Radical Reactions

DOI: 10.1002/anie.200601567

Radical Additions of Xanthates to Vinyl Epoxides and Related Derivatives: A Powerful Tool for the Modular Creation of Quaternary Centers**

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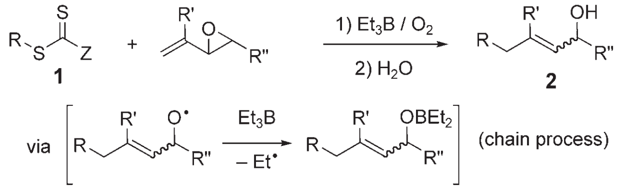
Over the past ten years, we have developed a new radical chain process based on the degenerative exchange of a thiocarbonyl thio group (Z-C(=S)S-), and especially of xanthates (or dithiocarbonates, **1**).[1] This chemistry has provided a simple, efficient, and reasonably general solution to a longstanding problem in organic synthesis, namely the intermolecular creation of carbon–carbon bonds on nonactivated alkenes. This degenerative exchange also constitutes the basis of the extremely powerful reversible addition fragmentation chain transfer/macromolecular design through interchange of xanthates (RAFT/MADIX) technology for the synthesis of block polymers.[2]

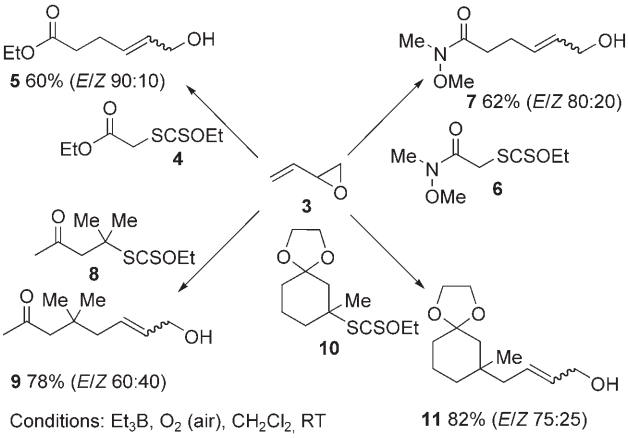
We have mainly used peroxides to initiate the radical addition, although irradiation with a tungsten halogen lamp was used when lower reaction temperatures were desired. The autooxidation of boranes, first reported by Brown and Midland,[3] and ingeniously exploited as a reaction initiating system by Oshima and co-workers,[4a,b] also proved to be quite efficient with xanthates, thereby allowing reactions to be performed at room temperature or below.[5,6] We have now found that the application of organoboranes to mediate the xanthate transfer is in fact far more powerful than initially anticipated. In particular, additions to vinyl epoxides and related derivatives have proved especially useful.

As outlined in Scheme 1, the addition of a radical $R^{\bullet}$ derived from the xanthate **1** to the vinyl epoxide leads to opening of the epoxide ring and the formation of an alkoxy radical. The latter is rapidly intercepted by triethylborane to give a borinate and an ethyl radical, which propagates the chain reaction by reacting with the starting xanthate. Xanthates are highly radicophilic and a chain process can be readily sustained. As for the borinate intermediate, it is hydrolyzed on aqueous workup to afford the allylic alcohol **2**. Overall, combining the efficacious xanthate-transfer process with the use of triethylborane as both an initiator and controlling agent for quenching the highly reactive alkoxy radical results in a powerful C–C bond-forming process that is especially effective for the creation of quaternary centers.



Scheme 1. Triethylborane-mediated radical addition of a xanthate to a vinyl epoxide.

Preliminary examples of this approach are shown in Scheme 2. Thus, exposure of the commercially available butadiene monoepoxide (**3**) and xanthate **4** to triethylborane and air gave rise to the corresponding allylic alcohol **5** in 60 % yield (Scheme 2). This transformation parallels the ones reported by Brown and co-workers,[7] and later by the research groups of Oshima,[8] Roberts,[9a] and Kim.[9b] However, these pioneering studies were of rather limited synthetic scope because of severe constraints in the choice of substrates. Xanthates, in contrast, do not suffer from such limitations, as demonstrated by the other examples shown in Scheme 2. For example, reaction of xanthate **6** directly furnished the Weinreb amide **7** (in similar yield to that of the reaction that gave **5**), whereas the formation of allylic alcohols **9** and **11**, both containing a newly created quaternary center, proved to be even more efficient.



Scheme 2. Addition of various xanthates to butadiene monoepoxide.

The vinyl epoxide can be varied substantially, thus allowing the synthesis of more complex structures. Three such examples are shown in Scheme 3, in which xanthate **13**, a compound readily available by Michael addition of potassium *O*-ethyl xanthate to the cyclobutenone **12**[10] under acidic conditions, is used as the starting material.[11] The radical addition to epoxides **3**, **14**, and **15** provided the corresponding functionalized cyclobutanones **16**, **17**, and **18** in good yield, each containing a new quaternary center.

