Radical-chain reductive carboxyalkylation of electron-rich alkenes: carbon–carbon bond formation mediated by silanes in the presence of thiols as polarity-reversal catalysts

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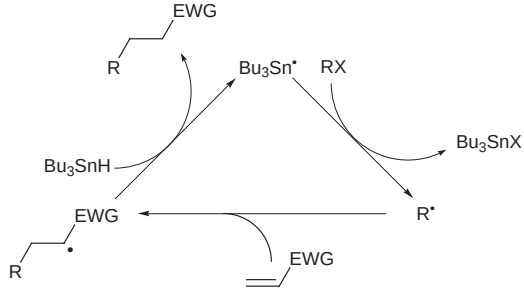
The reductive carboxyalkylation of electron-rich alkenes by α-halogenoesters in the presence of triphenylsilane under free-radical conditions is catalysed by thiols: prochiral alkenes give optically-active adducts when the thiol catalyst is homochiral.

The reductive alkylation of electron-poor alkenes, using alkyl halides or psuedohalides in the presence of tributyltin hydride, is a radical-chain reaction of considerable importance for intermolecular C–C bond formation.[1] The propagation stage of this process, which is sometimes referred to as the 'tin method' or the 'Giese reaction', is illustrated in Scheme 1.



Scheme 1

This reaction suffers from certain limitations, notably the use of toxic organotin compounds and the need to keep the tin hydride concentration low in order to avoid trapping the radical R• to form RH before it has time to add to the alkene. The latter problem is more severe when the alkene is electron-rich, because simple alkyl radicals are nucleophilic, and the reaction is not then a practical method for C–C bond formation. Trialkylgermanes[2] and tris(trimethylsilyl)silane[3] have been employed in place of the tin hydride as they are less toxic and also less efficient hydrogen-atom donors. There are also a few examples of the successful use of α-halogenoesters, which yield relatively electrophilic α-alkoxycarbonylalkyl radicals, in conjunction with tributyltin hydride to bring about reductive alkylation of electron-rich alkenes.[4]

We have reported that the principle of polarity-reversal catalysis,[5] in this instance by thiols, may be applied to promote the overall abstraction of electron-rich hydrogen by nucleophilic alkyl radicals from silicon in simple triorganosilanes, through the catalytic cycle of reactions (1) and (2), and we have described how this silane–thiol couple can serve as an effective replacement for trialkyltin hydrides in many radical-chain processes.[6]

$$R^{\bullet} + XSH \rightarrow RH + XS^{\bullet} \quad (1)$$

$$XS^{\bullet} + R_3SiH \rightarrow XSH + R_3Si^{\bullet} \quad (2)$$

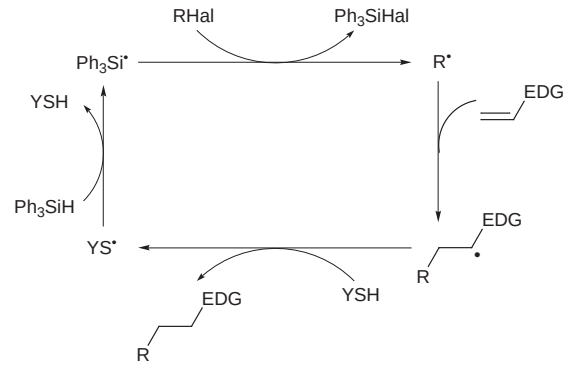
$$Bu^tON{=}NOBu^t \rightarrow 2Bu^tO^{\bullet} + N_2 \quad (3)$$

The SH group of a thiol provides electron-deficient hydrogen, which favours hydrogen-atom transfer to the nucleophilic alkyl radicals that are formed by addition to electron-rich alkenes, while polar effects will discriminate against the abstraction of hydrogen from thiols by electrophilic radicals.[7] With these considerations in mind, we reasoned that reductive alkylation of electron-rich alkenes, mediated by the silane–thiol couple, could be a viable method for C–C bond formation when the alkyl halide provides an electrophilic alkyl radical. In this communication we report the translation of these ideas into practice, along with the results of preliminary attempts to develop asymmetric syntheses based on this new methodology.

Table 1 Reductive carboxyalkylation of alkenes using organic halides in the presence of triphenylsilane, catalysed by thiol and initiated by TBHN in dioxane at 60 °C

