

Novel features of iron-mediated radical reactions: an unusual mode of silyloxycyclopropane fission, and a new method for radical chain termination using CH_2I_2

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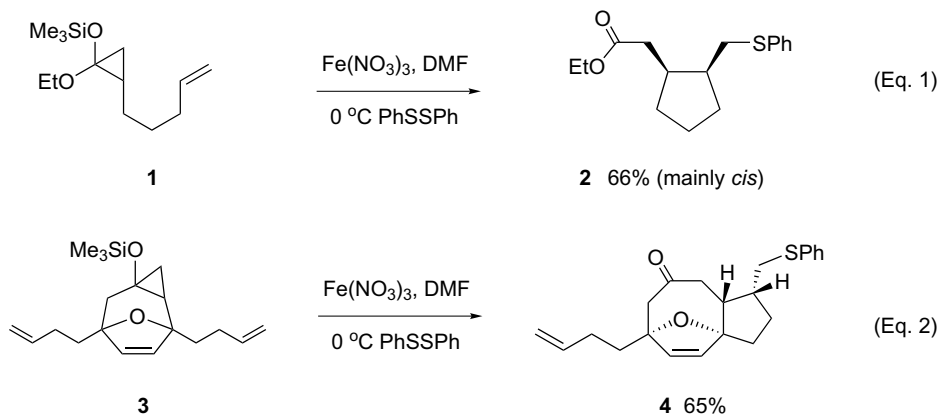
Abstract— $\text{Fe}(\text{NO}_3)_3$ mediated radical reactions of silyloxycyclopropanes derived from a range of bicyclic ketones are described, and include examples that undergo an unexpected regiochemical mode of cyclopropane cleavage. The inclusion of CH_2I_2 in such reactions allows the synthesis of iodinated products.

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The Booker-Milburn research group has described a substantial body of work involving the use of various iron salts to mediate synthetically useful radical reactions involving the cleavage of cyclopropane derivatives.^{1–3} Early work involved treatment of appropriate silyloxycyclopropanes with FeCl_3 ,¹ but the power and versatility of the method was subsequently extended by reactions involving additional types of cyclopropane and by use of alternative iron salts.^{2,3} In a typical reaction sequence, a silyloxycyclopropane or cyclopropa-

none silyl ketene acetal bearing an unsaturated appendage is reacted with $\text{Fe}(\text{NO}_3)_3$ and a suitable radical trap, resulting in the formation of cyclised products, for example, conversion of **1** into sulfide **2**, Eq. 1.

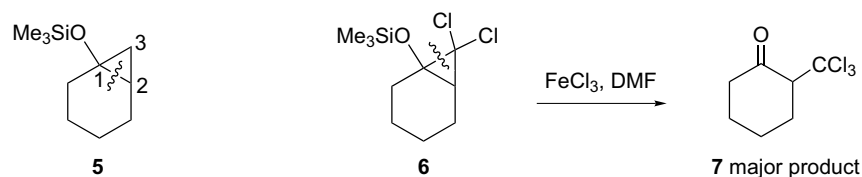
We became interested in this chemistry as a means to generate moderately complex polycyclic systems that might allow access to natural products having the fused [5.8.5] ring system characteristic of the ophiobolin and fusicoccin families. As shown (Eq. 2) we used the



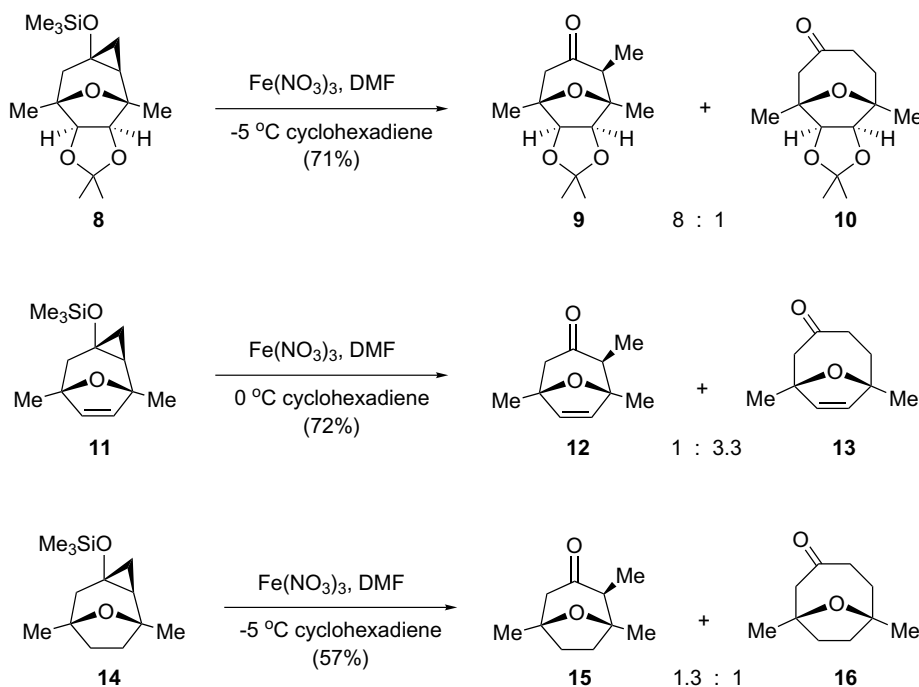
Scheme 1.