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[**] N.C. thanks the Ministère de l'Education Nationale, de la Recherche et de la Technologie (France) for a fellowship.

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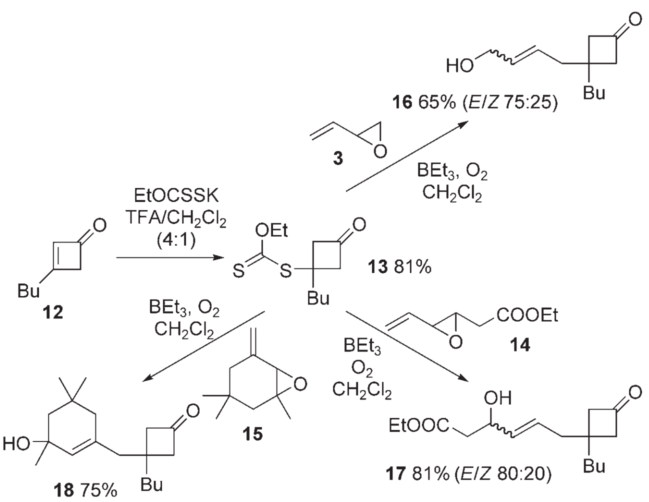
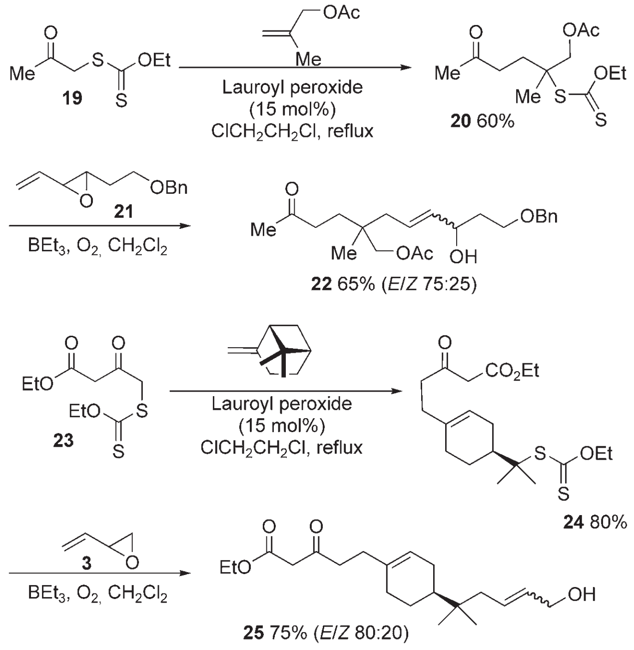


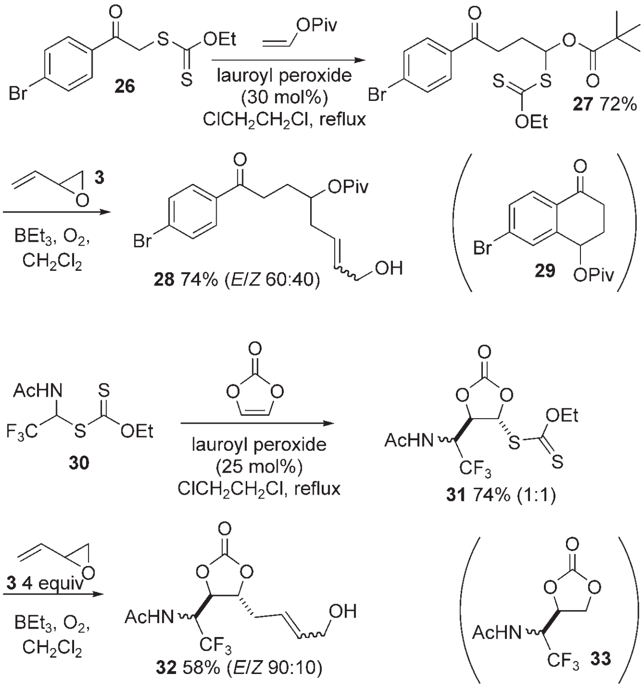
Scheme 3. Addition of a cyclobutanone xanthate to vinyl epoxides. TFA = trifluoroacetic acid.

The rapid assembly of intricate architectures can also be made by using a modular approach that depends on the unique ability of xanthates to add across non-activated olefins. This strategy is illustrated by the two sequences in Scheme 4. Thus, addition of xanthate **19** derived from chloroacetone to methallyl acetate gave adduct **20** in 60 % yield. Triethylborane-mediated addition to the functionalized vinyl epoxide **21** gave triol **22**, in which two of the alcohol groups are differentially protected. The xanthate entity has thus served to create two carbon–carbon bonds and at the same time to generate a quaternary center. Overall, the synthesis of triol **22** required just two steps from simple substrates. The second transformation leading to optically pure **25** incorporates a fragmentation of the cyclobutane ring of (−)-β-pinene. It was notable that the first addition of the ketoester xanthate **23** leading to the cyclohexene **24** occurs smoothly at the carbon atom bearing the least acidic hydrogen atoms. The ketoester motif in the final product **25** can be used for further manipulation.