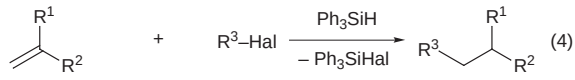
Entry	Alkene	R³Hal	Thiol	Adduct	Adduct yield (%)[a]
1	**1a**	**2a**	MTG	**3aa**	78
2	**1a**	**2a**	TPST	**3aa**	88[b]
3	**1a**	**2b**	MTG	**3ab**	75
4	**1a**	**2b**	TPST	**3ab**	72
5	**1a**	**2c**	TPST	**3ac**	78
6	**1b**	**2a**	TPST	**3ba**	86
7	**1b**	**2b**	TPST	**3bb**	75
8	**1c**	**2a**	TPST	**3ca**	85
9	**1d**	**2a**	TPST	**3da**	78
10	**1e**	**2a**	TPST	**3ea**	60
11	**1f**	**2a**	TPST	**3fa**	63
12	**5**	**2a**	TPST	**6**	76
13	**7**	**2a**	TPST	**8**	63[b]
14	**7**	**2a**	**10**	**8**	63 (24% ee)[c]
15	**7**	**2a**	**11**	**8**	64 (27% ee)[c]
16	**7**	**2b**	**10**	**9**	72 (19% ee)[d,e]

[a] Isolated yields based on alkene; satisfactory spectroscopic and analytical data were obtained for all new compounds. [b] The yield was similar in benzene solvent. Only a trace of adduct was formed in the absence of thiol. [c] The ee was determined by chiral-stationary-phase HPLC analysis (Chiralcel-OD column, eluent: hexane–isopropyl alcohol 99 : 1); the enantiomer in excess was eluted second. [d] The ee was determined by ^{1}H NMR analysis using a homochiral shift reagent [Eu(hfc)$_3$]. [e] The ee was the same when **11** was used as catalyst.



Scheme 2

All reactions were carried out at 60 °C and were initiated by thermal decomposition of di-*tert*-butyl hyponitrite (TBHN, $t_{\frac{1}{2}}$ = *ca.* 55 min),[8] which produces *tert*-butoxyl radicals [eqn. (3)] that go on to abstract hydrogen from the silane and/or the thiol to afford chain-carrying silyl or thiyl radicals. When a dioxane solution containing isopropenyl acetate **1a** (2.50 mmol), triphenylsilane (3.25 mmol), dimethyl chloromalonate **2a** (3.75 mmol) and TBHN (0.125 mmol) was heated under argon for 2 h, examination of the reaction mixture by ^{1}H NMR spectroscopy showed that < 1% of the adduct **3aa**‡ had been formed. However, when the experiment was repeated in the presence of methyl thioglycolate (MeO_2CCH_2SH, MTG, 0.125 mmol, 5 mol% based on alkene) under otherwise identical conditions, the adduct **3aa** was isolated in 78% yield. A somewhat higher yield was obtained in the presence of triphenylsilanethiol (TPST, 5 mol%) as catalyst (Table 1, entries 1 and 2). The reductive carboxyalkylation of **1a** [eqn. (4)] evidently proceeds



(4)

1a R^1 = OAc, R^2 = Me
b R^1 = OAc, R^2 = Bu^t
c R^1 = $OSiMe_2Bu^t$, R^2 = Me
d R^1 = OBu, R^2 = H
e R^1 = Pentyl, R^2 = Me
f R^1 = CH_2OAc, R^2 = Me

2a $(MeO_2C)_2CH$–Cl
b MeO_2CCH_2–Br
c $(EtO_2C)_2CMe$–Br

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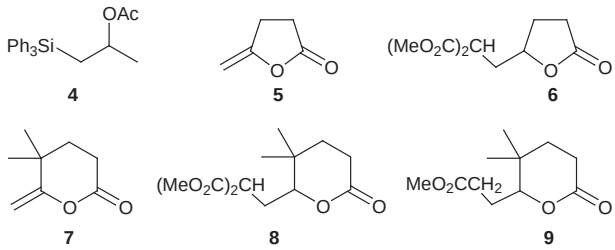
by a radical-chain mechanism, the propagation stage of which is shown in Scheme 2. A similarly high yield of the adduct **3ab** was obtained when dimethyl chloromalonate was replaced with methyl bromoacetate **2b** in the presence of either MTG or TPST (entries 3 and 4), but with methyl chloroacetate under the same conditions the yield of **3ab** was reduced to 40% and a large amount (50%) of the adduct **4** was also isolated. Evidently, the

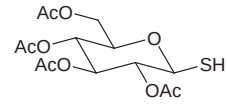


4 **5** **6** **7** **8** **9**

triphenylsilyl radical adds to the C=C bond[6d,e] in **1a** at about the same rate as it abstracts halogen from the chloroacetate, while with the more reactive bromoacetate halogen-atom abstraction is much faster than addition to the alkene. A good yield of the adduct **3ac** was obtained from the reductive carboxyalkylation of isopropenyl acetate with diethyl 2-bromo-2-methylmalonate (entry 5).§

Similar addition reactions were carried out with the alkenes **1b**–**f** and the results are summarised in Table 1:¶ essentially no adduct formation occurred in the absence of thiol catalyst. The methylenelactones **5** and **7** also functioned well as acceptors (entries 12 and 13).‖

The stereogenic centres in the adducts **8** and **9** are formed when the prochiral chain-carrying radicals, produced by addition to these alkenes, abstract hydrogen from the thiol catalyst (Scheme 2). If the thiol is homochiral then the hydrogen-atom transfer will be enantioselective and optically-active adducts should result. Reductive carboxyalkylation of the methylenelactone **7** using the carbohydrate-derived thiols **10** and **11** as catalysts gave the adducts **8** and **9** with an enantiomeric excess (ee) up to 27% (entries 14–16).** Although the optical purities obtained so far are low, the results



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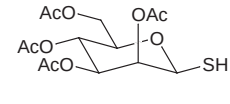

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are encouraging because the transfer of chirality is catalytic and the reactions are carried out at relatively high temperatures. Efforts to design more effective homochiral thiol catalysts are underway.