Keywords: Cyclopropane; Iodination; Radical cyclisation; Iron salts.

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Scheme 2.



Scheme 3.

Booker-Milburn method to good effect, starting with silyloxycyclopropanes derived from various substituted oxa-bridged ketones, such as **3**.⁴ During the course of this work we have uncovered two novel aspects of the iron chemistry, which have some significance, and may have further synthetic utility, and which are described below.

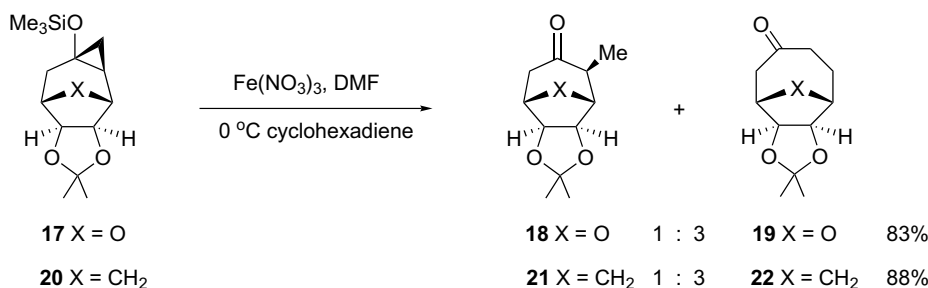
An important aspect of the iron method is the highly regiocontrolled nature of the cyclopropane opening, which inevitably furnishes products arising from the more substituted of the two possible intermediate radicals.⁵ This feature ensures that ring-fused silyloxycyclopropanes, such as **3**, undergo ring-expansion,⁶ rather than the alternative mode of reaction that would give an α -methyl substituted ketone—i.e. as shown in **5** it is C(1)–C(2) that cleaves, not C(1)–C(3).

Only in the biased case of dichlorocyclopropane **6** has the alternative mode of ring cleavage been seen to predominate using iron salts, giving mainly **7** (Scheme 2).^{7,8} Therefore we were very surprised to find that some of the iron-mediated reactions of silyloxycyclopropanes related to **3** gave non ring-expanded products, sometimes as the major component, as shown in Scheme 3.

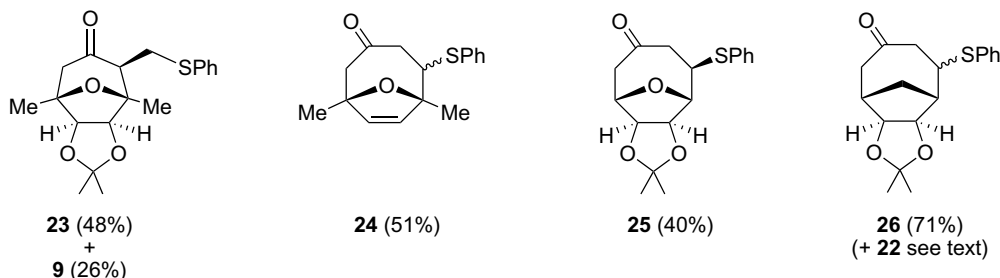
The reactions were carried out using 1,4-cyclohexadiene as additive, which is the established method for obtaining clean hydrogen atom quenching of the product radicals.^{2,3} The formation of α -methyl ketones **9**, **12** and **15** in these reactions, as single diastereoisomers, was very clear from the ^1H NMR spectra, which showed a diagnostic high-field doublet for the new methyl substituent in each case.⁹ The variation in the ratio of ‘normal’, ring-expanded product, to the unexpected product, was rather intriguing, as the part of the oxabicyclic system quite remote from the reacting cyclopropane seemed to be having a pronounced effect.

Since we expected that the bridging oxygen, and perhaps the nature of the bridgehead substituents (i.e., methyl groups in Scheme 3), might also influence the reaction outcome we tested further substrates, as shown in Scheme 4.

