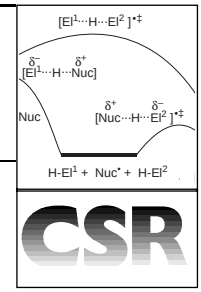
Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry



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The rates and selectivities of the hydrogen-atom abstraction reactions of electrically-neutral free radicals are known to depend on polar effects which operate in the transition state. Thus, an electrophilic species such as an alkoxyl radical abstracts hydrogen much more readily from an electron-rich C–H bond than from an electron-deficient one of similar strength. The basis of *polarity-reversal catalysis* (PRC) is to replace a single-step abstraction, that is slow because of unfavourable polar effects, with a two-step process in which the radicals and substrates are polarity-matched. This review explores the concept of PRC and describes its application in a variety of situations relevant to mechanistic and synthetic organic chemistry.

1 Introduction

Within the context of the reactions of electrically-neutral free radicals, the term 'polar effect' is used to describe the influence on the activation energy of any charge transfer which may occur on proceeding from the reactant(s) to the transition state. The dependence of reactivity and selectivity in radical chemistry on such polar effects has been recognised for more than 50 years and was emphasised by Walling in his seminal monograph which was published in 1957.[1]

The transition state for the hydrogen-atom transfer reaction shown in eqn. (1) may be represented in valence-bond terms as a hybrid of the structures **1a–d** and, within a series of reactions

$$A^{\bullet} + H{-}B \longrightarrow A{-}H + B^{\bullet} \quad (1)$$

$$[A^{\bullet}\ H{-}B]^{\ddagger} \leftrightarrow [A{-}H\ B^{\bullet}]^{\ddagger} \leftrightarrow [A^{-}\ H^{\bullet}\ B^{+}]^{\ddagger} \leftrightarrow [A^{+}\ H^{\bullet}\ B^{-}]^{\ddagger}$$
1a **1b** **1c** **1d**

for which the overall enthalpy change is similar, the activation energies would be expected to decrease as the contributions from the charge-separated structures **1c** and **1d** increase. If the structure **1c** is more important than **1d**, the radical $A^{\bullet}$ may be described as *electrophilic* and $B^{\bullet}$ is said to be *nucleophilic*, while if structure **1d** is the more important, $A^{\bullet}$ is nucleophilic and $B^{\bullet}$ is electrophilic. For such a series of reactions, the activation energy is predicted to decrease as the electronegativity difference between $A^{\bullet}$ and $B^{\bullet}$ increases. If $El^{\bullet}$ and $Nuc^{\bullet}$ represent electrophilic and nucleophilic radicals, respectively, the hydrogen-atom abstraction reactions (2) and (3) should be favoured because of polar effects, while reactions (4) and (5) will not be favoured.

$$El^{\bullet} + H{-}Nuc \longrightarrow El{-}H + Nuc^{\bullet} \quad (2)$$
$$Nuc^{\bullet} + H{-}El \longrightarrow Nuc{-}H + El^{\bullet} \quad (3)$$
FAVOURED

$$El^{1\bullet} + H{-}El^{2} \longrightarrow El^{1}{-}H + El^{2\bullet} \quad (4)$$
$$Nuc^{1\bullet} + H{-}Nuc^{2} \longrightarrow Nuc^{1}{-}H + Nuc^{2\bullet} \quad (5)$$
DISFAVOURED

Our own interest in the exploration and exploitation of polar effects arose out of a research programme designed to investigate the properties of boron-containing isoelectronic analogues of well-known carbon-centred radicals and this work began with a study of the borane radical anion $H_3B^{\bullet-}$ (which is isoelectronic with the methyl radical $H_3C^{\bullet}$)[2] and of various ligated boryl radicals of the types $L{\rightarrow}\dot{B}H_2$ and $L{\rightarrow}\dot{B}HR$, in which L is a phosphine, an amine or a sulfide.[3] Amine–alkylboryl radicals ($R_3N{\rightarrow}\dot{B}HR$) are isoelectronic analogues of secondary alkyl radicals ($R_3C{-}\dot{C}HR$) and are very readily generated by hydrogen-atom transfer to *tert*-butoxyl radicals from the corresponding amine–alkylborane complex [eqn. (6)].[4] Although radical philicity is clearly a *relative* attribute,[5] a radical that has a high ionisation energy (IE) and a high electron affinity (EA) will usually exhibit electrophilicity, while a low IE and EA will usually confer nucleophilic properties. In general, radicals that have a high Mulliken electronegativity [(IE + EA)/2] will be electrophilic and those with a low electronegativity will be nucleophilic.[6] Alkoxyl radicals are thus electrophilic, while amine–boryl radicals have particularly low ionisation energies (5.47 eV has been calculated for $H_3N{\rightarrow}\dot{B}HMe$)[5] and are very nucleophilic, accounting for the high rate of reaction (6) which is an example of the general type shown in eqn. (2); for reaction (6), the charge-separated structure [Bu^tO^- $H^{\bullet}$ $RHB{\leftarrow}NR_3$] (*cf.* **1c**) is an important contributor to the transition state. EPR studies have shown that amine–alkylboryl radicals rapidly abstract hydrogen from acetonitrile [eqn. (7)], while the corresponding abstraction by *tert*-butoxyl radicals [eqn. (8)] is very sluggish.[4] The cyanomethyl radical derived from acetonitrile is electrophilic and these results can be

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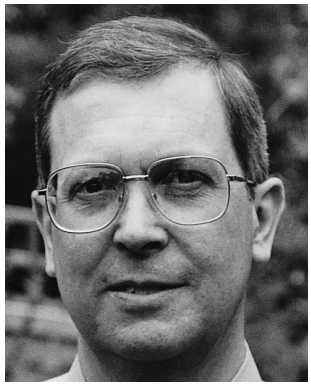


understood in terms of polar effects, since reactions (7) and (8) constitute examples of the general processes shown in eqns. (3) and (4), respectively. Consistent with these observations, the *overall* abstraction of hydrogen from acetonitrile by the electrophilic alkoxyl radical is promoted by a small amount of amine–alkylborane, through the sequence of rapid reactions (6) and (7) which replace the relatively inefficient single step (8).[7] The polarity of the radical that abstracts hydrogen from the acetonitrile is thereby reversed (from an electrophilic alkoxyl radical to a nucleophilic amine–boryl radical) thus facilitating the overall transfer of hydrogen and, for this reason, the process is referred to as *polarity-reversal catalysis*.[4,7]

$$Bu^tO^\bullet + R_3N{\rightarrow}BH_2R \longrightarrow Bu^tOH + R_3N{\rightarrow}\dot{B}HR \quad (6)$$

$$R_3N{\rightarrow}\dot{B}HR + CH_3CN \longrightarrow R_3N{\rightarrow}BH_2R + H_2\dot{C}CN \quad (7)$$

$$Bu^tO^\bullet + CH_3CN \longrightarrow Bu^tOH + H_2\dot{C}CN \quad (8)$$

2 Polarity-reversal catalysis (PRC)

The principle underlying polarity-reversal catalysis of hydrogen-atom transfer is generalised in Scheme 1. The lack of

$El^{1\bullet} + H{-}El^2 \xrightarrow{slow} H{-}El^1 + El^{2\bullet}$ uncatalysed reaction

$El^{1\bullet} + \mathbf{H{-}Nuc} \xrightarrow{fast} H{-}El^1 + \mathbf{Nuc}^\bullet$
$\mathbf{Nuc}^\bullet + H{-}El^2 \xrightarrow{fast} \mathbf{H{-}Nuc} + El^{2\bullet}$ } catalytic cycle

$El^{1\bullet} + H{-}El^2 \xrightarrow[fast]{+\ H{-}Nuc\ catalyst} H{-}El^1 + El^{2\bullet}$ overall reaction

$Nuc^{1\bullet} + H{-}Nuc^2 \xrightarrow{slow} H{-}Nuc^1 + Nuc^{2\bullet}$ uncatalysed reaction

$Nuc^{1\bullet} + \mathbf{H{-}El} \xrightarrow{fast} H{-}Nuc^1 + \mathbf{El}^\bullet$
$\mathbf{El}^\bullet + H{-}Nuc^2 \xrightarrow{fast} \mathbf{H{-}El} + Nuc^{2\bullet}$ } catalytic cycle

$Nuc^{1\bullet} + H{-}Nuc^2 \xrightarrow[fast]{+\ H{-}El\ catalyst} H{-}Nuc^1 + Nuc^{2\bullet}$ overall reaction

Scheme 1

stabilising charge-transfer in the transition state for the direct abstraction shown in eqn. (4) is overcome by including an *hydridic* catalyst H–Nuc, when the single-step process is replaced by a cycle of two hydrogen-atom transfer reactions both of which benefit from favourable polar effects. Similarly, the slow direct abstraction reaction (5) is promoted by a *protic* catalyst H–El.[5]† Of course, the activation energy for hydrogen-atom transfer depends on factors other than polar effects[6] and careful consideration must be given to the strengths of the bonds involved when choosing a suitable polarity-reversal catalyst: the activation energy for an endothermic reaction cannot be less than ($\Delta H^\circ + RT$), no matter how favourable are the polar factors! Reference to Fig. 1 clarifies the situation for reaction (4) and its polarity-reversal-catalysed equivalent. Because of the exponential dependence of the rate constant on the activation energy for a reaction, two steps with low activation energies can lead to a faster overall reaction than is achieved in a single-step process which has a much higher activation energy. Ideally, the overall enthalpy change associated with an uncatalysed exothermic reaction should be partitioned so that both steps of the catalytic cycle are themselves exothermic. For example,

§ The enantioselectivity factor is the rate constant for abstraction from the faster reacting enantiomer relative to the rate constant for abstraction from the less-reactive enantiomer.

