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Carbon–carbon bond formation by radical addition–fragmentation reactions of *O-tert*-alkyl enols and *O*-cyclopropylcarbinyl enols

Yudong Cai and Brian P. Roberts*

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

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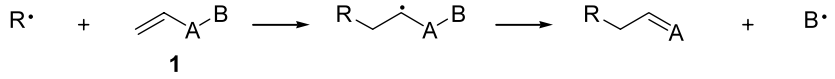
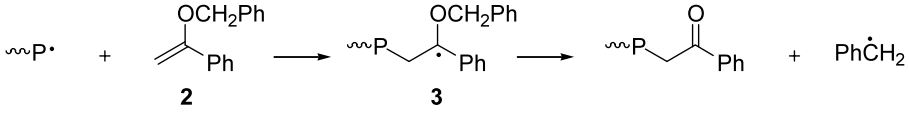
Abstract—Terminal alkenes of the type $H_2C{=}C(OR^1)X$, in which R^1 is a tertiary alkyl or a 1-cyclopropylethyl group and X = Ph, $OSiMe_2Bu^t$, OEt or H, undergo radical-chain reactions with organic halides R^2Hal to give carbonyl compounds $R^2CH_2C(=O)X$.

The addition–fragmentation sequence generalised in Scheme 1 is of central importance in several radical-based methods for the construction of carbon–carbon bonds.[1,2] For example, allylation can be achieved using allylstannanes or allylic sulfides as the radical acceptor **1**. Compounds of the type **1** have also found extensive use as addition–fragmentation chain-transfer agents (AFCTAs) in the radical polymerisation of vinylic monomers, where they provide an effective tool for controlling the molar mass of the polymer produced, as well as for introducing functional end groups.[3] Meijs, Rizzardo and co-workers[4] have described the use of *O*-benzyl enols, including α-benzyloxystyrene **2**, as AFCTAs for the preparation of low molecular weight polystyrene and poly(methyl methacrylate), when β-scission of an intermediate benzyloxyalkyl radical **3** terminates one polymer chain and provides a benzyl radical to seed the growth of another (Scheme 2).

The thermal rearrangement of an α-alkoxystyrene **4** to give an α-alkylated acetophenone **5**, which involves a formal 1,3-shift of the *O*-alkyl group, was first described by Claisen in 1896.[5] The mechanism was investigated in the 1950s by Wiberg and co-workers[6] who concluded that a radical-chain pathway is followed, by way of the addition–fragmentation cycle shown in Scheme 3. Although the potential of this type of reaction as a synthetic tool for the construction of carbon–carbon bonds was explicitly recognised some time ago,[7] it has received little attention outside the area of polymer chemistry. Our own interest in the β-scission of α-alkoxyalkyl radicals, both with regard to mechanistic studies[8] and applications in synthesis,[9] encouraged us to explore the use of *O*-alkylated enols of the type **6** for carbon–carbon bond formation by the radical addition–fragmentation mechanism set out in Scheme 4. However, while this work was in progress, a



Scheme 1.



Scheme 2.

Keywords: radicals and radical reactions; alkylation; addition reactions; fragmentation reactions.
* Corresponding author.

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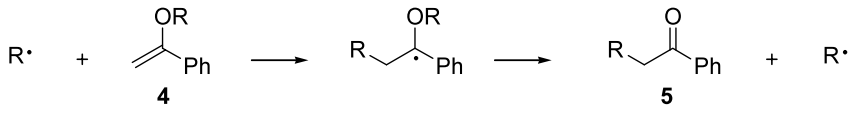
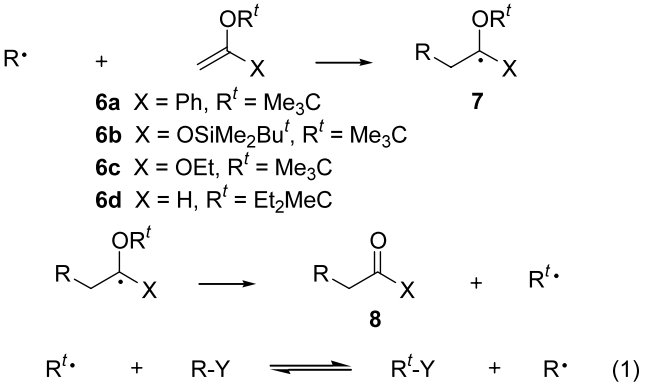


Scheme 3.

