

# Preparation of Five-Membered Rings via the Translocation–Cyclization of Vinyl Radicals

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**Abstract:** Vinyl radicals have a propensity to rearrange via intramolecular 1,5-hydrogen transfer to the more-stable alkyl radicals, which themselves possess a suitable structure to undergo rapid 5-*exo-trig* cyclizations. This tandem radical translocation–cyclization process represents a useful tool for the preparation of a wide range of five-membered rings. Moreover, this reaction is highly selective and, due to its radical nature, tolerates a variety of functional groups. During the last decade, tin-free procedures have emerged, rendering this process very attractive for the synthesis of natural products and their analogues. Selected examples of this strategy illustrating the scope of the method are described.

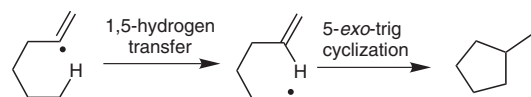
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**Key words:** radical reactions, cyclizations, hydrogen transfer, tin-free methods, stereoselectivity

## 1 Introduction

For a long time, hydrogen transfer was considered a side reaction in radical processes. However, it was soon realized that the intramolecular hydrogen transfers could be exploited for synthetic purposes, such as the functionalization of a remote position considered unreactive under classical reaction conditions.<sup>1</sup> Heiba and Dessau reported the first example of the translocation of a vinyl radical followed by a cyclization process nearly 40 years ago.<sup>2</sup> The synthetic utility of this process was only later demonstrated in 1988 when Parsons and co-workers<sup>3</sup> and, shortly af-

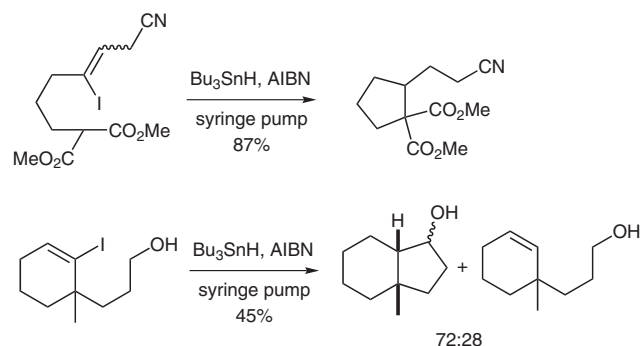
ter, Curran and co-workers<sup>4</sup> started to investigate this procedure. The crucial contribution of Curran and co-workers, who reported a systematic investigation of intramolecular hydrogen atom transfers starting from vinyl and aryl radicals, has generated strong interest among the community of synthetic organic chemists.<sup>4,5</sup> Nowadays, hydrogen transfers are a useful synthetic tool for achieving a surprisingly large range of transformations. In this short review article, we will focus on the remarkable translocation of vinyl radicals applied to the preparation of ring systems according to Scheme 1.



**Scheme 1** General scheme for the translocation–cyclization of vinyl radicals

## 2 Vinyl Radicals from Vinyl Halides

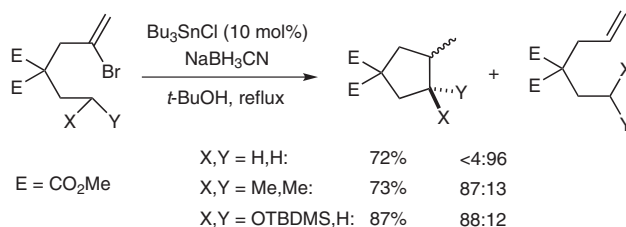
In 1988, Curran and co-workers reported a radical translocation–cyclization process starting from a vinyl halide. In this example, the vinyl radical underwent a 1,5-hydrogen atom transfer to generate an alkyl radical with an alkene aptly positioned for intramolecular radical cyclization. The reaction proved to be very efficient for a wide range of substrates leading to cyclopentane derivatives in moderate to high yields (e.g., Scheme 2).<sup>4,6</sup>



**Scheme 2** 1,5-Hydrogen transfers of vinyl radicals generated from vinyl halides

The ratio of the cyclized versus the reduced noncyclized compounds is influenced by the nature of the substituents. Slow addition techniques or the use of in-situ-generated tributyltin hydride (the Stork protocol) are employed to obtain good yields of the desired cyclization products (Scheme 3).<sup>5</sup> Experiments with deuterated tin hydride have demonstrated that the reduction occurs only at the vinyl radical stage. Under the optimized reaction conditions, the cyclization of the translocated radical is faster than its reduction by the tin hydride.