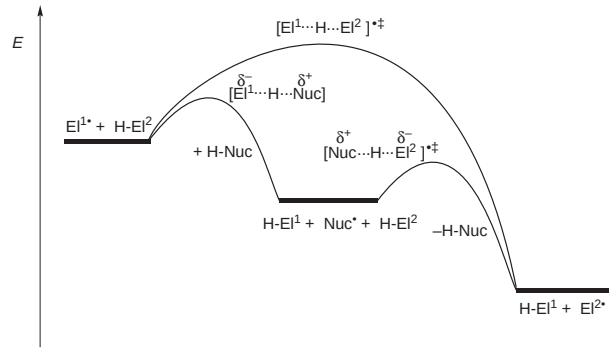


Fig. 1 Schematic potential energy diagram illustrating the principle of PRC for promotion of a hydrogen-atom transfer of the type shown in eqn. (4) by an hydridic catalyst H–Nuc.

abstraction of hydrogen from acetonitrile by the *tert*-butoxyl radical [eqn. (8)] is exothermic by *ca.* 47 kJ mol^{-1}.[8] Calculations[5] indicate that D*H*(B–H) in an amine–alkylborane is *ca.* 432 kJ mol^{-1} and the two steps in the cycle for the catalysed abstraction [eqns. (6) and (7)] are exothermic by *ca.* 8 and 39 kJ mol^{-1}, respectively.

The control of regioselectivity that can be exercised using PRC is clearly illustrated by the normal and catalysed reactions of *tert*-butoxyl radicals with bis(2-cyanoethyl) ether, as studied by EPR spectroscopy.[4] The transient radical products of elementary reactions can be detected in solution in steady-state concentration (*ca.* 5×10^{-7} mol dm^{-3}) during continuous photochemical generation of the reactant radicals directly in the microwave cavity of the EPR spectrometer.[9] Thus, when a cyclopropane solution containing di-*tert*-butyl peroxide and bis(2-cyanoethyl) ether was irradiated with UV light at −57 °C, the EPR spectrum of the α-alkoxyalkyl radical **2** [eqns. (9) and (10a)] was observed (Fig. 2a).[5] The H–COR and H–CCN bonds

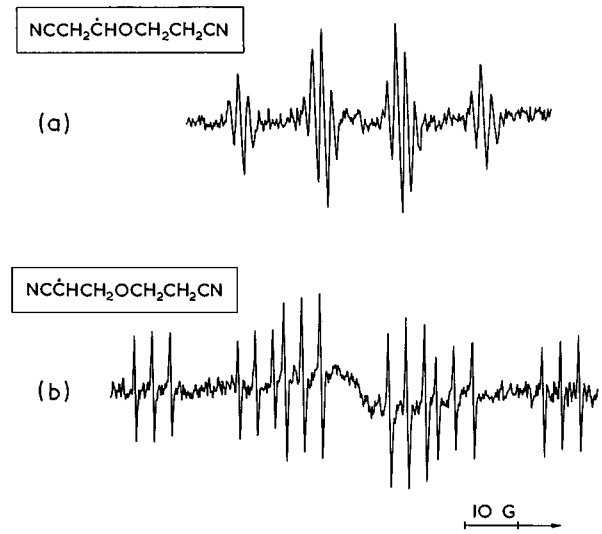
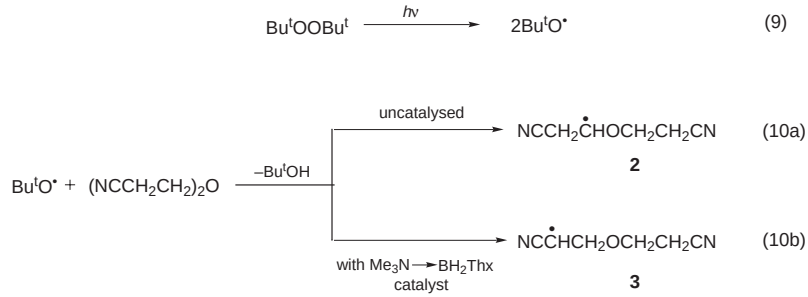


Fig. 2 EPR spectra obtained when *tert*-butoxyl radicals are generated in the presence of bis(2-cyanoethyl) ether at −57 °C, (a) in the absence of a catalyst and (b) in the presence of $Me_3N{\rightarrow}BH_2Thx$.

are of similar strength,[8] but α-alkoxyalkyl radicals are nucleophilic (the corresponding cation is relatively stable), while α-cyanoalkyl radicals are electrophilic and polar effects direct abstraction to the H–COR group. However, in the presence of 10 mol% trimethylamine–thexylborane ($Me_3N{\rightarrow}BH_2Thx$)‡ as an hydridic polarity-reversal catalyst, the EPR spectrum of the α-cyanoalkyl radical **3** was detected to the exclusion of that of **2** [eqn. (10b)] (Fig. 2b). Now the *tert*-butoxyl radical reacts more readily with the amine–borane than with the ether, on

‡ The 1,1,2-trimethylpropyl ('*tert*-hexyl') residue (Me_2CHCMe_2–) is commonly referred to as the thexyl group (Thx).



account of the very favourable polar effects for the former reaction, and then the highly nucleophilic amine–boryl radical abstracts hydrogen selectively from the H–CCN group to yield **3** and regenerate the catalyst. The rate constant for abstraction of hydrogen from $Me_3N{\rightarrow}BH_2Thx$ by the *tert*-butoxyl radical has been estimated[5] to be 4.7×10^7 dm^3 mol^{-1} s^{-1} at −84 °C and, if the Arrhenius *A*-factor is assumed to be 10^9 dm^3 mol^{-1} s^{-1}, the corresponding activation energy would be *ca*. 5 kJ mol^{-1}.

3 Amine–boranes as hydridic polarity-reversal catalysts

Extensive EPR studies of elementary reactions have been used to explore the utility of amine–boranes as hydridic catalysts for the overall transfer of electron-deficient hydrogen to electrophilic alkoxyl radicals. Thus, in the presence of a catalytic amount of amine–alkylborane, hydrogen is rapidly and selectively abstracted from a C–H group α to the carbonyl substituent in esters, lactones, ketones, imides, acetic anhydride and related compounds.[5,10] For example, at −52 °C the uncatalysed reaction of *tert*-butoxyl radicals with methyl methoxyacetate **4** gives a mixture of radicals resulting from competitive abstraction of hydrogen from the ether $-CH_3$ group and from the α-CH_2 group, while in the presence of $Me_3N{\rightarrow}BH_2Thx$ only abstraction from the latter was detected. The uncatalysed reaction of *tert*-butoxyl radicals with cholesteryl acetate **5** gives a mixture of radicals resulting from unselective abstraction from the cholesteryl moiety (Fig. 3a), but abstraction from the acetyl group to give the radical **6** was not detectable by EPR spectroscopy. However, in the presence of $Me_3N{\rightarrow}BH_2Thx$, abstraction from the electron-deficient α-CH_3 group occurs selectively and **6** is the only radical detected (Fig. 3b). With tetrahydro-4*H*-pyran-4-one **7**, *tert*-butoxyl radicals abstract hydrogen mainly adjacent to the endocyclic oxygen atom, while in the presence of an amine–alkylborane catalyst abstraction takes place exclusively α to the carbonyl group, as judged by EPR spectroscopy.