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Notes and References

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‡ The adduct **3aa** arises from **1a** and **2a**, the adduct **3ab** arises from **1a** and **2b** and so on.

§ Triphenylbromosilane is formed in reactions involving bromides. This bromosilane is a Lewis acid and is also very sensitive to hydrolysis, so that care must be taken if the reactants or adduct are sensitive to acid.

¶ No adducts could be obtained from the enol acetate $PhC(OAc)=CH_2$. It is likely that the oxygen-conjugated benzylic radicals formed by addition to this alkene do not abstract hydrogen from the thiol catalyst at a sufficient rate to maintain a chain reaction.

‖ *Typical procedure*. A solution in dry dioxane (4 cm^3) containing isopropenyl acetate **1a** (0.250 g, 2.50 mmol), triphenylsilane (0.846 g, 3.25 mmol), dimethyl chloromalonate (0.625 g, 3.75 mmol), TBHN (22 mg) and triphenylsilanethiol (37 mg) was stirred and heated at 60 °C under an atmosphere of dry argon for 2 h. The solvent was removed by evaporation under reduced pressure, the residue was dissolved in Et_2O (10 cm^3) and the solution was washed with 5% aqueous $NaHCO_3$, then with saturated brine and then dried ($MgSO_4$). After evaporation of the ether, light petroleum (bp 40–60 °C) (5 cm^3) was added and the slurry was filtered to remove most of the triphenylsilanol, which was washed on the sinter with a little petroleum. After evaporation of the solvent from the filtrate, the residue was purified by flash-chromatography (eluent: petroleum–Et_2O 95 : 5 to 5 : 1) to give the adduct **3aa** as a clear oil (0.511 g, 88%). δ_H 1.24 (3 H, d, *J* 6.2, Me), 2.00 (3 H, s, Ac), 2.35 (2 H, m, C*H*$_2$CH), 3.46 [1 H, dd, *J* 8.6 and 6.1 $(MeO_2C)_2$C*H*], 3.72(7) (3 H, s, OMe^A), 3.73(2) (3 H, s, OMe^B), 4.89 (1 H, m, C*H*OAc); δ_C 20.1, 21.1, 34.7, 48.4, 52.7 (2C), 68.7, 169.3, 169.5, 170.4.

** Enantioselective reductive carboxylkylation of **7** could also be mediated by tributyltin hydride. When triphenylsilane was replaced by tin hydride (1.3 equiv.), added slowly during 2 h as a dioxane solution also containing TBHN, but otherwise essentially under the conditions of entry 14, the adduct **8** was isolated in 80% yield and showed an ee of 25%. This result also demonstrates that thiols can act as polarity-reversal catalysts for the abstraction of hydrogen from tin hydrides by alkyl radicals.

1 B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, 1986; W. B. Motherwell and D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, 1992.
2 P. Pike, S. Hershberger and J. Hershberger, *Tetrahedron Lett.*, 1985, **26**, 6289.
3 B. Giese, B. Kopping and C. Chatgilialoglu, *Tetrahedron Lett.*, 1989, **30**, 681.
4 B. Giese, H. Horler and M. Leising, *Chem. Ber.*, 1986, **119**, 444; T. F. Herpin, W. B. Motherwell and M. J. Tozer, *Tetrahedron: Asymmetry*, 1994, **5**, 2269.
5 V. Paul and B. P. Roberts, *J. Chem. Soc., Chem. Commun.*, 1987, 1322; V. Paul and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1183; H.-S. Dang and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1993, 891.
6 (*a*) R. P. Allen, B. P. Roberts and C. R. Willis, *J. Chem. Soc., Chem. Commun.*, 1989, 1387; (*b*) J. N. Kirwan, B. P. Roberts and C. R. Willis, *Tetrahedron Lett.*, 1990, **31**, 5093; (*c*) S. J. Cole, J. N. Kirwan, B. P. Roberts and C. R. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1991, 103; (*d*) H.-S. Dang and B. P. Roberts, *Tetrahedron Lett.*, 1995, **36**, 2875; (*e*) M. B. Haque and B. P. Roberts, *Tetrahedron Lett.*, 1996, **37**, 9123; (*f*) H.-S. Dang and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1998, 67.
7 B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2155; B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2719.
8 H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 1966, 6163; G. D. Mendenhall, *Tetrahedron Lett.*, 1983, **24**, 451.

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