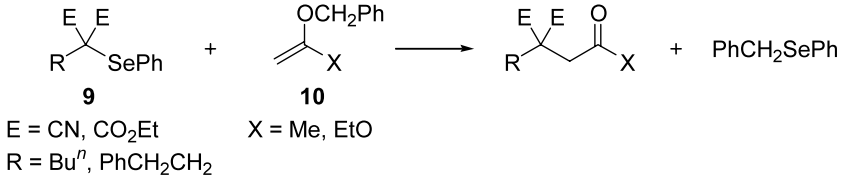
report by Roepel[10] appeared describing the radical reactions of α-phenylselenyl-malononitriles or -malonic esters **9** with the *O*-benzyl enols **10** according to Scheme 5. Prompted by this disclosure, we now present a preliminary account of our studies of the reactions of halogen-atom donors with the *O*-*tert*-alkyl enols **6a–d** to give carbonyl compounds of the type **8** (Scheme 4, Y = Br or I).

Our initial choice of an *O*-*tert*-alkyl substituent for **6** was guided by two considerations. First, previous kinetic studies of the β-scission of cyclic and acyclic *tert*-alkoxyalkyl radicals have shown that such species undergo relatively rapid C–O cleavage to give *tert*-alkyl radicals,[8] in accord with the ease with which tertiary alcohols can be deoxygenated by making use of this process.[9] Second, although the C–H bond strength decreases appreciably along the series Me–H<1°-R–H< 2°-R–H<3°-R–H, the corresponding bonds to more electronegative elements, including bromine and iodine, vary much less in strength.[8c,11] For example, the C–I bond dissociation enthalpies for Me–I, Et–I, Pr^i–I and Bu^t–I are reported to be 239, 236, 234 and 231 kJ mol^{-1}, respectively; for comparison DH(PhCH$_2$–I) is significantly smaller at 215 kJ mol^{-1}.[12] Thus, not only should an adduct radical of the type **7** undergo relatively rapid β-scission to give the tertiary alkyl radical R^t•, but the latter should (in contrast to a benzyl radical[10]) be fairly easily transformed into a new addendum radical, by transfer of an electronegative atom or group, as generalised by the equilibrium process shown in Eq. (1) of Scheme 4.



Scheme 4.

We directed our attention first to radical-chain reactions of α-*tert*-butoxystyrene[13] **6a**, which were expected to yield phenyl ketones of the type **11**. When α-*tert*-butoxystyrene was heated alone in refluxing benzene under argon, no change was detected by NMR spectroscopy after 3 h. However, in the presence of 5 mol% azobis(isobutyronitrile) (AIBN) or dilauroyl peroxide (DLP), similar treatment resulted in the complete conversion of **6a** to neopentyl phenyl ketone **11a**, which was isolated in ca. 95% yield.[14] When ethyl bromoacetate (3 equiv.) was present along with AIBN, NMR analysis after removal of the solvent showed complete conversion of **6a** to a mixture of ethyl 4-oxo-4-phenylbutanoate **11b** and **11a** in the ratio 70:30.[15] The *tert*-butyl radical resulting from the β-scission of **7** now abstracts bromine from BrCH$_2$CO$_2$Et in competition with its addition to the styrene **6a**. When the latter was added slowly by syringe pump to the bromoester and AIBN (10 mol%) in refluxing benzene, the product ratio **11b**:**11a** increased to 95:5. For all reactions in the presence of halogen-atom donors, a small amount of 2,4,6-collidine or 2,2,6,6-tetramethylpiperidine was also added as a sterically hindered base to suppress acid-catalysed elimination of alkene from (or adventitious hydrolysis of) the *O*-alkylated enols. Slow addition of **6a** was not necessary when the bromoacetate was replaced as halogen-atom donor by the much more reactive ethyl iodoacetate (2 equiv.) and **11b** was then produced in high yield without competitive formation of **11a**. Several similar reactions of α-*tert*-butoxystyrene **6a** and of the *O*-*tert*-alkyl enols **6b–d** with sources of relatively electrophilic carbon-radical addenda were carried out and the results are summarised in Table 1.[16] Although the silyl esters **12** could be isolated by careful chromatography on Florisil®, because of their sensitivity to hydrolysis it was usually more convenient to convert them first to alkyl esters.[18] For example, the mixed succinate ester **12a** was readily desilylated by DMF-catalysed reaction with oxalyl chloride and, without isolation, the resulting acid chloride was converted to diethyl succinate **13a** (83% from **6b**) by treatment with ethanol and pyridine.[18a] A similar radical-chain



Scheme 5.