Reaction of *tert*-butoxyl radicals with an equimolar mixture of *tert*-butyl methyl ether and diethyl malonate at −84 °C afforded only the EPR spectrum of the *tert*-butoxymethyl radical (Fig. 4a), while the only spectrum observed in the presence of $Me_3N{\rightarrow}BH_2Thx$ was that of $H\dot{C}(CO_2Et)_2$, resulting from abstraction of electron-deficient α-hydrogen from the malonate (Fig. 4b).[5] PRC by $Me_3N{\rightarrow}BH_2Bu$ has also been used to generate the radicals $R\dot{C}(CO_2Et)_2$ (R = H, alkyl or CO_2Et), for kinetic studies of their addition reactions with alkenes and with *tert*-butyl isocyanide, by α-hydrogen-atom abstraction from the corresponding esters in the presence of *tert*-butoxyl radicals.[11]

The selectivity of amine–borane-promoted hydrogen-atom transfer to the *tert*-butoxyl radical depends on the nature of the catalyst, because it is the amine–boryl radical that is responsible for hydrogen abstraction. This is clearly illustrated by the relative reactivities of CH_3CO_2Et, $MeCH_2CO_2Et$ and Me_2CHCO_2Et towards catalysed abstraction of hydrogen from their α-C–H groups (Table 1).[5,10] The data can be understood in terms

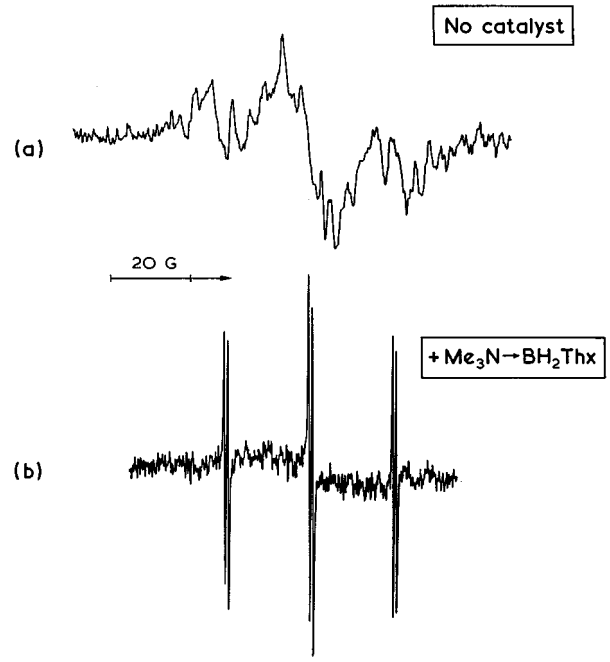
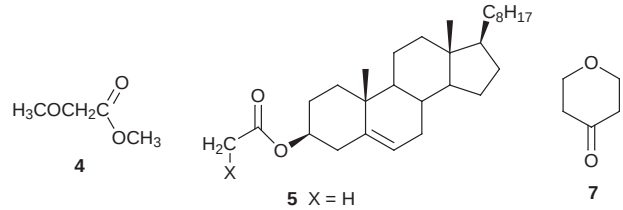


Fig. 3 EPR spectra obtained when *tert*-butoxyl radicals are generated in the presence of cholesteryl acetate at −33 °C, (a) in the absence of a catalyst and (b) in the presence of $Me_3N{\rightarrow}BH_2Thx$.



of the decreasing strength of the α-C–H bond along the series CH_3CO_2Et > $MeCH_2CO_2Et$ > Me_2CHCO_2Et, coupled with the increased steric protection that α-methylation affords to an α-C–H group. In particular, while Me_2CHCO_2Et is 1.1 times more reactive than $MeCH_2CO_2Et$ towards the amine–boryl radical $Me_3N{\rightarrow}\dot{B}HMe$, it is 9.2 times *less* reactive than the propanoate towards the more sterically-hindered $Me_3N{\rightarrow}\dot{B}HThx$. A similar trend was found for amine–borane-catalysed hydrogen abstraction from the two types of α-C–H group present in 3-methylbutan-2-one [$Me_2CHC(O)CH_3$], where $Me_3N{\rightarrow}\dot{B}HThx$ shows a strong preference for abstraction from the less-hindered methyl group, while $Me_3N{\rightarrow}\dot{B}HBu$ abstracts the more weakly bound, but less accessible, tertiary α-hydrogen atom.[10]

Competitive hydrogen-atom abstraction from cyclopenta-1,3-diene and from cyclohepta-1,3,5-triene, for which the strengths of the C–H bonds are fairly similar, has been examined.[12] The cyclopentadienyl cation is antiaromatic, while the cycloheptatrienyl cation is a stabilised aromatic species, and it has been shown that electrophilic *tert*-butoxyl radicals

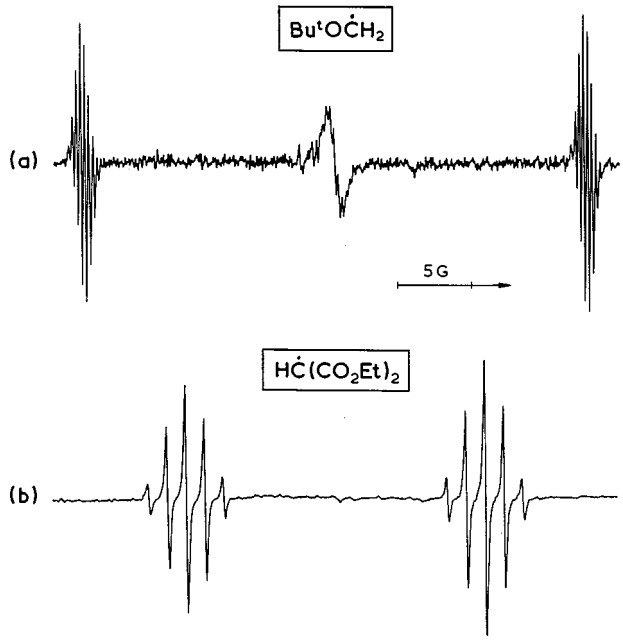


Fig. 4 EPR spectra obtained when *tert*-butoxyl radicals are generated in the presence of an equimolar mixture of *tert*-butyl methyl ether and diethyl malonate at −84 °C, (a) in the absence of a catalyst and (b) in the presence of $Me_3N{\rightarrow}BH_2Thx$. The central multiplet in the spectrum of Bu^{t}OĊH$_2$ is broadened as a consequence of restriction of rotation about the Ċ–O bond.

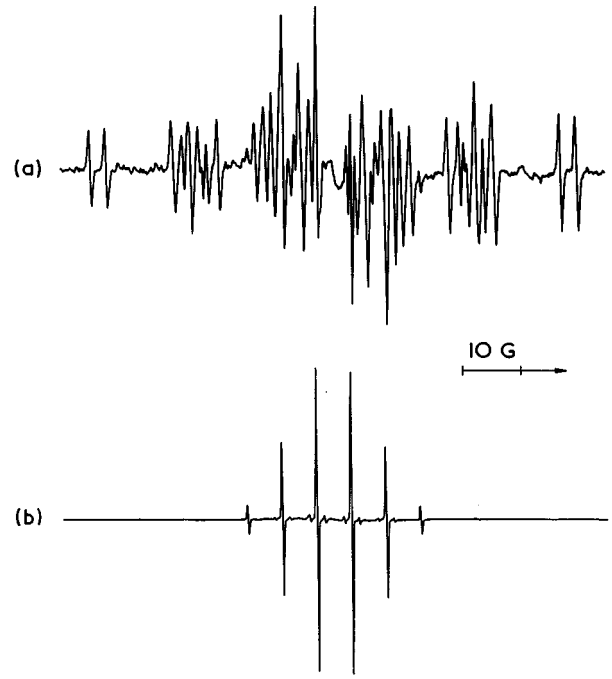
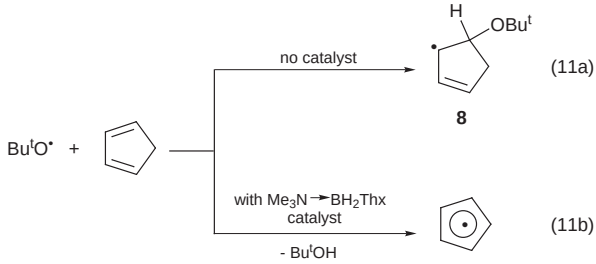


Fig. 5 EPR spectra obtained when *tert*-butoxyl radicals are generated in the presence of cyclopenta-1,3-diene at −116 °C, (a) in the absence of a catalyst and (b) in the presence of $Me_3N{\rightarrow}BH_2Thx$.

Table 1 Relative rates of α-hydrogen-atom transfer from esters to the *tert*-butoxyl radical, catalysed by amine–boranes at −84 °C

Amine–borane catalyst	Ester reactivity (per molecule)		
	CH_3CO_2Et	$MeCH_2CO_2Et$	Me_2CHCO_2Et
$Me_3N{\rightarrow}BH_3$	(1)	6.3	7.2
$Me_3N{\rightarrow}BH_2Me$	(1)	6.7	7.3
$Me_3N{\rightarrow}BH_2Bu^s$	(1)	4.9	2.4
$Me_3N{\rightarrow}BH_2Thx$	(1)	4.6	0.5

abstract hydrogen much more slowly from the diene than from the triene, as would be expected on the basis of polar effects. However, in the presence of $Me_3N{\rightarrow}BH_2Thx$ as hydridic polarity-reversal catalyst hydrogen abstraction (now by the nucleophilic amine–boryl radical) takes place exclusively from the diene, because the cyclopentadienyl anion is aromatic while the cycloheptatrienyl anion is not: the structure [$Me_3N{\rightarrow}\dot{B}HThx\ \dot{H}\ R^-$] contributes to the transition state only when R is cyclopentadienyl. In fact, in its reaction with cyclopentadiene alone, the *tert*-butoxyl radical prefers to *add* to the ring to give the cyclopentenyl adduct **8** [eqn. (11a)] (see Fig. 5a) rather than to abstract hydrogen to give the cyclopentadienyl radical. However, in the presence of an amine–alkylborane as polarity-reversal catalyst, only the cyclopentadienyl radical was detected by EPR spectroscopy [eqn. (11b)] (see Fig. 5b).[12]

