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Radical-chain functionalisation at C–H centres using an *O*-oxiranylcarbinyl *O*-silyl ketene acetal

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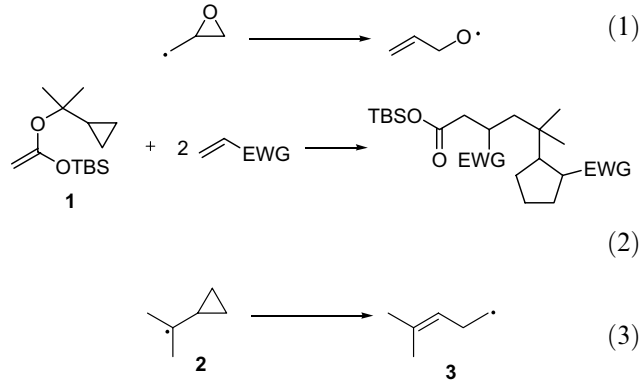
Abstract—A readily prepared *O*-oxiranylcarbinyl *O*-silyl ketene acetal has been used to bring about functionalisation at various types of saturated C–H group, through the intermediacy of an oxiranylcarbinyl radical that undergoes rapid ring opening to give a highly reactive allyloxyl radical.

The ring-opening rearrangement of an oxiranylcarbinyl radical to give an allyloxyl radical, the simplest example of which is shown in Eq. 1, provides a useful means of converting a carbon-centred radical into an oxygen-centred species that is a more potent abstractor of hydrogen atoms from C–H groups.[1] This type of rearrangement, which has often been exploited in organic synthesis,[1] takes place much more rapidly than ring opening of the equivalent cyclopropylcarbinyl radical, where the oxygen atom is replaced by the isoelectronic methylene group.[2] We have reported recently that the *O*-cyclopropylcarbinyl *O*-*tert*-butyldimethylsilyl ketene acetal **1** can be used to bring about radical [3+2] annulation of an electron-poor alkene, as generalised in Eq. 2 (EWG = electron-withdrawing group).[3] A key step in the chain mechanism of this reaction involves ring opening of the cyclopropylcarbinyl radical **2** to give the but-3-enyl radical **3** (Eq. 3), which then adds to the electron-poor alkene.[3,4]



It occurred to us that an oxiranylcarbinyl analogue of **1** might provide a useful source of allyloxyl radicals that could react subsequently in a number of ways, in particular by direct or catalysed[5] abstraction of hydrogen from a C–H group in a suitable substrate molecule, leading ultimately to functionalisation at this site. In order to explore this possibility, we chose to investigate radical reactions of the *O*-oxiranylcarbinyl *O*-*tert*-butyldimethylsilyl ketene acetal **4**, which was prepared as shown in Scheme 1.[6] Our main reasons for choosing **4** were, (i) the ready availability of isophorone oxide **5**,[7] (ii) the stereoelectronic predisposition of the derived oxiranylcarbinyl radical **8** to undergo rapid regioselective ring opening to give the allyloxyl radical **9** and (iii) the inability of this allyloxyl radical to rearrange by intramolecular 1,5-hydrogen-atom transfer from the sterically-inaccessible allylic C–H groups. The first type of reaction we envisaged applies to functionalisation at a C–H centre with an attached electron-withdrawing substituent and the proposed chain propagation cycle is generalised in Scheme 2. For a similar thermodynamic driving force and similar steric effects, a relatively electrophilic radical of the type **11** that is produced by hydrogen-atom abstraction from this class of substrate, should add more rapidly to the electron-rich double bond in **4** than will a nucleophilic radical.[8] However, the

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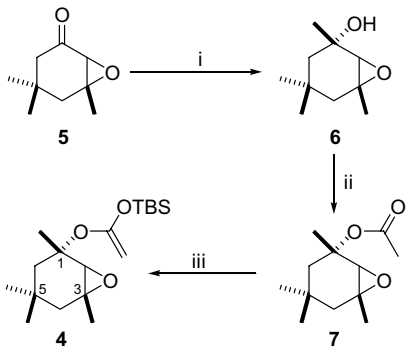
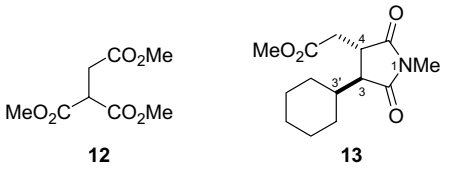