11a R = Me_3C
11b R = EtO_2CCH_2
11c R = EtO_2CMe_2
11d R = $(EtO_2C)_2CH$
11e R = $(EtO_2C)_2CMe$

12a R = EtO_2CCH_2
12b R = $(EtO_2C)_2CMe$

13a R = EtO_2CCH_2
13b R = $(EtO_2)_2CMe$

14a R = EtO_2CCH_2
14b R = $(EtO_2)_2CMe$

Table 1. Addition–fragmentation reactions of *O*-*tert*-alkyl enols in refluxing benzene or cyclohexane[a]

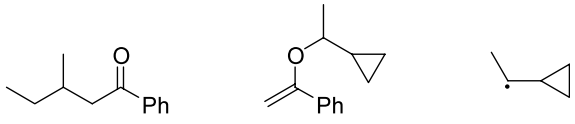
Entry	Radical acceptor $H_2C{=}C(OR^t)X$	Halogen-atom donor R–Y (equiv.)	Conditions[b,c]	Product(s)[d]	Isolated yield (%)
1	**6a**	$BrCH_2CO_2Et$ (3)	AIBN,[e] Ben, SP	**11b**+**11a** (95:5)	85 (**11b**)
2	**6a**	ICH_2CO_2Et (2)	AIBN, Ben	**11b**	82
3	**6a**	$BrCMe_2CO_2Et$ (3)	AIBN, Ben	**11c**	85
4	**6a**	$BrCH(CO_2Et)_2$ (2)	AIBN, Ben	**11d**	84
5	**6a**	$BrCMe(CO_2Et)_2$ (2)	AIBN, Ben	**11e**	91
6	**6b**	$BrCH_2CO_2Et$ (2)	DLP, Cyc	**12a**	83[f]
7	**6b**	$BrCMe(CO_2Et)_2$ (1.2)	DLP, Cyc	**12b**	73[f]
8	**6c**	$BrCH_2CO_2Et$ (1.2)	DLP, Cyc	**13a**	64
9	**6c**	$BrCMe(CO_2Et)_2$ (1.2)	DLP, Cyc	**13b**	52
10	**6d**	$BrCH_2CO_2Et$ (0.5)	DLP, Cyc	**14a**	30[g]
11	**6d**	$BrCMe(CO_2Et)_2$ (0.5)	DLP, Cyc	**14b**	50[g]

[a] Internal temperature ca. 85°C; total reaction time generally 3 h.
[b] Unless stated otherwise, 5 mol% of initiator (based on acceptor) was used; 2,4,6-collidine (10 mol%) was present in each case.
[c] Ben = benzene solvent, Cyc = cyclohexane solvent; SP = slow addition of the acceptor during the first 1.5 h using a syringe pump.
[d] Product ratio estimated by ^1H NMR spectroscopy.
[e] 10 Mol% initiator present.
[f] Isolated as the all-ethyl esters (see text).
[g] Conversion of bromide estimated by ^1H NMR spectroscopy.

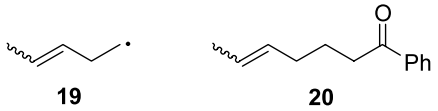
reaction of *O*-*tert*-butyl *O*-ethyl ketene acetal **6c** with ethyl bromoacetate yielded diethyl succinate directly (64%), but the greater acid sensitivity of **6c** compared with **6b** often proved to be a disadvantage.

According to Roepel,[10] the chemistry shown in Scheme 5 was not successful for the production of aldehydes from benzyl vinyl ether (X = H). Therefore, it is noteworthy that the aldehydes **14a** and **b** could be obtained from reactions of *O*-3-methyl-3-pentyl vinyl ether **6d** (entries 10 and 11),[19] albeit so far in relatively low yield.

