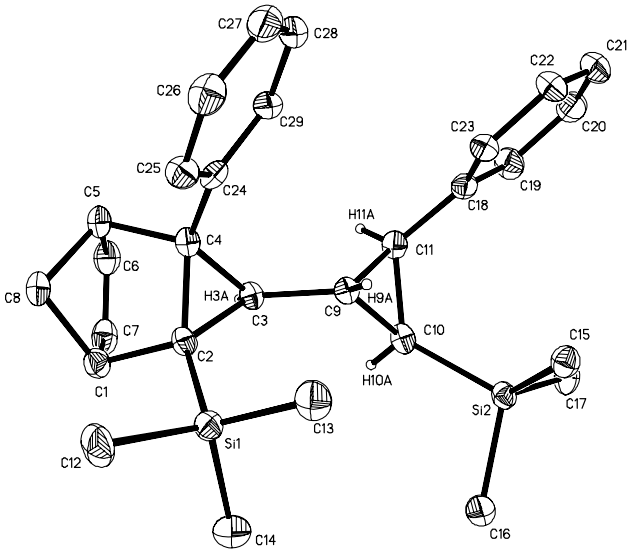
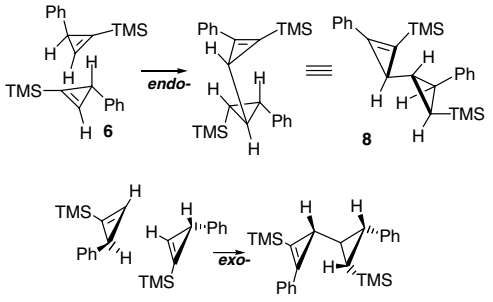


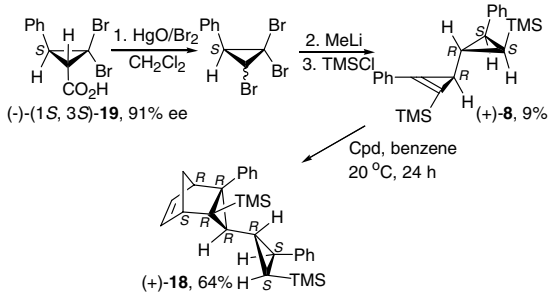
Figure 1. X-ray crystal structure of CPD cycloadduct **18**.

The structure of the adduct **18** (Fig. 1) shows that the dimer **8** was formed from two identical molecules of **6**, rather than two enantiomeric molecules, and that the reaction occurs through an *endo*-transition state (Scheme 7). The formation of one isomer of **8** from **6** creates eight chiral centres in **18** from the single chiral centre in **6**.



Scheme 7.

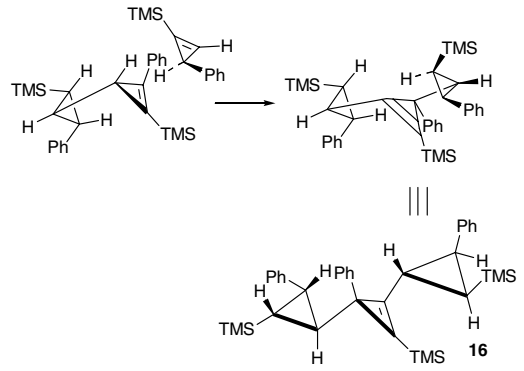
To exploit this, the corresponding trimethylsilylcyclopropene was obtained from the optically active acid **19** as shown below (Scheme 8). Surprisingly, the dimer was isolated in only low yield; trimers **16** and **17** were identified by NMR in a complex mixture with other products. The reason for the difference between the reactions of the racemic and optically active cyclopropenes is the subject of further analysis; however, the isolation of the two trimers from optically active monomer indicates that they are made up of three identical monomer molecules and not of enantiomeric molecules. Trapping of (+)-**8** with cyclopentadiene gave a 64% yield of the adduct (+)-**18** of the corresponding enantiomerically enriched cyclopropene.