Compound **17** is closely related to **8**, but lacks the bridgehead methyl groups, whereas in **20** the bridging oxygen is replaced by a methylene. Somewhat surprisingly, we obtained the same distribution of products, in similar yield, for each of these two compounds. Comparison of the result for **8** with that obtained with **17**



Scheme 4.



indicates an important effect of the bridgehead substituents. Presumably the bridgehead methyl groups in **8** inhibit radical termination at the adjacent position by a steric effect, whereas in **17** quenching at that position, leading to ketone **19**, is much easier. The close similarity of the results in Scheme 4 for **17** and **20** seems to rule out an influence of the bridging oxygen on the outcome, at least for reactions involving iron salts.¹⁰

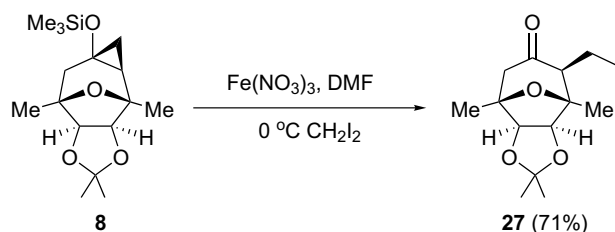
As illustrated in Scheme 1, PhSSPh can be employed as an additive in the $\text{Fe}(\text{NO}_3)_3$ reactions, which allows useful functionalisation of the product radicals, leading to sulfide products. Reactions run in this way, using the silyloxycyclopropanes **8**, **11**, **17** and **20**, gave the products **23–26**.¹¹

The formation of phenylthiomethylene derivative **23**, accompanied by small amounts of **9**, confirms the unusual regiochemistry seen earlier for reaction of starting cyclopropane **8**. Somewhat surprisingly, the other systems, which had each provided products from *both* modes of cyclopropane cleavage in the cyclohexadiene reactions, gave only the ring expanded products **24–26** (in the case of **26** ca. 15% of **22** was also observed in the crude mixture). Also, in the case of **24** and **26** substantial amounts of *endo*-sulfide were obtained (in fact the *endo* product was predominant for **24**), indicating a loss of facial selectivity for radical quenching in these systems.

These results point to a finely-balanced situation, whereby the regiochemical outcome of the iron-mediated reaction depends upon local steric effects, somewhat remote electronic effects, and also the nature of the radical trapping agent.

Only in the case of the acetonide-containing substrate **8** had we observed reproducible ‘abnormal’ cyclopropane

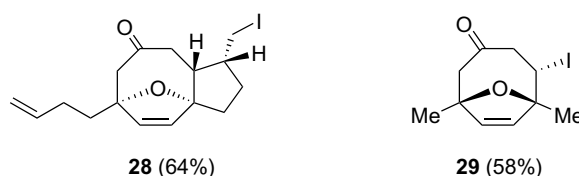
cleavage to give the two unexpected products **9** and **23**. During further exploration of the reactions of this compound we found that $\text{Fe}(\text{NO}_3)_3$ reactions under typical conditions, but with the inclusion of CH_2I_2 , gave rise to efficient iodine atom incorporation (Scheme 5).

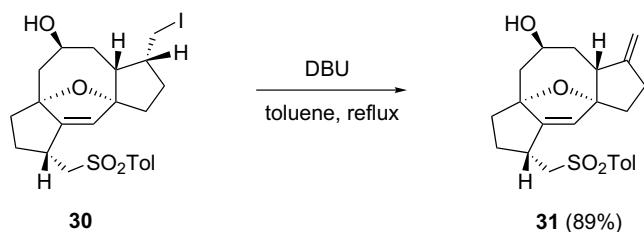


Scheme 5.

As far as we are aware, this type of reaction, leading to rather versatile iodides, has not been reported previously. The β -iodoketone **27** was fully characterised and showed a particularly diagnostic high-field signal in the ^{13}C NMR (-1.5 ppm) corresponding to the CH_2I group.^{12,13}

We also tested this new method in reactions utilising cyclopropanes **3** and **11**, and isolated the iodoketones **28** and **29** in good yield.





Scheme 6.

The formation of iodoketones, rather than chloro analogues, available using $\text{Fe}(\text{NO}_3)_3\text{-NCS}_2$,² may offer distinct advantages in certain cases. For example, we found that elimination of HI from complex iodide **30** (prepared in a few steps from **29**) to generate exomethylene compound **31** was particularly facile under mild conditions (Scheme 6).