Scheme 4. Creation of quaternary centers by a modular approach. Bn = benzyl.

This modular approach is not limited to the formation of quaternary centers; for example, it could be applied to alkenes bearing an ester or a carbonate as shown by the two transformations in Scheme 5. Radical addition of phenacyl xanthate **26** to vinyl pivalate furnished adduct **27** in high yield, and exposure of the latter to vinyl epoxide **3** in the presence of triethylborane and air resulted in the clean formation of allylic alcohol **28**. Interestingly, no tetralone **29** was observed, indicating that the intermolecular addition of the intermediate radical to the vinyl epoxide **3** is faster than the intramolecular ring closure onto the aromatic nucleus, despite the modest radicophilicity of the non-activated vinyl group. We had previously reported that tetralones can be readily obtained by treatment of xanthates such as **27** with peroxide.[12] There is thus a considerable degree of flexibility in the way xanthates may be employed.

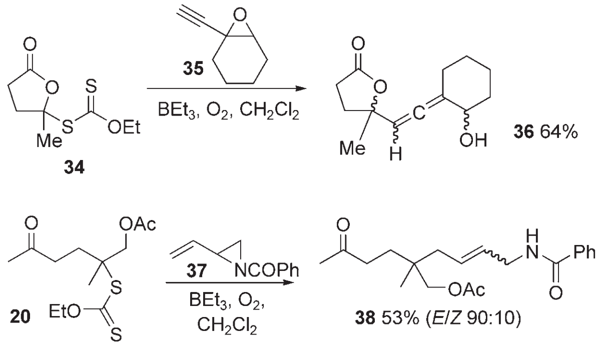


Scheme 5. Further modular assembly of complex structures. Piv = pivaloyl.

A more significant competition between the intermolecular addition process and intramolecular ring closure was observed with adduct **31**, derived from the addition of xanthate **30** to vinylidene carbonate.[13] The mixture of the two diastereoisomers of adduct **31** could be separated, but the subsequent triethylborane-mediated allylation of one of the two epimers to afford **32** occurred in only moderate yield

(40 %; *E*/*Z* 80:20), because of a competing hydrogen abstraction from the solvent to give **33** as the main side product. The reaction was repeated on the other epimer, but with the amount of vinyl epoxide increased to four equivalents and with the solvent 1,2-dichloroethane replaced by chloroform. The yield of **32** could thereby be improved to 58 %. Interestingly, there was also a slight change in the ratio of the geometrical isomers (*E*/*Z* 90:10, Scheme 5).

By analogy with earlier studies by Brown and co-workers in which the addition of ethyl and cyclopentyl radicals (generated from the corresponding boranes) to alkynes was described,[14] we attempted a similar transformation involving the highly functionalized xanthate **34** derived from levulinic acid (Scheme 6).[15] The reaction with alkyne epoxide **35** was somewhat sluggish, although clean and gave rise to the unusual allene **36**, which was isolated as a mixture of diastereoisomers. We also found it was possible to replace the epoxide by an aziridine ring (Scheme 6). The reaction of adduct **20** with aziridine **37** was also slow, but furnished **38** in useful yield (53 %). As far as we are aware, vinylic aziridines have not hitherto been used in this manner.



Scheme 6. Additions to an alkyne epoxide and to a vinyl aziridine.

It is clear from this preliminary study that the triethylborane-mediated radical reaction of xanthates with vinyl epoxides and vinyl aziridines represents a very powerful tool for the formation of carbon–carbon bonds under mild conditions. The approach is flexible, convergent, very easy to implement experimentally, and involves readily available starting materials and reagents. It is also worth noting that nonracemic products could be prepared by starting with optically pure vinyl epoxides, obtained for example by the kinetic resolution procedure developed by Jacobsen and co-workers.[16]

Experimental Section

Typical procedure for the radical addition on vinyl epoxides and aziridine: Triethylborane (1.0 M solution in hexane, 2 equiv) was added every 30 minutes over two hours to a stirred solution of the xanthate (1 equiv) and vinyl epoxide (2 equiv) in CH_2Cl_2 (1 mL mmol^{-1}) under nitrogen at room temperature. During the addition, the syringe needle was lowered into the solution. Furthermore, a small volume of air (about a quarter of the volume of the borane solution) was introduced by syringe following each addition of triethylborane. After stirring the reaction mixture overnight, the mixture was diluted with CH_2Cl_2 and then washed once with water and once with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel to give the desired products.

Received: April 20, 2006
Revised: August 5, 2006
Published online: September 14, 2006

Keywords: allylation · allylic alcohols · radical reactions · vinyl epoxides · xanthates

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