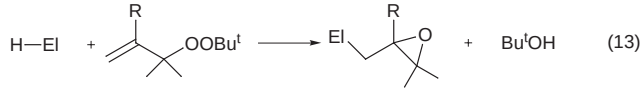


An interesting example of PRC is provided by the reactions of the primary and secondary amine–boranes $RNH_2{\rightarrow}BH_3$ and $R_2NH{\rightarrow}BH_3$ with *tert*-butoxyl radicals.[13] Although the EPR spectra of the corresponding aminyl–borane radicals $R\dot{N}H{\rightarrow}BH_3$ and $R_2\dot{N}{\rightarrow}BH_3$ were observed as the ultimate reaction products, it is clear that these electrophilic species are formed indirectly through the intermediacy of the less stable, but nucleophilic, amine–boryl radicals $RNH_2{\rightarrow}\dot{B}H_2$ and $R_2NH{\rightarrow}\dot{B}H_2$. Polar effects direct abstraction by Bu^{t}O$^\bullet$ initially to the B–H group and the amine–boryl radicals formed then rapidly abstract hydrogen from the parent amine–borane to give the thermodynamically more stable isomeric aminyl–borane radicals [*e.g.* eqn. (12)]. The amine–borane is here serving as a polarity-reversal catalyst for hydrogen abstraction from itself!

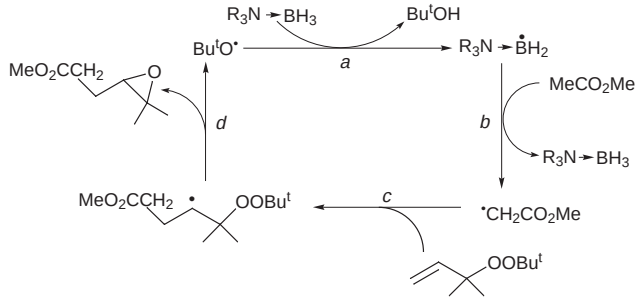
$$Me_2NH{\rightarrow}BH_3 \xrightarrow[-Bu^tOH]{Bu^tO^\bullet} [Me_2NH{\rightarrow}\dot{B}H_2] \xrightarrow[-Me_2NH{\rightarrow}BH_3]{+Me_2NH{\rightarrow}BH_3} Me_2\dot{N}{\rightarrow}BH_3 \qquad (12)$$

3.1 Radical-chain reactions

PRC has been used to control reactivity and selectivity in radical-chain reactions for functionalisation α to an ester carbonyl group.[14] Thus, in the presence of quinuclidine–borane as catalyst, methyl acetate, dimethyl malonate, triethyl methanetricarboxylate and ethyl cyanoacetate (H–El) each react with allylic *tert*-butyl peroxides at 30 °C in benzene solvent to give products resulting from 2,3-epoxypropylation at an α-C–H group, as generalised in eqn. (13).[14] The propagation stage of

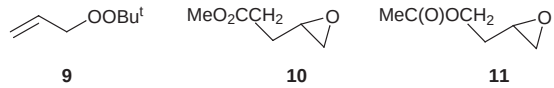


this radical-chain process is illustrated in Scheme 2 for the reaction of methyl acetate with *tert*-butyl 1,1-dimethylallyl peroxide. The function of the amine–borane is to increase the rate of overall hydrogen-atom transfer from the ester to the *tert*-butoxyl radical and to direct abstraction exclusively to the electron-deficient α-C–H group (Scheme 2, steps *a* and *b*); no epoxypropylation at the ester-methyl group was detected.



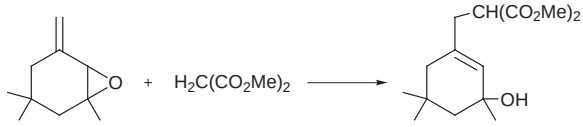
Scheme 2

In the absence of the amine–borane, such epoxypropylation reactions are sluggish and require a much higher temperature. For example, when a dilute solution of allyl *tert*-butyl peroxide **9** in methyl acetate as solvent was heated in an autoclave at 140 °C for 10 h, the epoxypropylation product consisted of **10** and **11** in the ratio of 7:3, reflecting the low selectivity with which the *tert*-butoxyl radical abstracts hydrogen from the two types of C–H bond present in the ester.[15]



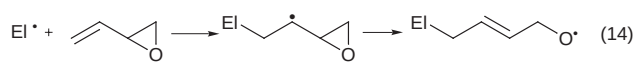
9 **10** **11**

Related chain reactions of esters with vinylic epoxides to yield allylic alcohols are also catalysed by amine–boranes (*e.g.* Scheme 3).[15] Again, the role of the amine–borane is to promote



Scheme 3 *Reagents and conditions*: Bu^{t}OOBu^t + UV light initiator, amine–borane catalyst, 30 °C.

regioselective abstraction of hydrogen from the α-C–H group of the ester, but now steps *c* and *d* in Scheme 2 are replaced by the addition of the electrophilic carboxyalkyl radical to the vinyl epoxide to give an intermediate oxiranylcarbinyl radical, which then undergoes rapid ring opening [eqn. (14)]. The allyloxyl

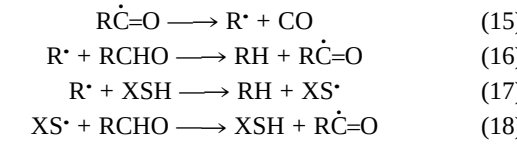


(14)

radical thereby produced goes on to abstract hydrogen from the amine–borane catalyst to give the allylic alcohol and regenerate the chain-carrying amine–boryl radical.

4 Thiols and selenols as protic polarity-reversal catalysts

As part of a Faraday Society Discussion in 1953, Barrett and Waters reported that thiols catalyse the radical-chain decarbonylation of aldehydes [eqns. (15) and (16)].[16] In the general discussion that followed this paper, F. R. Mayo suggested an explanation for the catalysis based on the key role of polar effects. Mayo pointed out that the chain-propagating abstraction of hydrogen from an aldehyde by an alkyl radical [eqn. (16)] does not benefit from favourable polar effects in the transition state, because both the alkyl radical and the acyl radical are nucleophilic: the reaction is thus an example of the general type represented in eqn. (5). Mayo proposed that the catalysis of the overall hydrogen transfer reaction (16), through the cycle of reactions (17) and (18), could be understood because the thiyl radical is electrophilic. In the general terminology adopted here, the thiol is acting as a protic polarity-reversal catalyst for reaction (16) and this type of catalytic cycle can be used with advantage in several classes of radical-chain reaction.



(15)

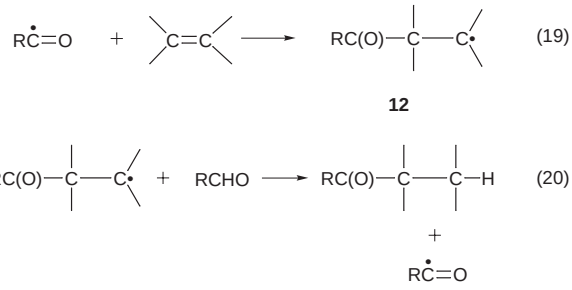
(16)

(17)

(18)

4.1 Hydroacylation of alkenes

The intermolecular radical-chain addition of an aldehyde to an alkene to give a ketone (hydroacylation) was first studied half-a-century ago and the simple addition of primary aldehydes (RCH_2CHO) to electron-deficient alkenes (*e.g.* α,β-unsaturated ketones and dialkyl maleates) can give good yields of adducts. However, a major problem with the propagation stage of the radical-chain pathway [reactions (19) and (20)] remains the inefficiency with which the acyl-radical adduct **12** abstracts hydrogen from the aldehyde [reaction (20)].[17]

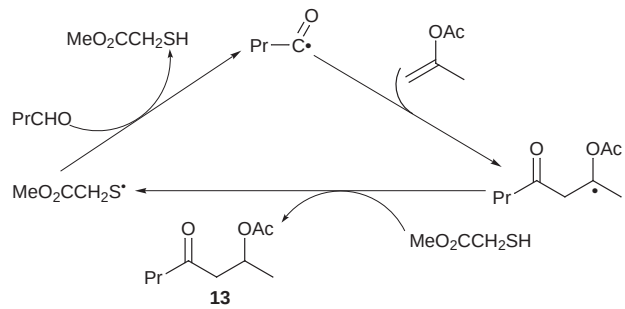


(19)

12

(20)