Scheme 1. Reagents and conditions: (i) MeLi in Et_2O–THF, 1 h at −78 °C, 20% aq NH_4Cl quench (cf. Ref. 10); (ii) Ac_2O/Et_3N + 20 mol% DMAP, 20 h at rt; (iii) LDA in THF–hexanes at −78 °C, then TBSCl followed by 1 equiv HMPA at −78 °C, then rt for 12 h.

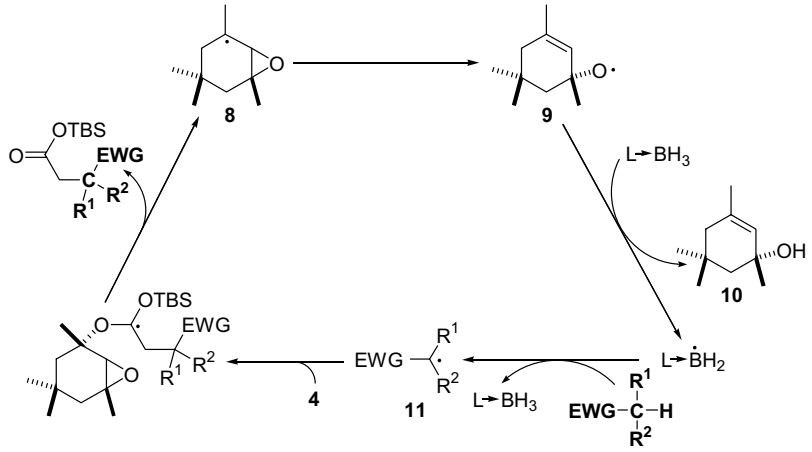
direct abstraction of hydrogen from the substrate by the allyloxyl radical **9** to give **11** will be disfavoured by polar effects, because the allyloxyl radical is also electrophilic.[5,9] To overcome this problem, a hydridic polarity-reversal catalyst[5] (an amine– or phosphine–borane complex) is included to mediate the desired hydrogen-atom transfer, as shown in Scheme 2.

When a benzene solution containing the ketene acetal **4** (1.0 mmol) and dimethyl malonate (3.0 mmol) was heated at 70 °C for a total of 2.5 h, in the presence of di-*tert*-butyl hyponitrite[11] (TBHN; three additions of 0.05 mmol made initially and after 20 and 40 min) as a thermal source of *tert*-butoxyl radicals, ^{1}H NMR spectroscopic analysis showed that ca. 95% of **4** remained unchanged with only ca. 5% converted to the allylic alcohol **10**. However, repetition of this experiment in the additional presence of quinuclidine–borane[12] (0.20 mmol) resulted in the complete consumption of **4** and the trimethyl ester **12** was isolated in 87% yield, after treatment of the initially-formed silyl ester with tetrabutylammonium fluoride (TBAF) and methyl iodide.[13] In the presence of the amine–borane, but without the TBHN initiator, no reaction took place. Tributylphosphine–borane also functioned as a hydridic polarity-reversal catalyst for the reaction of **4** with dimethyl malonate although, presumably because of the weaker B–H bond in this complex compared with that in the amine–borane,[14] it was slightly less effective (see Table 1, entry 1). A number of other esters containing electron-poor α-C–H groups reacted with **4** in the presence of a ligated borane according to Scheme 2 and the results are summarised in Table 1. For the corresponding functionalisation of ethyl acetate, in which the α-C–H bonds are relatively strong,[14] the phosphine–borane was ineffective as a polarity-reversal catalyst (entry 4).