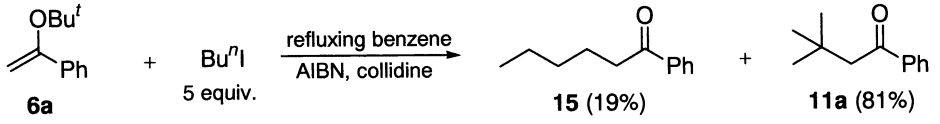
Phenyl ketones derived from reactions of **6a** with sources of nucleophilic radical addenda proved more difficult to obtain in preference to the styrene-rearrangement product **11a**. Thus, treatment of **6a** with *n*-butyl iodide (5 equiv.) in refluxing benzene, containing AIBN (5 mol%) and collidine (10 mol%), resulted in its complete conversion to a 19:81 mixture of ketones **15** and **11a** after 3 h (Scheme 6). Evidently here the *tert*-butyl radical is being trapped by **6a** in preference to the primary *n*-butyl radical. Slow addition of **6a** using a syringe pump raised the proportion of **15** to 34%, but it appears that the equilibrium (1) in Scheme 4 lies impractically far to the left in this case. Replacing the *n*-butyl iodide with *s*-butyl iodide (3 equiv.), with all the reagents present initially, improved the situation such that the product ketone ratio **16**:**11a** was 35:65. In refluxing octane solvent, in the presence of 2,2,6,6-tetramethylpiperidine (TMP; 20 mol%) and using di-*tert*-pentyl peroxide (DTPP; 30 mol%) as initiator, the ratio **16**:**11a** could be raised to 52:48.



16 **17** **18**



19 **20**



6a + Bu^nI (5 equiv.) → refluxing benzene, AIBN, collidine → **15** (19%) + **11a** (81%)

Scheme 6.

Attachment of a cyclopropyl group at an alkyl-radical centre leads to some stabilising delocalisation of the unpaired electron[12,20] and would also be expected to increase the nucleophilicity (reduce the ionisation energy) of the radical, compared with an acyclic alkyl substituent, suggesting that a secondary cyclopropylcarbinyl radical will behave in many respects like a simple tertiary alkyl radical. Therefore, we reasoned that radical adducts of the *O*-cyclopropylcarbinyl enol **17** should undergo β-scission with similar facility to the acyclic *tert*-alkoxyalkyl radical analogues **7**, to give the 1-cyclopropylethyl radical **18** that will undergo rapid ring opening to give the *primary* homoallylic radical **19**.[21] The latter should then abstract iodine more efficiently than the *tert*-butyl radical in an exchange process of the type shown Eq. (1) of Scheme 4.

We were pleased to find that when **17** was treated with *n*-butyl iodide (5 equiv.), DTPP (30 mol%) and TMP (20 mol%) in refluxing octane, with all reagents present initially, the enol ether was completely converted to mainly the *n*-butyl adduct **15** (85%) along with 15% of the ketone **20**. A similar reaction using *s*-butyl iodide (3 equiv.) afforded the ketone **16** containing only 4% of **20**.

We conclude that *O*-*tert*-alkyl and *O*-cyclopropylcarbinyl enols offer considerable promise for the formation of carbon–carbon bonds under tin-free conditions.[22] Synthetic and kinetic (radical-clock) studies using these compounds are on-going and will be reported in a full paper.

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14. Under the same conditions, the *O*-benzyl analogue, α-benzyloxystyrene **2**, rearranged only partially (40%) to $PhCH_2CH_2C(O)Ph$.
15. Under the same conditions, α-benzyloxystyrene afforded only $PhCH_2CH_2C(O)Ph$ (38%) and no **11b**.
16. *Representative procedure*: Diethyl bromomalonate (0.956 g, 4.0 mmol), α-*tert*-butoxystyrene **6a** (0.352 g, 2.0 mmol), AIBN (16.4 mg, 0.10 mmol), 2,4,6-collidine (26.4 μl, 0.20 mmol) and dry benzene (4 mL) were added to a dry, argon-filled flask, containing a magnetic stirrer bar and equipped with a condenser. The flask was then immersed in an oil bath, pre-heated to 90°C, and the reaction mixture was stirred at reflux under argon for 3 h. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography on silica gel, using petroleum (bp 40–60°C)-diethyl ether (4:1 v/v) as eluent, to give diethyl phenacylmalonate[17] **11d** (0.466 g, 84%) as a colourless oil. NMR (500 MHz for ^1H, 125.7 MHz for ^{13}C; $CDCl_3$ solvent, *J* in Hz): δ_H 1.29 (6H, t, *J* 7.1, Me), 3.62 (2H, d, *J* 7.1, CH_2COPh), 4.06 (1H, t, *J* 7.1, CH), 4.23 (4H, m, CH_2Me), 7.46–8.00 (5H, m, Ph); δ_C 14.0, 37.8, 47.2, 61.7, 128.1, 128.6, 133.5, 136.0, 169.0, 196.5. Found: C, 64.9; H, 6.4. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%. Satisfactory spectroscopic and analytical data were obtained for all new compounds described herein.
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