In view of the foregoing discussion, it would be anticipated that thiols would act as polarity-reversal catalysts for radical-chain hydroacylation reactions, provided that loss of the thiol by addition to the alkene does not cause problems, and it has been shown that thiols do indeed promote the addition of primary aldehydes to a variety of alkenes under mild conditions.[17] While thiol catalysis is effective for the hydroacylation of electron-rich, -neutral and -poor alkenes, it is most efficient for addition to electron-rich double bonds. For example, the addition of butanal to isopropenyl acetate at 60 °C, in the presence of di-*tert*-butyl hyponitrite as initiator and methyl thioglycolate (MeO_2CCH_2SH) as catalyst, affords the adduct **13** in 80% yield (see Scheme 4), while a similar reaction in the absence of thiol gives only 8% yield. Such addition of an aldehyde to an enol derivative provides a non-ionic route to acylated or silylated aldol adducts.[17]



13

Scheme 4

4.2 Dehalogenation, deoxygenation and desulfurisation by silanes

A trialkylsilyl group shows many properties in common with those of an acyl group. Both are π-acceptors, the corresponding

radicals are both nucleophilic and the Si–H bond in R_3SiH is weaker than many aliphatic C–H bonds, as is the aldehydic C–H bond in RCHO. Currently-quoted bond dissociation enthalpies (in kJ mol^{-1}) are: MeC(O)–H 374, Et_3Si–H 398, and $(Me_3Si)_3Si$–H 351.[8,18] For comparison, D*H*(MeS–H) is 365 kJ mol^{-1} and D*H*(Bu_3Sn–H) is 308 kJ mol^{-1}.[8]

The removal of a functional group G from an organic compound R–G and its replacement by hydrogen to give R–H is a basic transformation of considerable importance in synthetic organic chemistry. Tributyltin hydride is pre-eminent amongst reagents for the homolytic reductive removal of functional groups and such reactions follow the chain mechanism generalised in eqns. (21) and (22) [reaction (21) is sometimes a stepwise addition–elimination process]. However, for practical

$$Bu_3Sn^{\bullet} + R\text{–}G \longrightarrow Bu_3Sn\text{–}G + R^{\bullet} \quad (21)$$

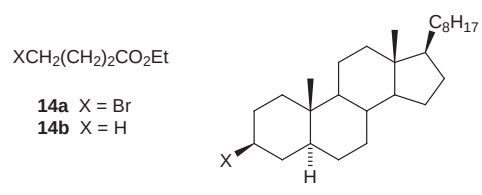
$$R^{\bullet} + Bu_3Sn\text{–}H \longrightarrow R\text{–}H + Bu_3Sn^{\bullet} \quad (22)$$

and ecological reasons it would be desirable to use simple, readily available silanes in place of trialkyltin hydrides. The corresponding propagation cycle using triethylsilane is shown in eqns. (23) and (24) and, while reaction (23) is generally faster than its tin counterpart, reaction (24) is relatively slow

$$Et_3Si^{\bullet} + R\text{–}G \longrightarrow Et_3Si\text{–}G + R^{\bullet} \quad (23)$$

$$R^{\bullet} + Et_3Si\text{–}H \longrightarrow R\text{–}H + Et_3Si^{\bullet} \quad (24)$$

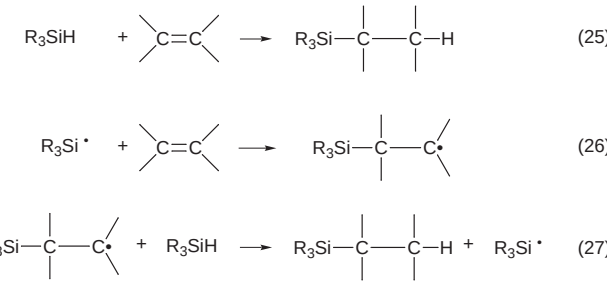
at moderate temperatures, because of the greater strength of the Si–H bond as compared with the Sn–H bond. As a consequence, reductions using simple silanes are not generally viable under mild conditions. Although reaction (24) is usually exothermic, in common with the corresponding abstraction of hydrogen from an aldehyde [eqn. (16)], it does not benefit from favourable polar effects because both the alkyl radical and the silyl radical are nucleophilic. This analysis suggests that the overall hydrogen-atom transfer shown in eqn. (24) should be promoted by a protic polarity-reversal catalyst and it has been shown that thiols can serve in this capacity.[19] The trialkylsilane–thiol couple acts an effective replacement for tributyltin hydride for the reduction of alkyl halides (bromides and chlorides — the latter are not usually reduced efficiently by the tin hydride), dialkyl sulfides and the *S*-methyl dithiocarbonate (xanthate) esters derived from primary and secondary alcohols. For example, ethyl 4-bromobutanoate **14a** was reduced to ethyl butanoate **14b** in essentially quantitative yield by four equivalents of triethylsilane in refluxing cyclohexane, in the presence of dilauroyl peroxide as initiator and *tert*-dodecanethiol (mixture of isomers) as polarity-reversal catalyst.[19] Reduction of cholestanyl xanthate **15a** with triethylsilane in refluxing octane, with di-*tert*-butyl peroxide initiator and *tert*-dodecanethiol catalyst, afforded cholestane **15b** in 94% isolated yield. However, appreciable yields of cholestane were obtained from the peroxide-initiated reduction by triethylsilane *in the absence* of a thiol catalyst and it seems likely that this reduction is promoted by a thiol formed *in situ* from the xanthate.[19]



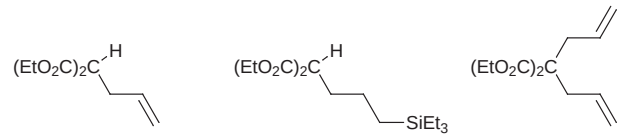
15a X = OC(S)SMe
15b X = H

4.3 Hydrosilylation of alkenes

Hydrosilylation of alkenes [eqn. (25)] is an important method for the formation of Si–C bonds and such addition reactions can proceed by a radical-chain mechanism [eqns. (26) and (27)] or under the influence of various transition metal catalysts, in particular rhodium, palladium and platinum complexes. However, radical-chain hydrosilylation of alkenes using trialkylsilanes has not found much use in synthesis because the hydrogen-atom abstraction step [eqn. (27)] is relatively slow at moderate temperatures and competing telomerisation of the alkene can also be a problem. Again, reaction (27) should be subject to PRC by thiols and, provided addition of the catalyst to the alkene can be suppressed, thiols should therefore catalyse the radical-chain hydrosilylation of alkenes. This has been realised in practice[20,21] and when addition of the thiol catalyst to the alkene was a problem, this could usually be overcome by adding the former slowly to the reaction mixture using a syringe pump. For example, a good yield of the triethylsilane adduct **17**



was obtained by hydrosilylation of diethyl allylmalonate **16** at 60 °C using *tert*-dodecanethiol as protic polarity-reversal catalyst. However, the potential difficulty caused by loss of the thiol by addition to the alkene is highlighted by the very low yield of silane-addition products obtained from the corresponding reaction of diethyl diallylmalonate **18**.[20] Here it appears that addition of the thiyl radical to one of the double bonds is rendered effectively irreversible by the rapid 5-*exo*-cyclisation of the adduct radical and it is evident that, for the thiol catalysis to be successful, any addition of the thiyl radical to the alkene should be reversible under the reaction conditions.

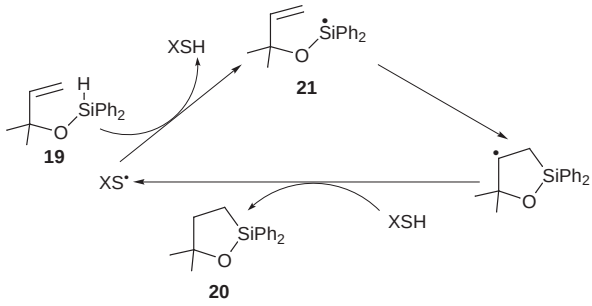


16 **17** **18**

Thiol catalysis of hydrosilylation is more effective for the addition of arylsilanes than trialkylsilanes, presumably because the weaker Si–H bond in the former results in more rapid abstraction of hydrogen by the thiyl radical to form the corresponding silyl radical.[21] Furthermore, methyl thioglycolate (MeO_2CCH_2SH) and triphenylsilanethiol (Ph_3SiSH) are generally more efficient hydrosilylation catalysts than *tert*-dodecanethiol, again probably because of an increase in the rate of abstraction of hydrogen from the silane by the thiyl radical, this time because of an increase in the strength of the S–H bonds and in the electrophilicities of the thiyl radicals involved.[21–23] Thiols have also been shown to catalyse the addition of tris(trimethylsilyl)silane [$(Me_3Si)_3SiH$] to alkenes.[23]

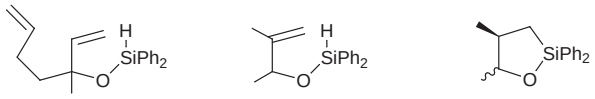
Intramolecular radical-chain hydrosilylation, leading to the cyclisation of alkenyloxysilanes, is also catalysed by thiols.[22] For example, the allyloxydiphenylsilane **19** (see Scheme 5) underwent almost quantitative cyclisation to give the oxasilacyclopentane **20** at 60–65 °C in the presence of di-*tert*-butyl hyponitrite as initiator and *tert*-dodecanethiol as catalyst; no cyclisation took place in the absence of thiol. The propagation stage of the chain reaction is shown in Scheme 5 and involves 5-*endo*-cyclisation of the intermediate silyl radical **21**.