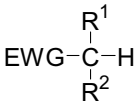
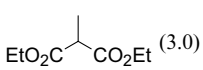
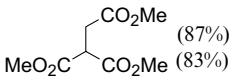
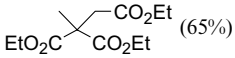
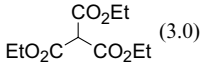
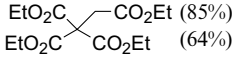
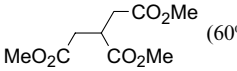
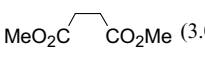
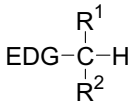
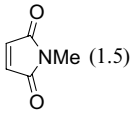
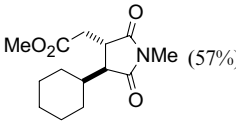
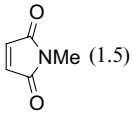
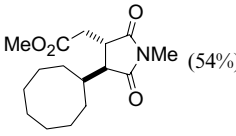
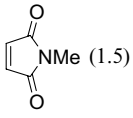
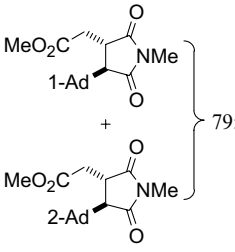
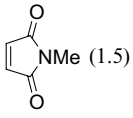
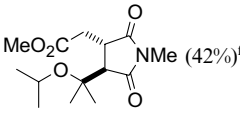
On the other hand, if electron-donating groups (EDGs, which include simple alkyl groups) are attached to the C–H centre in the substrate, polar effects[5,9] will now favour the direct abstraction of hydrogen by the electrophilic allyloxyl radical **9** to give a relatively nucleophilic carbon radical **14**. In contrast, polar effects now disfavour the addition of **14** to the electron-rich ketene acetal **4** and so the hydridic polarity-reversal catalyst was replaced by a stoichiometric amount of an electron-poor alkene, in order to convert **14** to a more electrophilic addendum radical **15**, as shown in the propagation cycle generalised in Scheme 3.

Functionalisation at C–H centres with attached electron-donating groups proceeded as anticipated according to Scheme 3, although the isolated yields of methyl esters were only moderate; the results are included in Table 1. For example, reaction of **4** with excess cyclohexane in the presence of TBHN as initiator and *N*-methylmaleimide (NMM) as the electron-poor alkene, afforded the pyrrolidine-2,5-dione **13** in 57% yield (entry 6).[17] Analogous functionalisation of cyclooctane, adamantane and diisopropyl ether was also successful using NMM as the electron-poor alkene. Adamantane



Scheme 2.

Table 1. Functionalisation at C–H centres using the *O*-oxiranylcarbinyl *O*-*tert*-butyldimethylsilyl ketene acetal **4**

Class of C–H group	Entry	Conditions[a]	C–H donor (equiv)	Catalyst[b] or co-reactant (equiv)	Product[c] (isolated yield)
 (Scheme 2)	1	A	 (3.0)	Quin→BH_3 (0.2) Bu_3P→BH_3 (0.2)	 (87%) (83%)
	2	A	(3.0)	Bu_3P→BH_3 (0.2)	 (65%)
	3	A	 (3.0)	Quin→BH_3 (0.2) Bu_3P→BH_3 (0.2)	 (85%) (64%)
	4	B	CH_3CO_2Et (4.0)	Quin→BH_3 (0.2) Bu_3P→BH_3 (0.2)	 (55%) (14%)[d]
	5	B	 (3.0)	Quin→BH_3 (0.2)	(60%)
 (Scheme 3)	6	C	 (*ca.* 14)	 (1.5)	 (57%)
	7	C	 (ca. 11)	 (1.5)	 (54%)
	8	D	 (5.0)	 (1.5)	 79:21 (50%)[e]
	9	C	 (ca. 14)	 (1.5)	 (42%)[f]

[a] Generally 1 mmol of acetal **4**; the total reaction time was usually 2.5 h. A = benzene solvent, bath temp 70 °C; TBHN (0.05 equiv) added initially and again after 20 and 40 min; B = refluxing benzene solvent, TBHN initiator (0.20 equiv) in benzene added by syringe pump during 100 min; C = acetal **4** dissolved in CH donor, bath temp 90 °C, separate solutions of TBHN (0.20 equiv) and of co-reactant in benzene added by syringe pump during 1 h; D = acetal **4** and CH donor dissolved in benzene, otherwise as C.