Scheme 8.

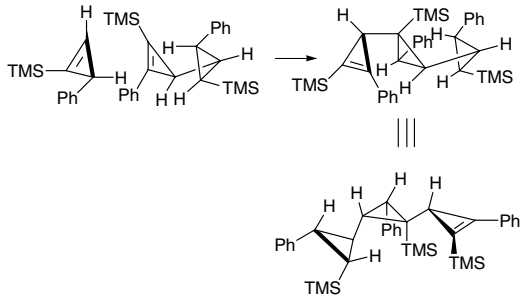
The regiochemistry of the major trimer **16** was assigned based on an *endo*-transition state as in the ene-dimerisation, on the basis of the above requirement that the same enantiomer of the cyclopropene must add to the dimer (Scheme 9).

It is consistent with the stereochemistry recently reported for the ene-trimer of 1-phenylcyclopropene.[12b] On the other hand, the structure of the minor isomer



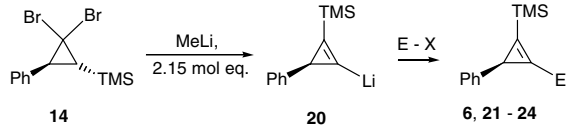
Scheme 9.

appears to require an *exo*-transition state (Scheme 10). The alternative *endo*-transition state would lead to a product in which the phenyl and trimethylsilyl groups on the centre ring were reversed, that is, that involved C–C bond formation to the phenyl-substituted carbon in the cyclopropene of the dimer. These two structures could be distinguished on the basis of the position of the CHPh group in the proton NMR spectrum (δ 1.8), the corresponding signal for a $CHSiMe_3$ group appearing at about δ 0.5 in other cases.



Scheme 10.

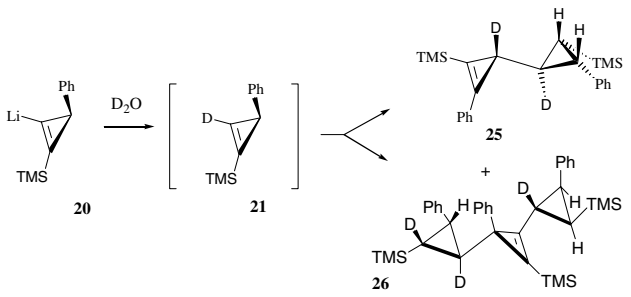
The *trans*-isomer **14** reacted with 2.15 mol equiv of methyllithium at −90 °C followed by quenching with methyl iodide, trimethylsilyl chloride or carbon dioxide which led to a lithium–hydrogen exchange in the intermediate cyclopropene **6** to produce **20** which was trapped by electrophiles to give the corresponding 1,2-disubstituted 3-phenylcyclopropenes **21**–**24** mostly in good yields (Scheme 11).



No	6	21	22	23	24
E	H	D	Me	TMS	COOH
%	94	-	97	90	57

Scheme 11.

Attempts to trap the intermediate **20** with deuterated water, however, did not produce the deuterated cyclopropene **21**. Instead, the dimer **25**[23] and trimer **26**[24] (Scheme 12) were observed. Even under the same conditions under which **6** had been observed directly by ^{1}H NMR, no **21** could be observed, suggesting that the ene-dimerisation of the 2-D compound proceeds somewhat faster than that of the 2-H compound. This might result from a secondary isotope effect in the dimerisation which converts two pseudo-sp C–H(D) bonds into cyclopropane C–H(D) bonds. Ab initio calculations have been preformed at the B3LYP/6-31G* level of theory for a model ene-dimerisation of 1,2-dideuteriocyclopropene by both the *exo*- and *endo*-transition states.[25] In both cases, the deuterium isotope effect for the dimerisation reaction, k_H/k_D, was calculated at 0.86,[26] in line with the effect expected for a normal inverse secondary isotope effect. Further calculations are being carried out to see if this difference is amplified in more substituted systems. This possible explanation, and the observation that only one trimer was observed from **21**, whereas two were formed in a 3:1 ratio from **6** are currently being investigated.