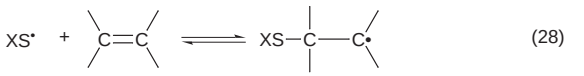
The attempted thiol-catalysed tandem cyclisation of the allyloxysilane **22** failed, presumably for the same reason as did



Scheme 5

the intermolecular addition of triethylsilane to diethyl diallylmalonate **18**, because addition of thiyl radicals to either end of the diene system is rendered irreversible by the rapid 5-*exo*-cyclisation of the adduct radical formed. For effective catalysis of hydrosilylation, the conditions must be chosen such that the major fate of the thiyl radical is to be converted into a silyl radical which then adds irreversibly to the C=C group. Both reactions (28) and (29) are potentially reversible and detailed

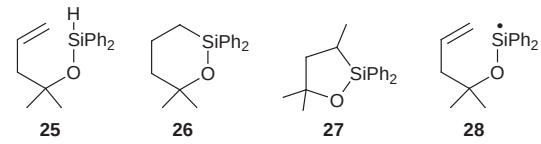




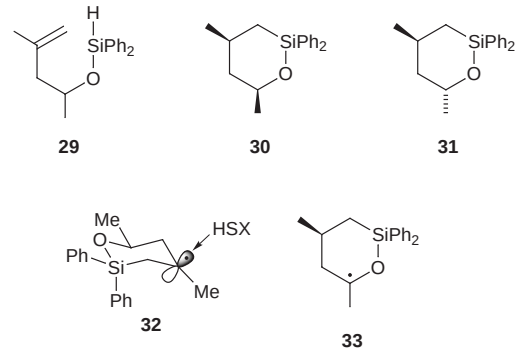
kinetic analysis of catalysed hydrosilylation reactions is a complex problem. The efficiency with which the thiyl radical is converted into the silyl radical will depend on the structures of the particular radicals involved and on the natures and relative concentrations of the thiol, silane and alkene. The kinetics and thermodynamics of the thiyl radical–silane reaction (29) are of critical importance for catalysed hydrosilylation and also for the successful use of the silane–thiol couple in other situations. Accepted values for D*H*(Et_3Si–H) and D*H*(MeS–H) at the time the silane–alkanethiol couple was first introduced for reduction[19] indicated that the abstraction of hydrogen from triethylsilane by an alkanethiyl radical was *exothermic* by *ca.* 7 kJ mol^{-1}, but currently promulgated values (see above) imply that it is *endothermic* by *ca.* 33 kJ mol^{-1},[8] as has been noted by Zavitsas.[24] However, in our view, since the alkanethiol–triethylsilane couple functions effectively at moderate temperatures, reaction (29) is very unlikely to be endothermic in the forward direction by more than 10–20 kJ mol^{-1} when X = R = simple alkyl. It seems likely that the S–H bond in an alkanethiol may be stronger, and/or the Si–H bond in a trialkylsilane may be weaker, than the most recently proposed values. Alternatively, some of the alkanethiol may be converted to R_3SiSH, in which the S–H bond is probably stronger,[19] under the reaction conditions.[23]

Another drawback with the silane–thiol system is illustrated by the low yield of intramolecular hydrosilylation product obtained from the *tert*-dodecanethiol-catalysed cyclisation of the allyloxysilane **23** to give the oxasilacyclopentane **24**.[22] It was thought likely that the alkanethiyl radical abstracts hydrogen from the allylic C–H groups in **23** (in particular the C–H group adjacent to oxygen), to give a stabilised allylic radical incapable of propagating the chain, in competition with the desired abstraction from the Si–H group. This interpretation was supported by the observation that the corresponding cyclisation of **19** (see Scheme 5), which lacks such allylic C–H groups, was inhibited by a small amount of allyloxytrimethylsilane ($Me_3SiOCH_2CH{=}CH_2$), which does possess them. The silanethiols Pr^i_3SiSH and Ph_3SiSH turned out to be much more effective catalysts for the cyclisation of **23** and reasonably good yields of **24** were obtained in their presence. It was suggested that a silanethiyl radical abstracts hydrogen more rapidly and/or selectively from the Si–H group in **23** than does an alkanethiyl radical.

Thiol-catalysed cyclisation of homoallyloxysilanes was also successful and, again, silanethiols were generally the most successful catalysts. For example, the but-3-enyloxysilane **25** underwent radical-chain cyclisation to give a 72:28 mixture of the oxasilacyclohexane **26** and the oxasilacyclopentane **27** arising from competitive 6-*endo*- and 5-*exo*-ring closure, respectively, of the intermediate silyl radical **28**.[22]



Finally, cyclisation of the homoallyloxysilane **29** gives only the oxasilacyclohexanes **30** and **31**, because 5-*exo*-cyclisation of the intermediate silyl radical is retarded by the methyl group on the double bond, and the *cis*:*trans* ratio in the product depends on the nature of the thiol catalyst. The less stable *trans*-isomer predominates because equatorial attack of the thiol on the intermediate oxasilacyclohexyl radical **32** is favoured over axial attack, which would incur a repulsive steric interaction with the axial phenyl group attached to silicon. However, it was also shown that the *trans*-isomer was converted to the more stable *cis* form in the presence of initiator and Ph_3SiSH at 65 °C, although almost no isomerisation took place in the presence of MeO_2CCH_2SH.

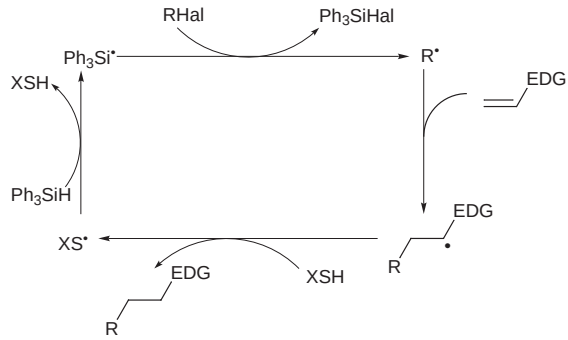


Presumably, the relatively electrophilic $Ph_3SiS^•$ abstracts hydrogen reversibly from the activated C–H bond adjacent to oxygen, allowing isomerisation to take place *via* the intermediate radical **33**.[22]

4.4 Reductive carboxyalkylation of alkenes

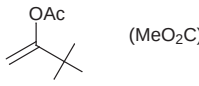
Depending on the nature of the substituents present, a silyl radical generally abstracts bromine from an alkyl bromide much more rapidly than it adds to a terminal alkene.[18] Abstraction of bromine from an α-bromoester would be expected to be still more rapid, and the resulting α-carboxyalkyl radical should add relatively rapidly to an electron-rich alkene to give a nucleophilic carbon-centred radical, which in turn should abstract

hydrogen relatively rapidly from a thiol, all because of favourable polar effects in the respective transition states. This analysis suggests that inclusion of an α-bromoester in a reaction system designed originally for thiol-catalysed hydrosilylation of an electron-rich alkene could result in interception of the silyl radical by the halogenoester and lead to reductive carboxyalkylation of the alkene through the chain-propagation cycle shown



Scheme 6

in Scheme 6 (EDG = electron-donating group). Such reactions have been shown to provide viable methods for C–C bond formation and specially-reactive chlorides, such as dimethyl chloromalonate, may be used with advantage in place of the corresponding bromides.[25] For example, reductive carboxyalkylation at 60 °C of the enol acetate **34** with dimethyl chloromalonate and triphenylsilane, in the presence of Ph_3SiSH as protic polarity-reversal catalyst, affords the adduct **35** in good yield (86%).



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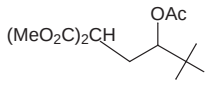

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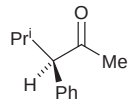

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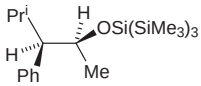

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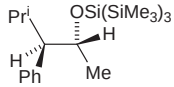
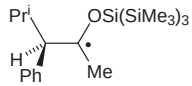


37b



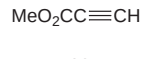
38

4.5 Hydrosilylation of ketones

The radical-chain hydrosilylation of ketones with tris(trimethylsilyl)silane, initiated by di-*tert*-butyl hyponitrite at 30 °C, is evidently catalysed by *tert*-dodecanethiol, although this was not stated explicitly.[26,27] Presumably, the mechanism is analogous to that of the thiol-catalysed hydrosilylation of an alkene; the chain-carrying α-siloxyalkyl radical, formed by addition of $(Me_3Si)_3Si^•$ to the carbonyl-oxygen atom, is nucleophilic and abstracts hydrogen more rapidly from the thiol catalyst than from the silane. For example, addition of $(Me_3Si)_3SiH$ to the ketone **36** gives a 12.6:1 mixture of the adducts **37a** and **37b** and the predominance of the former reflects the preference for the thiol to attack the intermediate radical **38** from its less-hindered bottom face. The isomer ratio should depend on the nature of the thiol, but this was not investigated. Assuming that the thiol catalyst is the sole or major hydrogen-atom donor, the results of experiments involving the $(Me_3Si)_3SiD$–RSH couple appear to require that H/D exchange between the thiol and the silane [*cf.* eqn. (29)] is rapid under the reaction conditions.