In conclusion, we have established that the $\text{Fe}(\text{NO}_3)_3$ mediated radical reactions of silyloxycyclopropanes can occur with either regiochemical mode of cyclopropane fission. The observance of the 'abnormal' mode of reaction, especially for substrate **8**, illustrates that the behaviour of polyoxygenated systems may not always be predictable. The use of the $\text{Fe}(\text{NO}_3)_3\text{-CH}_2\text{I}_2$ combination for radical cyclisation–iodination sequences should add further to the utility of the Booker-Milburn method.

Acknowledgements

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- Other closely related methods can lead to the alternative mode of cleavage, but usually as a minor pathway see: (a) Rinderhagen, H.; Mattay, J. *Chem. Eur. J.* **2004**, *10*, 851; (b) Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Ikeno, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 85.
- For the origins of this method see: Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073.
- Blanco, L.; Mansouri, A. *Tetrahedron Lett.* **1988**, *29*, 3239.
- Booker-Milburn and co-workers have also observed this type of cleavage in reactions involving both $\text{Fe}(\text{NO}_3)_3$ and $\text{Cu}(\text{OAc})_2$, but in this case *exo*-methylene products are

formed, see: Booker-Milburn, K. I.; Cox, B.; Grady, M.; Halley, F.; Marrison, S. *Tetrahedron Lett.* **2000**, *41*, 4651.

- Typical experimental for cyclopropane cleavage: In a typical procedure 1,4-cyclohexadiene (3 equiv) was added to a solution of $\text{Fe}(\text{NO}_3)_3\cdot 9\text{H}_2\text{O}$ (3 equiv) in DMF (dried and degassed according to the procedure of Booker-Milburn) and this stirred mixture cooled to 0°C before addition of the silyloxycyclopropane (1 equiv) over 5 min. The solution was stirred for a further 1 h at –5°C before pouring into water, and product extraction using EtOAc. In some cases product yields and ratios were enhanced by conducting slow addition of the cyclopropane.

Product ratios were estimated from ^1H NMR spectra of the crude product mixtures, and pure products were isolated following flash column chromatography on silica gel using Et_2O –petroleum ether mixtures as eluant.

Ketone **9** was isolated as the less polar component as a white solid mp 85–86°C; (found C, 64.71; H, 8.50. $\text{C}_{13}\text{H}_{20}\text{O}_4$ requires C, 64.98; H, 8.39). ν_{max} (CHCl_3)/ cm^{-1} 2936, 1713, 1458, 1375; δ_{H} (500 MHz, CDCl_3) 4.27 (2H, s, 2-H, 6-H), 2.58 (1H, d, *J* 15, *exo* 10-H), 2.17 (1H, q, *J* 7, 8-H), 2.18 (1H, d, *J* 15, *endo* 10-H), 1.52 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.20 (3H, d, *J* 7, CH_3); δ_{C} (67.8 MHz, CDCl_3) 211.2 (C), 112.3 (C), 85.8 (CH), 84.7 (CH), 84.2 (C), 82.4 (C), 52.9 (CH), 48.5 (CH_2), 26.0 (CH_3), 24.9 (CH_3), 19.9 (CH_3), 16.1 (CH_3), 12.7 (CH_3); *m/z* (EI) 240 (M^+ , 16%), 99 (45), 98 (100). (Found M^+ 240.1360. $\text{C}_{13}\text{H}_{20}\text{O}_4$ requires M, 240.1362).

Ring expanded ketone **10** was the polar product, also as a white solid mp 49–52°C. ν_{max} (CHCl_3)/ cm^{-1} 2921, 2872, 1698, 1456 and 1373; δ_{H} (500 MHz, CDCl_3) 4.65 (1H, d, *J* 6, CH), 4.58 (1H, d, *J* 6, CH), 2.76 (1H, d, *J* 16, *exo* 8-H), 2.69 (1H, d, *J* 16, *endo* 8-H), 2.56 (1H, ddd, *J* 15, 7, 5, 10-H), 2.44 (1H, ddd, *J* 15, 11, 5, 10-H), 1.90 (1H, ddd, *J* 15, 11, 5, 11-H), 1.80 (1H, ddd, *J* 15, 7, 5, 11-H), 1.53 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.32 (3H, s, CH_3); δ_{C} (125.8 MHz, CDCl_3) 209.1 (C), 112.3 (C), 87.4 (CH), 86.9 (CH), 83.8 (C), 81.3 (C), 57.0 (CH_2), 39.2 (CH_2), 35.1 (CH_2), 25.9 (CH_3), 24.5 (CH_3), 23.9 (CH_3), 23.0 (CH_3); *m/z* (EI) 240 (M^+ 3%), 225 (57), 99 (100). (Found M^+ 240.1361. $\text{C}_{13}\text{H}_{20}\text{O}_4$ requires M, 240.1362).