Scheme 12.

Acknowledgements

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15. Cyclopropene **6** was a colourless oil, δ_H (500 MHz) (−40 °C): 0.28 (9H, s), 2.61 (1H, s), 7.17–7.56 (6H, m); δ_C (125 MHz): −1.3+, 20.2+, 116.7, 119.6+, 124.7+, 125.0+, 127.7+, 148.4; ν_{max} (film, cm^{-1}): 3025 m, 2955 s, 2897 m, 1693 s, 1602 m, 1492 m, 1446 s, 1248 s, 841 s, 756 s, 698 s.
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17. Dimer **8** was a colourless oil, δ_H (500 MHz): −0.28 (9H, s), −0.01 (1H, dd, *J* 7.3, 10.4 Hz), 0.36 (9H, s), 1.45 (1H, ddd, *J* 4.1, 4.7, 7.3 Hz), 1.96 (1H, d, *J* 4.1 Hz), 2.20 (1H, dd, *J* 4.7, 10.4 Hz), 7.23–7.62 (10H, m); δ_C (125 MHz): −0.9+, −0.6+, 14.4+, 23.5+, 25.9+, 27.6+, 116.8, 125.6+, 127.8+, 128.63+, 128.65+, 129.2+, 129.4+, 130.7, 136.9, 141.5; ν_{max} (film, cm^{-1}): 2954 s, 2897 m, 1768 m, 1602 m, 1488 m, 1446 m, 1248 s, 930 m, 912 m, 840 s, 756 s, 691 s.
18. Cyclopropanes **9** and **14** were prepared by dibromocyclopropanation of the corresponding *trans*- or *cis*-1-phenyl-2-trimethylsilylethenes using $CHBr_3$, 50% NaOH–H_2O, cetyltrimethylammonium bromide, and CH_2Cl_2 (88% and 90%, respectively). Compound **14**, a colourless oil, δ_H (500 MHz): 0.13 (9H, s), 1.48 (1H, d, *J* 13.2 Hz), 3.24 (1H, d, *J* 13.2 Hz), 7.28–7.46 (5H, m); δ_C (125 MHz): −0.06+, 30.4+, 32.3, 38.9+, 127.3+, 127.9+, 130.2+, 135.8; ν_{max} (film, cm^{-1}): 2955 s, 2897 s, 1496 s, 1445 s, 1253 s, 1030 s, 1019 s, 965 s, 842 s, 803 s, 766 s, 732 s, 697 s, 654 s. Compound **9**, a white powder, mp 20–21 °C, showed δ_H (500 MHz): 0.30 (9H, s), 1.36 (1H, d, *J* 10.7 Hz), 2.85 (1H, d, *J* 10.7 Hz), 7.29–7.42 (5H, m); δ_C (125 MHz): −1.33+, 27.4+, 34.5, 39.1+, 127.5+, 128.2+, 128.7+, 137.1; ν_{max} (film, cm^{-1}): 2953 s, 1496 s, 1448 s, 1409 s, 1250 s, 1034 s, 1024 s, 954 s, 846 s, 755 s, 695 s.
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20. Compound **6** was relatively stable at −40 °C (an 11% solution in $CDCl_3$ of 50:41:5 monomer–dimer–trimer immediately after reaction rearranged to a 23:56:14 mixture in 27 h) but had reacted completely in 18 h either neat or as a 7% ethereal solution.
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22. Compound **16** (30% after chromatography) was a colourless oil, δ_H (500 MHz): −0.37 (9H, s), −0.16 (1H, dd, *J* 6.9, 10.4 Hz), −0.14 (9H, s), 0.14 (9H, s), 0.78 (1H, dd, *J* 6.6, 10.7 Hz), 1.80 (1H, dd, *J* 5.1, 6.9 Hz), 2.12 (1H, dd, *J* 5.1, 10.4 Hz), 2.59 (1H, dd, *J* 4.7, 6.6 Hz), 2.79 (1H, dd, *J* 4.7, 10.7 Hz), 7.12–7.59 (15H, m); δ_C (125 MHz): −0.96+, −0.72+, −0.65+, 13.1+, 17.78+, 17.84+, 23.2, 26.1+, 28.8+, 31.6+, 110.6, 123.3, 125.6+, 126.5+, 126.8+,