4.6 Applications to other reactions

PRC has been applied to the radical-chain addition of tributyltin hydride to terminal alkynes.[28] For example, the reaction of excess Bu_3SnH with methyl propiolate **39** to give the product of double hydrostannylation **40**, is catalysed by *p*-methoxythiophenol. The vinylstannane $MeO_2CCH{=}CHSnBu_3$ is formed first, but addition of $Bu_3Sn^•$ to this to give the radical **41** is highly reversible. In the presence of the arenethiol the adduct radical **41** (which is probably relatively nucleophilic by virtue of the presence of the two β-Bu_3Sn substituents) is rapidly and irreversibly trapped to give **40** and *p*-$MeOC_6H_4S^•$, which then goes on to abstract hydrogen from the tin hydride and regenerate the thiol catalyst. In the absence of the thiol, trapping of **41** by the tin hydride is inefficient.



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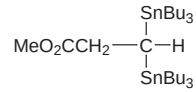

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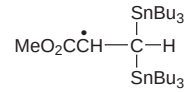


41

Most arenethiols are ineffective as polarity-reversal catalysts for hydrogen-atom transfer from silanes to alkyl radicals, because the ArS–H bond is appreciably weaker than that in an alkanethiol and the equilibrium shown in eqn. (29) lies far to the left. In fact, thiophenol *inhibited* the trace amount of addition of $PhMe_2SiH$ to isopropenyl acetate that was observed in the absence of any thiol.[17,21] An exception was provided by 2,4,6-tris(trifluoromethyl)thiophenol which *did* catalyse the hydrosilylation of isopropenyl acetate.[17] Presumably here the S–H bond is strengthened by the presence of the three electron-withdrawing CF_3 groups on the ring. The Si–H bond in a silane is much stronger than the Sn–H bond in the corresponding tin hydride, accounting for the efficacy of simple arenethiols as protic polarity-reversal catalysts for hydrogen transfer from the latter.

Crich and his co-workers have reported the use of benzeneselenol as a polarity-reversal catalyst for the abstraction of hydrogen from tin hydrides by carbon-centred radicals.[29–31] The electronegativity of selenium is only marginally less than that of sulfur and $PhSe^•$ is expected to exhibit electrophilic properties, like $PhS^•$. The Se–H bond is much weaker than the S–H bond and both enthalpic and polar factors favour abstraction of hydrogen from the selenol by a nucleophilic alkyl radical, a process which is extremely rapid at room temperature and significantly faster than the direct abstraction of hydrogen from the tin hydride.[32] However, polar effects favour abstraction of hydrogen by $PhSe^•$ from the tin hydride and the catalytic cycle involved is shown in eqns. (30) and (31). It was pointed

$$R^• + PhSeH \longrightarrow RH + PhSe^• \quad (30)$$

$$PhSe^• + Bu_3SnH \longrightarrow PhSeH + Bu_3Sn^• \quad (31)$$

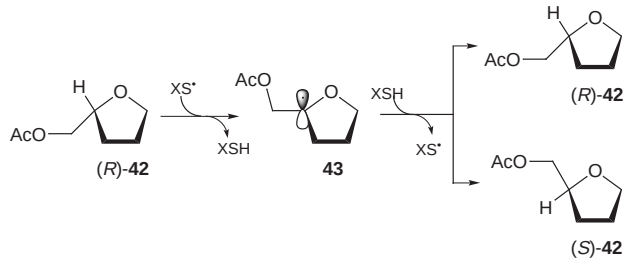
out that undesired radical rearrangement processes, which are sufficiently rapid to proceed in the presence of tin hydride alone, can be suppressed in the presence of PhSeH (added as such or formed *in situ* by reduction of PhSeSePh), because the precursor radical is trapped by the selenol before the rearrangement can take place.[29]

PRC by benzeneselenol of the overall transfer of hydrogen from tributyltin hydride to relatively unreactive radicals, such as allylic and cyclohexadienyl radicals, has proved useful in increasing the efficiency of chain reactions involving these species.[31] The much greater rate at which a nucleophilic carbon-centred radical $R^•$ abstracts hydrogen from PhSeH, as compared with Bu_3SnH, has also been exploited in experiments designed to measure the rate of rearrangement of $R^•$ using the so-called radical-clock method.[30] The 'clock reaction' is the trapping of the alkyl radical $R^•$ by a constant catalytic quantity of the selenol under pseudo-first-order conditions,[32] obviating the need to work with a large excess of the tin hydride in order to achieve simple reaction kinetics.

Exchange reactions of the type shown in eqn. (32), between

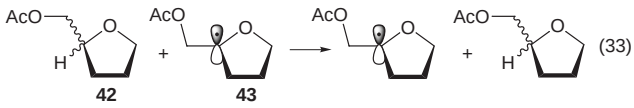
$$R^{1\bullet} + R^2\text{–}H \longrightarrow R^1\text{–}H + R^{2\bullet} \qquad (32)$$

one alkyl radical and a hydrocarbon to give a similar alkyl radical, generally have relatively large activation energies and are very slow at moderate temperatures. In the high-temperature pyrolyses of hydrocarbons in the gas phase, it has been demonstrated that the inclusion of HCl, HBr or H_2S can accelerate reactions of the type (32) and modify the end-product distributions from chain reactions that involve this elementary step.[33] This phenomenon was referred to as 'hydrogen transfer catalysis', although the probable part played by polar effects was not discussed. Thermoneutral or nearly thermoneutral hydrogen-atom transfer between two strongly nucleophilic carbon radicals [*cf.* eqn. (5)] should be particularly susceptible to PRC by a protic catalyst of the type H–El and, similarly, transfer between two electrophilic carbon radicals [*cf.* eqn. (4)] should respond well to PRC by an hydridic catalyst H–Nuc. It has been reported that radical-induced racemisation of (*R*)-tetrahydrofurfuryl acetate **42** at 60 °C can be induced by certain thiols (XSH), through the chain mechanism shown in Scheme 7.[34] The thiol is here acting as a polarity-reversal catalyst for the



Scheme 7

thermoneutral transfer of hydrogen between the nucleophilic radical **43** and the parent ester **42** [eqn. (33)]. The nature of the



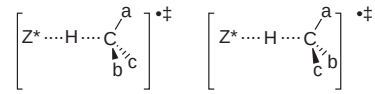
group X in the thiol is crucially important in determining catalyst efficiency and racemisation was most rapid when X was an electron-withdrawing group. Triphenylsilanethiol was the most effective of the thiols investigated, while simple alkanethiols were very inefficient catalysts, and it was thought that the π-electron withdrawing silyl substituent increases both the strength of the S–H bond in the thiol and the electrophilicity of $Ph_3SiS^{\bullet}$, compared with the situation when X is an alkyl group. It was pointed out that α-alkoxyalkyl radicals similar in structure to **43** are involved in the radical-induced strand cleavage of DNA under anaerobic conditions, as initial products of hydrogen abstraction from the 4′-position and, after strand cleavage, a similar α-alkoxyalkyl radical centre is generated in the oligonucleotide fragment. By promoting the reaction of this fragment radical with undamaged DNA, appropriate thiols might serve as polarity-reversal catalysts to amplify the radical-induced damage caused intentionally to the DNA in tumour cells *in vivo* during radio- or chemo-therapy.[34]

5 Enantioselective hydrogen-atom abstraction

Reactions that involve enantioselective atom transfer are relatively rare. Enantioselective hydrogen-atom transfer from and to carbon, mediated by a homochiral radical Z*$^{\bullet}$ and the closed-shell molecule Z*–H, is generalised in eqn. (34). This

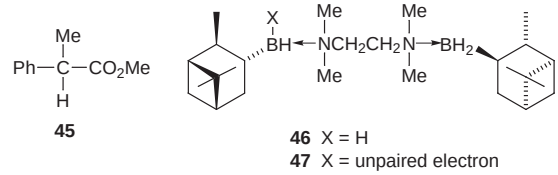
$$Z^{*\bullet} + HCabc \rightleftharpoons Z^*\text{–}H + {}^{\bullet}Cabc \qquad (34)$$

reaction proceeds through the diastereoisomeric pair of transition states **44a** and **44b** and it is the energy difference between

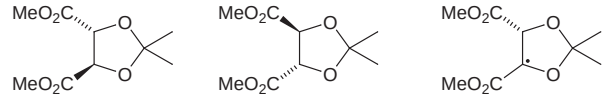


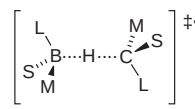
these two structures that determines the enantioselectivity of the hydrogen-atom transfer. If the compound Z*–H is a polarity-reversal catalyst, the possibility of catalytic enantioselective hydrogen-atom transfer arises in chain and non-chain processes that are promoted by PRC.