In their pioneering work in 1988, Parsons and co-workers reported an innovative method to prepare pyrrolizidine alkaloid precursors using a translocation–cyclization pro-



**Scheme 3** Substituent effects on the rate of the translocation process

cess (Scheme 4).<sup>3</sup> In this approach, a vinylic iodide is used to generate a stabilized allylic radical via a 1,5-hydrogen transfer. The tricyclic amine product was obtained in 85%

## Biographical Sketches



**Fabrice Dénès** was born in Paris, France, in 1975. After undergraduate study at the University Pierre et Marie Curie (Paris VI), he received his Ph.D. in 2002 for work under the supervision of Professors J.-F. Normant and F. Chemla on the development of a new access to 3-(methoxycarbonyl)pyrrolizidines using the intramolecular carbometalation of unactivated alkynes and al-

kenes with zinc enolates. From September 2002 to February 2005, he was a postdoctoral associate of Professor P. Renaud at the University of Berne, Switzerland. During this time, he worked on the development of novel tin-free methods to access polysubstituted cyclopentanes and pyrrolizidine and indolizidine derivatives using 1,5-hydrogen atom transfer. Since

2005, he has been a member of the group of Professor J. Lebreton and Dr. A. Guingant as a lecturer of organic chemistry at the University of Nantes, France. His research interests include the development of synthetic methods based on organometallic or radical reactions, as well as the synthesis of natural products and/or their analogues possessing biological activity.



**Florent Beaufils** was born in Audincourt, France, in 1976. After undergraduate study at the University of Dijon, he continued his education at the University of Berne, Switzerland, through his Ph.D. in 2004 under the supervision of Professor P. Renaud. During this time, he worked on the development of novel tin-free methods to access polysub-

stituted cyclopentanes and pyrrolizidine and indolizidine derivatives using 1,5-hydrogen atom transfer. In 2004, he was a postdoctoral associate of Professor A. Fürstner at the Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany. There, he was involved in the total synthesis of amphidinolide H and G. Since 2005, he has

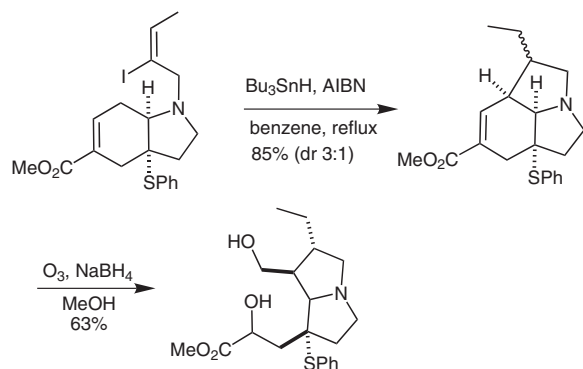
been the head of chemistry and quality control at Covalys Biosciences AG, Switzerland. His research interests focus on the development of novel technologies for protein labeling and immobilization, and the application of transition metal catalyzed methods in chemical biology and drug delivery.



**Philippe Renaud** was born in Neuchâtel, Switzerland, in 1959. After undergraduate study at the University of Neuchâtel, he continued his education at the ETH Zürich through his Ph.D. in 1986 under the supervision of Professor D. Seebach. In 1987, he was a postdoctoral associate of Professor M. A. Fox at the University of Texas at Austin, USA. He started an independent re-

search program in 1988 at the University of Lausanne, Switzerland. In 1992, he obtained the Alfred Werner Fellowship, which allowed him to continue his research work in Lausanne. He moved to the University of Fribourg in 1993 where he was an associate professor. Since 2001, he has been a professor of organic chemistry at the University of Berne. He has also been an