[b] Quin = Quinuclidine.

[c] The initially-formed silyl ester was converted to the alkyl ester shown.[13]

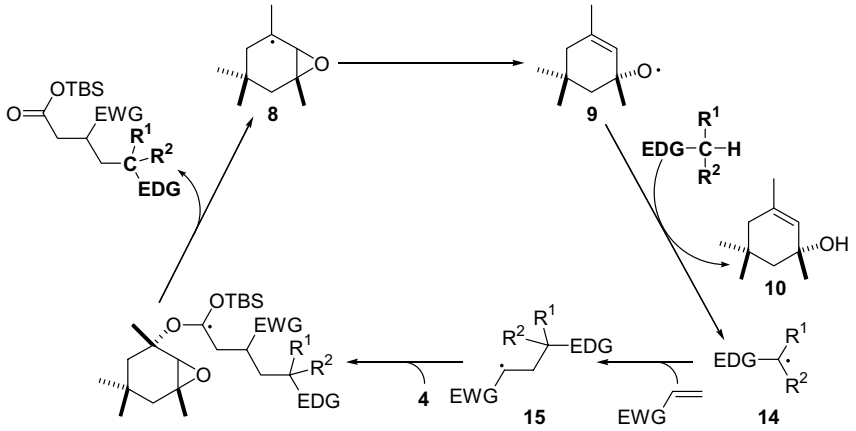
[d] Estimated by ^1H NMR spectroscopy.

[e] Combined yield.

[f] The low yield may reflect the relatively low boiling point (69 °C) of diisopropyl ether.

afforded a 79:21 mixture of two regioisomeric products containing either a 1-adamantyl group or a 2-adamantyl group, respectively, implying that the allyloxyl radical **9** has a greater tendency to abstract hydrogen from a tertiary C–H group than does the *tert*-butoxyl radical.[18] This difference in regioselectivity presumably reflects the greater steric demands of **9** compared with those of $Bu^tO^{\cdot}$.

Methodology for C–H functionalisation that is based on heavy-metal catalysed reactions can suffer from



Scheme 3.

environmental and/or economic drawbacks.[19] The present preliminary work suggests that suitable precursors of oxiranylcarbinyl radicals, that rapidly evolve into highly reactive allyloxyl radicals, offer promise as reagents for metal-free functionalisation at a range of types of C–H group, including those in simple hydrocarbons.