Enantioselective hydrogen transfer under conditions of PRC was first reported in 1991,[35] when it was shown that partial kinetic resolution of methyl 2-phenylpropanoate **45** could be achieved during UV photolysis of di-*tert*-butyl peroxide at −83 °C in the presence of the initially-racemic ester and a catalytic amount of the homochiral amine–borane complex **46**. In this non-chain process it is the homochiral amine–boryl radical **47** that is responsible for hydrogen abstraction from the α-C–H group in **45**, although the enantioselectivity was small and (*R*)-**45** was only *ca*. 2.4 times more reactive than the (*S*)-enantiomer.



The elementary enantioselective hydrogen-atom abstraction step has been studied in isolation using the EPR technique and high enantioselectivity factors (*s*)§ were obtained for abstraction from the α-C–H groups of dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **48** by the amine–boryl radical **47** and by related species which contain substituted isopinocampheyl groups.[36] It was found that (*S,S*)-**48** was 21 times more reactive towards **47** than (*R,R*)-**48** at −85 °C. Under the experimental conditions (photolysis of Bu^tOOBu^t in the presence of the ester and catalyst in an inert solvent) the radical **49** and its antipode go on to dimerise and disproportionate.





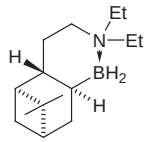
Partial kinetic resolution of a number of racemic chiral esters and of camphor was brought about by photolysis of Bu^tOOBu^t in their presence, along with a polarity-reversal catalyst of the type exemplified by **46**.[37] However, the values of *s* were generally small (≤ 5) and the enantiomeric excesses (ees) of the residual substrates were also relatively small (although, of course, this depends on the amount of substrate consumed). The

large value of *s* shown by **48** in its reaction with **47** allowed the racemic ester to be successfully resolved. Thus, after 75% of the initially-racemic tartrate had been consumed during photolysis of Bu^tOOBu^t in the presence of the ester and **46** as polarity-reversal catalyst at −90 °C, the ee of the remaining tartrate was 97% in favour of (*R*,*R*)-**48**. The sense of the observed enantioselectivity could often be understood on the basis that the more stable of the two transition states **44a** and **44b** is that in which there is a staggered arrangement of the groups attached to boron and to carbon, such that long-range torsional- and steric-interactions are minimised, as shown in structure **50** (L, M and S are large, medium and small groups).[37] However, in general, the transition state energies appear to be determined by a subtle interplay of steric, stereoelectronic and electrostatic interactions, together with the effects of hydrogen-bonding in appropriate systems.[38] *Ab initio* molecular orbital calculations for the prototypical abstraction of hydrogen from acetaldehyde by the ammonia–boryl radical [eqn. (35)] showed that the

$$H_3N{\rightarrow}\dot{B}H_2 + CH_3CHO \longrightarrow H_3N{\rightarrow}BH_3 + {}^{\bullet}CH_2CHO \qquad (35)$$

optimum transition-state geometry is influenced by: (i) stereoelectronic factors arising from the need to delocalise the unpaired electron and negative charge onto the carbonyl group, (ii) electrostatic interactions between the dipolar C=O and N→B groups and (iii) the existence of hydrogen-bonding between one NH group and the carbonyl-oxygen atom.[38]

Attempts to discover homochiral amine–borane complexes which are generally efficient polarity-reversal catalysts for the kinetic resolution of chiral carbonyl compounds, by enantioselective hydrogen abstraction from α-C–H groups, have not been very successful to date.[38,39] The polycyclic amine–borane **51** shows high thermal- and air-stability and, when it was used as a catalyst for the kinetic resolution of *O*-trimethylsilylpantolactone **52** at −74 °C, lactone with an ee of 84% in favour of (*R*)-**52** was isolated after 71% of the substrate had been consumed (*s* = *ca.* 5).[39]



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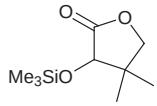
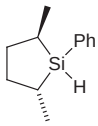


52

Partial kinetic resolution of racemic *trans*-2,5-dimethyl-1-phenyl-1-silacyclopentane **53** [the (2*R*,5*R*)-enantiomer is shown] has been brought about by its radical-chain reaction with a deficiency of alkyl bromide in the presence of the homochiral silanethiol **54** as polarity-reversal catalyst.[40] Enantioselective abstraction of hydrogen from **53** by the silanethiyl radical **55** takes place as part of the chain-propagation cycle, although the optical purities of the residual silane [(2*R*,5*R*)-enantiomer in excess] and of the bromosilane **56** [the (2*S*,5*S*)-enantiomer shown was in excess] obtained by this route were very low.



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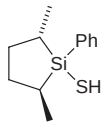

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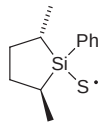

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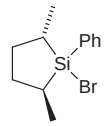
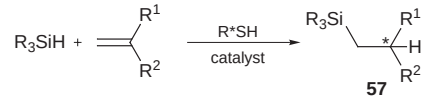


56

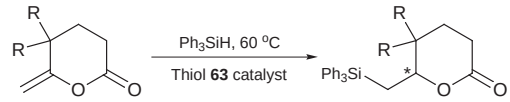
In the above examples of enantioselective hydrogen-atom transfer from and to carbon, the transition state **44** is approached from the left-hand side of eqn. (34), *i.e.* by the reaction of a homochiral radical Z*• with the chiral substrate. More recently, the combination of an achiral silane and a homochiral thiol as polarity-reversal catalyst has been utilised to bring about enantioselective hydrosilylation and enantioselective carboxyalkylation of prochiral alkenes.[21,23,25] In these reactions the transition state **44** is approached from the opposite direction, *i.e.* by the interaction of a prochiral carbon-centred radical •Cabc with a homochiral hydrogen-atom donor Z*–H.

Radical-chain hydrosilylation of a number of prochiral terminal alkenes [eqn. (36)] has been carried out at 60 °C in the presence of a homochiral thiol as polarity-reversal catalyst.[21,23]



57 (36)

The stereogenic centre in the adduct **57** is set when the intermediate β-silylalkyl radical abstracts hydrogen from the thiol and the most successful catalysts for inducing asymmetry in the adducts were derived from carbohydrates by introduction of an SH group at the anomeric position. For example, addition of triphenylsilane to the methylenelactones **58** and **59** afforded the adducts **60** and **61** in good chemical yield and moderate to high enantiomeric purity [eqn. (37)] when the pyranose thiols

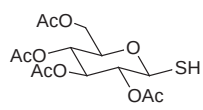


(37)

58 R = Me
59 R = Ph

60 R = Me (76% ee)
61 R = Ph (95% ee)

62 and **63** were used as catalysts (5 mol% based on alkene).[21,23] With the β-glucose thiol **62** as catalyst, the adduct **60** was obtained with a 50% ee and this was raised to 76% ee by using the β-mannose thiol **63**. Corresponding hydrosilylation of the diphenyl analogue **59** afforded the adduct **61** with an ee of 87% using the β-glucose thiol and with an ee of 95% (isolated chemical yield 90%) using the β-mannose thiol as catalyst. Evidently, the extra bulk provided by the *gem*-β-diphenyl groups in the intermediate radical **64** is responsible for the increase in ee over that obtained with the dimethyl analogue. As discussed previously for the silanethiols and methyl thioglycolate, the high chemical yields obtained using these carbohydrate thiols as catalysts are probably a result of the relatively high strength of the S–H bonds and the relatively high electrophilicities of the corresponding thiyl radicals, as compared with simple alkane-thiols and -thiyl radicals, as a result of the presence of several electronegative oxygen atoms in the molecules.[23]



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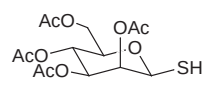

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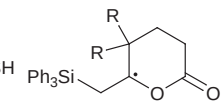

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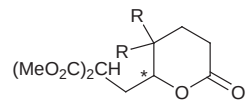

65

Enantioselective reductive carboxyalkylation (*cf.* Scheme 6) of the methylenelactone **58** has also been carried out using the thiols **62** and **63** as catalysts.[25] The hyponitrite-initiated reaction of **58** with dimethyl chloromalonate and triphenylsilane at 60 °C, in the presence of the β-glucose thiol **62**, gave the compound **65** with an ee of 24% and this value was raised slightly to 27% by using the β-mannose thiol **63** as catalyst.

6 Concluding remarks

The key role played by polar effects in free-radical chemistry is well established. The basic idea behind PRC is also not new, having been put forward by Mayo in 1953 to explain the catalysis by thiols of the radical-chain decarbonylation of aldehydes, as reported by Waters and co-workers.[16] However, it was some 34 years before the generality of the principle of PRC was recognised and applied in a variety of situations.[7] Aside from applications to different types of reaction (*e.g.* catalytic epimerisation at selected chiral carbon centres in molecules that possess several such centres), future progress in this area is likely to focus on the development of new hydridic and protic catalysts H–Nuc and H–El, in which the strengths of the bonds to hydrogen are tailored to requirements, and the search for generally-applicable homochiral catalysts H–Nuc* and H–El* designed to give greater chiral discrimination in enantioselective hydrogen-atom transfer.

7 Acknowledgements

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