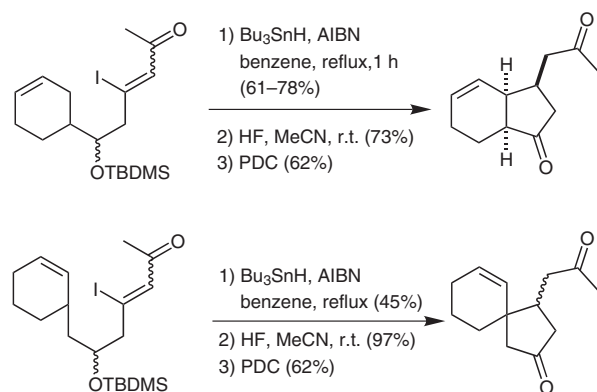
invited professor at the universities of Paris VI, Paris XI, Bordeaux, Melbourne, and Lyon. His research interests include the development of synthetic methods based on radical reactions, the use of Lewis acids for asymmetric reactions, and the synthesis of alkaloids and other biologically active compounds.



**Scheme 4** Radical translocation–cyclization involving an allylic radical intermediate

yield and was transformed into a substituted pyrrolizidine derivative by ozonolysis.

Shortly thereafter, Parsons and co-workers reported other 1,5-hydrogen transfers at allylic positions in the preparation of fused bicyclic and spirocyclic compounds (Scheme 5).<sup>3,7</sup>



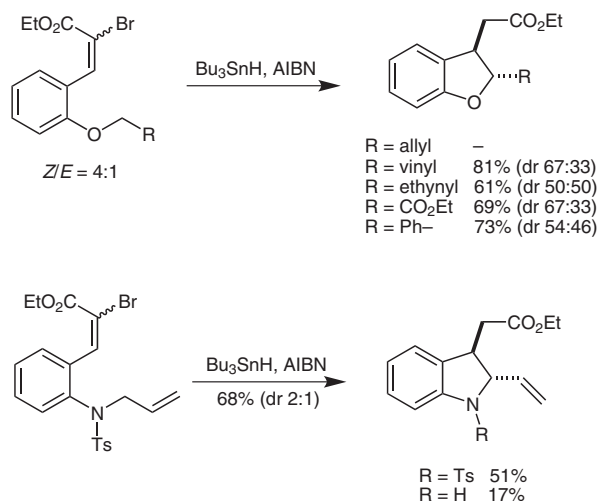
**Scheme 5** Radical translocation–cyclizations involving allylic radical intermediates

More recently, Reiser and co-workers reported the synthesis of 2,3-disubstituted dihydrobenzofurans and indoline derivatives via a cascade reaction involving an unusual 1,6-hydrogen atom transfer (Scheme 6).<sup>8</sup>

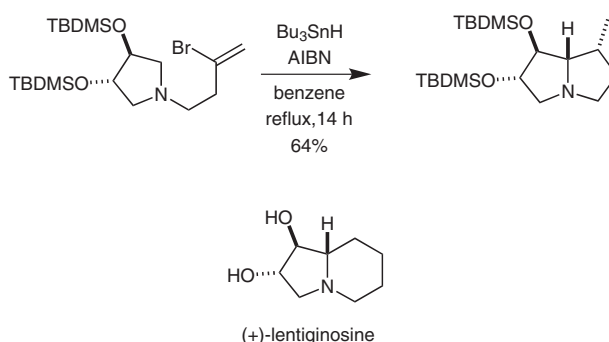
The translocation–cyclization reaction was also implemented by Robertson and co-workers in the synthesis of optically pure (6*S*,7*S*)-dihydroxyheliotridane, a close structural isomer of lentiginosine, a potent amyloglucosidase inhibitor.<sup>9</sup> The precursor was readily prepared from L-tartaric acid and converted into the desired protected pyrrolizidine in 64% yield (Scheme 7).