127.8+, 128.1+, 128.2+, 128.6+, 129.3+, 131.0, 131.1+, 139.2, 141.6; ν_{max} (film, cm^{-1}): 1840 m, 1601 m, 1496 m, 1445 m, 1247 s, 980 m, 909 s, 839 s, 756 s, 735 s, 699 s. Compound (**17**) isolated as a mixture with the trimer **16** showed δ_H (500 MHz): −0.19 (9H, s), 0.20 (9H, s), 0.30 (1H, dd, *J* 6.9, 10.4 Hz), 0.37 (9H, s), 1.53 (1H, ddd, *J* 4.4, 4.7, 6.9 Hz), 1.79 (1H, d, *J* 8.8 Hz), 2.28 (1 H, dd, *J* 4.7, 10.4 Hz), 2.48 (1H, s), 7.13–7.65 (15H, m); δ_C (125 MHz) including: −0.28+, −0.06+, 0.83+, 18.9+, 19.4+, 20.6, 26.9+, 28.4+, 29.6+, 32.9+, 115.2, 125.62+, 125.75+, 130.9, 136.5, 139.7, 140.4. Complete crystallographic data for compound **18** have been deposited with the Cambridge Crystallographic Data Centre (registration no. 283161).

23. Dimer **25** was a colourless oil, δ_H (500 MHz): −0.26 (9H, s), −0.01 (1H, d, *J* 10.4 Hz), 0.37 (9H, s), 2.21 (1H, d, *J* 10.4 Hz), 7.18–7.64 (10H, m); δ_C (125 MHz): −0.8+, −0.6+, 14.3+, 22.9+ (t, J_{CD} 25.7 Hz), 25.4+ (t, J_{CD} 23.5 Hz), 27.5+, 116.6, 125.6+, 127.8+, 128.63+, 128.65+, 129.2+, 129.4+, 130.7, 136.8, 141.5; ν_{max} (film, cm^{-1}): 2954 s, 2896 m, 1766 s, 1602 s, 1488 m, 1446 m, 1248 s, 979 m, 916 m, 841 s, 755 s, 698 s.
24. Trimer **26** was a colourless oil, δ_H (500 MHz): −0.37 (9H, s), −0.14 (9H, s), 0.15 (9H, s), 0.77 (1H, d, *J* 10.7 Hz), 2.13 (1H, s), 2.79 (1H, d, *J* 10.7 Hz), 7.13–7.47 (15H, m); δ_C (125 MHz): −0.97+, −0.75+, −0.68+, 12.9+, 17.6+, 17.7+, 22.9, 26.0+, 28.6+, 31.5+, 110.5, 123.2, 125.5+, 126.4+, 126.8+, 127.8+, 128.06+, 128.16+, 128.6+, 129.3+, 131.0, 131.1+, 139.2, 141.5; ν_{max} (film, cm^{-1}): 3079 m, 3059 m, 3027 s, 2952 s, 2895 m, 1840 s, 1601 s, 1496 s, 1445 s, 1403 m, 1247 s, 1071 m, 1030 m, 984 m, 966 m, 894 m, 837 s, 756 s, 698 s.
25. The activation energies calculated for hydrogen-substituted cyclopropene dimerisations (via both *endo*- and *exo*-transition states) were in good agreement with those published recently (Deng, Q.; Thomas, B. E.; Houk, K. N.; Dowd, P. *J. Am. Chem. Soc.* **1997**, *119*, 6902).
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