References and notes

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6. Each of the compounds **4**, **6** and **7** contains ca. 10% of the isomer in which Me-1 and Me-3 are *trans*. The *trans* isomer of the ketene acetal was consumed more rapidly than the *cis* compound **4** during C–H functionalisation reactions; the same product results from either isomer. Data for **4** containing 10% *trans* isomer (66% yield from **5**); purified by Kugelrohr distillation at 0.05 mmHg (oven temp. 125 °C) from a trace amount of 4,4′-methylenebis(2,6-di-*tert*-butylphenol) as a radical scavenger. Found: C, 65.9; H, 10.3. $C_{18}H_{34}O_3Si$ requires C, 66.2; H, 10.5%. NMR (500 MHz for ^{1}H, 125.7 MHz for ^{13}C; $CDCl_3$ solvent, *J* in Hz): δ_H 0.20 (6H, s, $SiMe_2$), 0.88 (3H, s, Me-5), 0.94 (9H, s, Bu^t), 1.01 (3H, s, Me-5), 1.20 (1H, d, *J* 14.5, ring-CH_2), 1.34 (3H, s, Me-3), 1.44 (3H, s, Me-1), 1.55 (1H, dd, *J* 14.8 and 1.6, ring-CH_2), 1.62 (1H, d, *J* 14.8, ring-CH_2), 1.80 (1H, dd, *J* 14.5 and 1.6, ring-CH_2), 3.03 (1H, s, H-2), 3.43 (1H, d, *J* 1.7, $=CH^AH^B$), 3.45 (1H, d, *J* 1.7, $=CH^AH^B$); δ_C–4.8, 18.0, 24.0, 24.4, 25.7, 29.3, 29.4, 31.3, 42.5, 42.8, 59.9, 63.8, 72.0, 78.4, 157.7. Identifying peaks for the *trans* isomer of **4**: δ_H 0.92 (9H, s, Bu^t), 1.32 (3H, s, Me-3), 1.39 (3H, s, Me-1), 2.98 (1H, s, H-2), 3.48 (1H, d, *J* 1.5, $=CH^AH^B$), 3.57 (1H, d, *J* 1.5, $=CH^AH^B$).
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14. The B–H bond in $H_3P{\rightarrow}BH_3$ is about 40 kJ mol^{-1} weaker than that in $H_3N{\rightarrow}BH_3$; see Baban, J. A.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1987**, 497–505. Our unpublished ab initio calculations at the G3 level[15] indicate that the values of DH_{298} for the B–H bonds in $Me_3P{\rightarrow}BH_3$ and $Me_3N{\rightarrow}BH_3$ are 387.9 and 427.7 kJ mol^{-1}, respectively, compared with the corresponding calculated values for the C–H bonds in Me_4C and C_2H_6 of 429.3 and 423.2 kJ mol^{-1}, respectively; the experimental value for ethane is 423.0 ± 1.6 kJ mol^{-1}. For an α-C–H bond in ethyl acetate the value of DH_{298} is ca. 402 kJ mol^{-1}.[16]
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16. Bordwell, F. G.; Zhang, S.; Zhang, X.-M.; Liu, W.-Z. *J. Am. Chem. Soc.* **1995**, *117*, 7092–7096.
17. *Representative procedure*: A solution of the ketene acetal **4** (327 mg, 1.0 mmol) in cyclohexane (1.5 mL) was stirred and heated under reflux (bath temp. 90 °C) while NMM (167 mg, 1.5 mmol) in benzene (2.0 mL) and TBHN (35 mg, 0.20 mmol) in benzene (0.5 mL) were added separately by syringe pump during 1 h. Care was taken to keep the TBHN solution at room temperature prior to its addition, by passing the PTFE transfer tube down the centre of the water-cooled condenser and ensuring that the solution dripped directly into the hot reaction mixture. After the additions, the solution was heated for a further 1.5 h before the solvent was removed by evaporation. The residue was dissolved in THF (1.0 mL), cooled in an ice bath and iodomethane (250 μL, 4.0 mmol) was added, followed by TBAF in THF (1.0 M, 1.2 mL). The solution was stirred at 0 °C for 2 h before saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was extracted

with CH_2Cl_2 (3×10 mL), the combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, using light petroleum (bp 40–60 °C)-diethyl ether–CH_2Cl_2 (16:4:5) as eluent, to afford *trans*-1-methyl-3-cyclohexyl-4-(methoxycarbonylmethyl)pyrrolidine-2,5-dione[3] **13** (153 mg, 57%). Mp 76–78 °C (from hexane–CH_2Cl_2); δ_H 1.00–1.35 (5H, complex, ring-CH_2), 1.48 (1H, m, ring-CH_2), 1.63–1.80 (4H, complex, ring-CH_2), 1.94 (1H, m, H-3′), 2.53 (1 H, apparent t, *J* 4.6, H-3), 2.66 (1 H, dd, *J* 17.0 and 4.6, $MeO_2CCH^AH^B$), 2.82 (1H, apparent q, *J* 5.1, H-4), 2.93 (1H, dd, *J* 17.0 and 5.6, $MeO_2CCH^AH^B$), 2.99 (3H, s, NMe), 3.67 (3H, s, OMe); δ_C 24.8, 25.8(9), 25.9(3), 26.2, 28.4, 30.1, 34.6, 38.6(6), 38.7(0), 50.9, 52.0, 171.2, 178.2, 178.5. Found: C, 62.8; H, 8.0; N, 5.2. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%.

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