Geometric factors also play a crucial role in the translocation process. During the preparation of spiroketals, Simpkins and co-workers observed an influence of the size of the heterocycle on the reaction, although this effect is difficult to predict and rationalize (Scheme 8).<sup>10</sup>

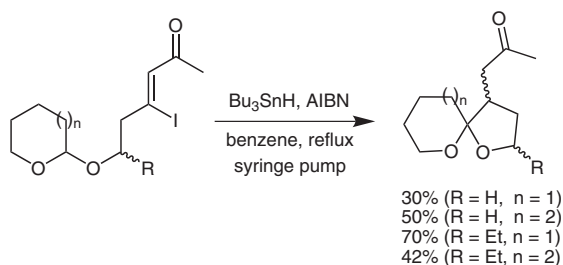
Chatgililoglu<sup>11</sup> and Miyasaka<sup>12</sup> and co-workers used this protocol for the generation of C-1' radicals in nucleosides. Starting from a dibromoalkene, Chatgililoglu and co-



**Scheme 6** Access to dihydrobenzofuran and indoline derivatives via 1,6-hydrogen transfer



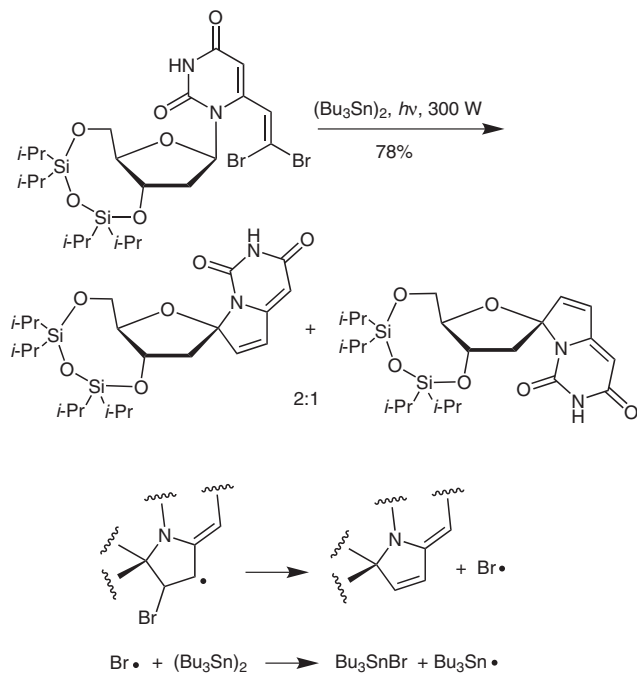
**Scheme 7** Radical translocation–cyclization in the synthesis of optically pure (6*S*,7*S*)-dihydroxyheliotridane



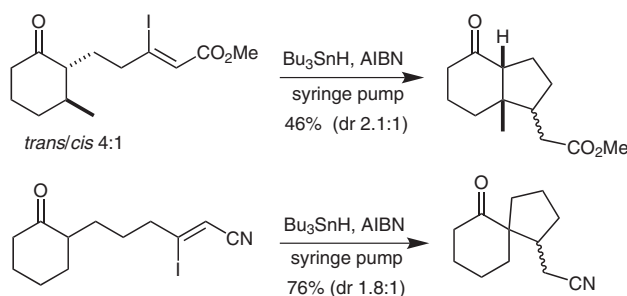
**Scheme 8** Geometric effects observed in the 1,5-hydrogen transfer process

workers developed the synthesis of a spiro nucleoside through a 5-*endo*-trig cyclization (Scheme 9). The presence of the second halogen atom allows a  $\beta$ -fragmentation, resulting in a new carbon–carbon double bond.

Sha and co-workers reported the cyclization of cycloalkanones bearing a  $\beta$ -iodo- $\alpha,\beta$ -unsaturated ester or nitrile side chain (Scheme 10).<sup>13</sup> The presence of an electron-withdrawing group on the alkene moiety is crucial for the success of the reaction. Translocation to a nonstabilized secondary or tertiary alkyl radical led to the fused bicyclic product in moderate yield. The preparation of spiro derivatives via translocation to the  $\alpha$ -position relative to the carbonyl group was more efficient.