- This type of reaction can also be carried out using manganese salts, see for example Ref. 5b, but using the hydroxycyclopropane, obtained by treatment of the silyl derivatives with K_2CO_3 in methanol. In most cases such reactions give similar product yields and ratios to the iron-mediated reactions.
- A solution of dried ferric nitrate was prepared by stirring a solution of $\text{Fe}(\text{NO}_3)_3\cdot 9\text{H}_2\text{O}$ (194 mg, 0.48 mmol) in dry DMF (6 mL) over molecular sieves under an atmosphere of argon for 2 h. This solution was then added over a period of 1 h to a solution of silyloxycyclopropane **8** (50 mg, 0.16 mmol) and PhSSPh (105 mg, 0.48 mmol) in dry degassed DMF (7 mL) at 0°C under nitrogen. The mixture was left to stir for 1.5 h and then partitioned between water (100 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous was extracted with further ethyl acetate (2 × 80 mL). The combined organic extracts were washed with water (3 × 50 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica (eluent petroleum ether/diethyl ether 4/1) to give phenylsulfanyl ketone **23** as a white solid (27 mg, 48%) and methyl ketone **9** (10 mg, 26%) as a colourless oil.

Data for phenylsulfanyl ketone **23**, mp 67–69°C; ν_{max} (CDCl_3)/ cm^{-1} 3982, 2936, 1713, 1382, 1083 and 877; δ_{H} (400 MHz; CDCl_3) 7.39–7.37 (2H, m, H–Ar), 7.33–7.21

- (3H, m, H–Ar), 4.27 (1H, d, *J* 6, 2-H), 4.24 (1H, d, *J* 6, 6-H), 3.38 (1H, dd, *J* 12 and 5, CH₂SPh), 3.19 (1H, dd, *J* 12 and 10, CH₂SPh), 2.58 (1H, d, *J* 15, *exo* 10-H), 2.41 (1H, dd, *J* 10 and 5, 8-H), 2.25 (1H, d, *J* 15, *endo* 10-H), 1.51 (3H, s, CH₃), 1.41 (3H, s, CH₃), 1.37 (3H, s, CH₃), 1.28 (3H, s, CH₃); δ_{C} (100 MHz; CDCl₃) 207.4 (C), 135.1 (C), 130.5 (CH), 129.0 (CH), 126.9 (CH), 112.5 (C), 85.3 (CH), 85.1 (C), 84.6 (CH), 83.4 (C), 58.1 (CH), 49.7 (CH₂), 31.6 (CH₂), 26.0 (CH₃), 24.9 (CH₃), 19.8 (CH₃) and 16.6 (CH₃); *m/z* (EI) Found 348.1389 (M⁺ C₁₉H₂₄O₄S requires 348.1395).
12. Data for iodoketone **27** (42 mg, 71%) isolated as a white solid; mp 127–128 °C; (Found C, 42.63; H, 5.19. C₁₃H₁₉O₄I requires C, 42.64; H, 5.23%); ν_{max} (CHCl₃)/cm⁻¹ 3002, 2937, 1716, 1254, 1208, 1131 and 1054; δ_{H} (500 MHz; CDCl₃) 4.29 (1H, d, *J* 6, 2-H), 4.24 (1H, d, *J* 6, 6-H), 3.53 (1H, dd, *J* 11 and 5, CH₂I), 3.35 (1H, dd, *J* 11 and 11, CH₂I), 2.56 (1H, d, *J* 14.5, *exo* 10-H), 2.48 (1H, dd, *J* 11 and 5, 8-H), 2.24 (1H, d, *J* 14.5, *endo* 10-H), 1.49 (3H, s, CH₃), 1.40 (3H, s, CH₃), 1.35 (3H, s, CH₃), 1.27 (3H, s, CH₃); δ_{C} (125 MHz; CDCl₃) 206.8 (C), 112.7 (C), 85.8 (C), 85.1 (CH), 84.4 (CH), 83.6 (C), 60.6 (CH), 48.9 (CH₂), 26.0 (CH₃), 25.0 (CH₃), 19.8 (CH₃), 16.5 (CH₃) and -1.5 (CH₂); *m/z* (CI) Found 367.0413 ((M+1)⁺. C₁₃H₂₀O₄I requires 367.0406).
13. The isolation of the iodoketone **27** gave us the opportunity to conduct a free radical reaction using alternative Bu₃SnH conditions, which gave products **9** and **10** in similar yields and ratios to the iron (and manganese) mediated reactions. This outcome lends support to the proposal that carbon-centred free radical intermediates are involved in the iron-mediated reactions.