**Scheme 9** Synthesis of a spironucleoside through a rare 5-endo-trig cyclization

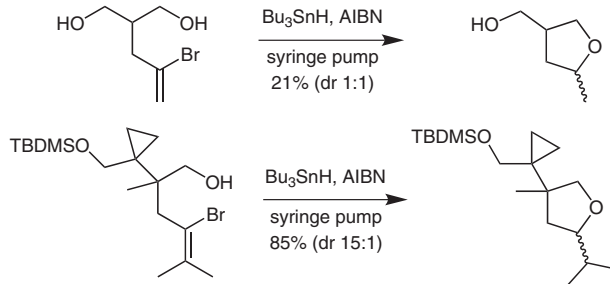


**Scheme 10** Radical translocation–cyclization of cycloalkanones bearing a  $\beta$ -iodo- $\alpha,\beta$ -unsaturated ester or nitrile side chain

The rate of hydrogen transfer depends on the bond dissociation energies (BDEs) of the formed and broken bonds. The BDE of an oxygen–hydrogen bond is higher than that of an  $\text{sp}^3$  carbon–hydrogen bond. Therefore, most radical cyclizations or reductions do not require the protection of a hydroxy group, and radical reactions are frequently carried out in protic solvents, such as *tert*-butyl alcohol (*t*-BuOH). On the other hand, the BDEs of  $\text{sp}^2$  carbon–hydrogen and oxygen–hydrogen bonds are in the same range. Based on this observation, Ihara and co-workers reported the preparation of tetrahydrofuran derivatives via the cyclization of alkoxy radicals, which were generated by an unprecedented 1,5-hydrogen transfer from a hydroxy group (Scheme 11).<sup>14</sup>

### 3 Vinyl Radicals Generated by Addition to Alkynes and Allenes

Vinyl radicals can be generated by the addition of carbon-centered, as well as heteroatom-centered, radicals to



**Scheme 11** 1,5-Hydrogen transfer for the generation of alkoxy radicals

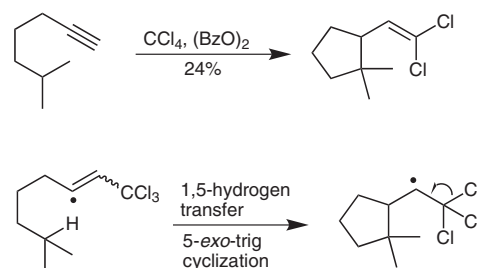
alkynes and also allenes. This approach is especially attractive since alkynes, particularly terminal alkynes, are easy to prepare compared with the formation of the vinyl halides described in Section 2.

### 3.1 Addition of Carbon-Centered Radicals

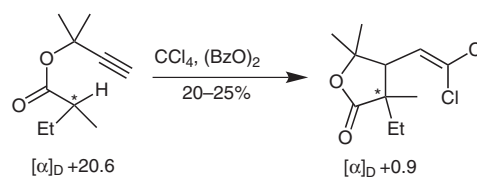
#### 3.1.1 Intermolecular Addition of Carbon-Centered Radicals

In 1967, Heiba and Dessau reported the intermolecular addition of polyhalomethanes, such as carbon tetrachloride, to terminal alkynes in the presence of benzoyl peroxide as an initiator (Scheme 12).<sup>2</sup> Together with the expected addition product, they observed the formation of a cyclic derivative arising from the translocation of the intermediate vinyl radical and subsequent cyclization. In this case, the radical obtained after cyclization undergoes a facile  $\beta$ -fragmentation of a chlorine atom.

The same authors reported an intriguing example of the partial retention of optical activity in the preparation of  $\gamma$ -lactones using the above procedure. Although the yield of the product remains modest (20–25%) and the enantiomeric excess was not determined, the residual optical activity suggests that the translocation–cyclization process possibly occurs without complete racemization of the stereogenic center (Scheme 13).<sup>15</sup>

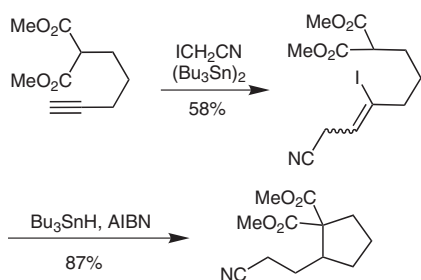


**Scheme 12** Addition of an electrophilic radical to an alkyne



**Scheme 13** Radical translocation–cyclization without complete racemization

When  $\text{CCl}_4$  is replaced by bromotrichloromethane ( $\text{BrCCl}_3$ ), only the product resulting from the simple addition to the alkyne is isolated. This illustrates that the rate of the halogen abstraction is critical for the formation of the translocation–cyclization products. In the case of  $\text{BrCCl}_3$ , the bromine atom is delivered too rapidly ( $k = 2.6 \times 10^8 \text{ M}^{-1}\cdot\text{s}^{-1}$ , *n*-butyl radical,  $80^\circ\text{C}$ )<sup>16</sup> to the vinyl radical for the hydrogen atom transfer to take place. Similarly, the addition of radicals derived from iodoacetone to terminal alkynes via an iodine atom transfer process have also been investigated and do not afford the translocation–cyclization products because of the very high rate of the iodine atom transfer.<sup>6</sup> The products of the translocation–cyclization process can be obtained, however, via the two-step procedure shown in Scheme 14.



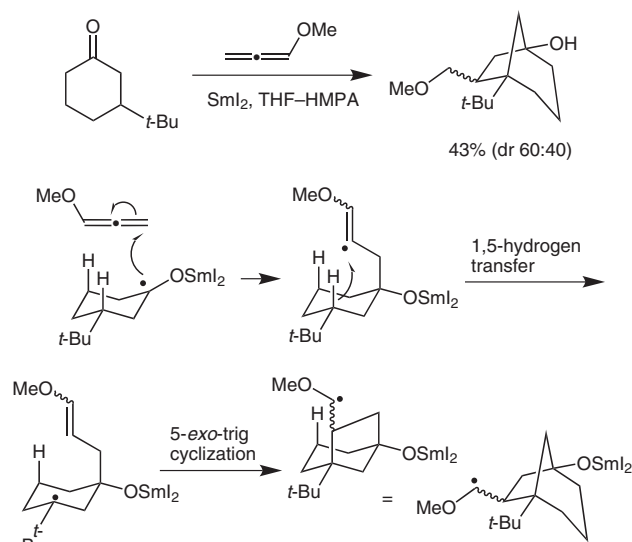
**Scheme 14** Cyclopentane derivative obtained via a two-step procedure

Hölemann and Reißig reported a successful intermolecular addition of samarium ketyl radicals to allenes.<sup>17</sup> The intermolecular addition to 1,3-diphenylallene occurs exclusively at the central carbon atom, whereas the addition to methoxyallene takes place at the terminal position affording 4-hydroxy-1-enol ether derivatives. Occasionally, the intermediate alkenyl radicals undergo a translocation–cyclization leading to the cyclopentanol derivatives in moderate yields. In the example depicted in Scheme 15, the major product arises via a regioselective 1,5-hydrogen transfer delivering the more-stable tertiary alkyl radical. Translocation of the alkenyl radicals to deliver primary alkyl radicals has also been observed.

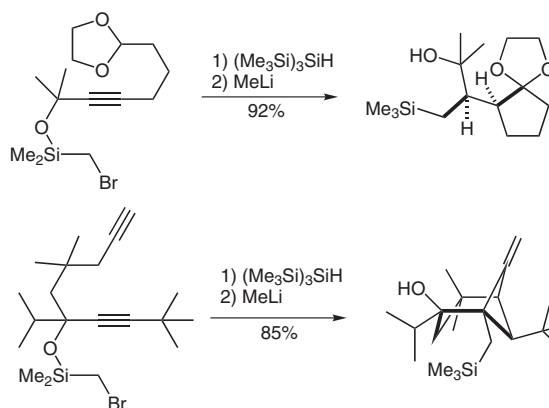
### 3.1.2 Intramolecular Addition of Carbon-Centered Radicals

Malacria and co-workers reported the cyclization of various (bromomethyl)silyl propargyl ethers followed by 1,5- or 1,6-hydrogen transfer and 5-*exo*-trig or 6-*endo*-trig cyclization, respectively (Scheme 16).<sup>18</sup>

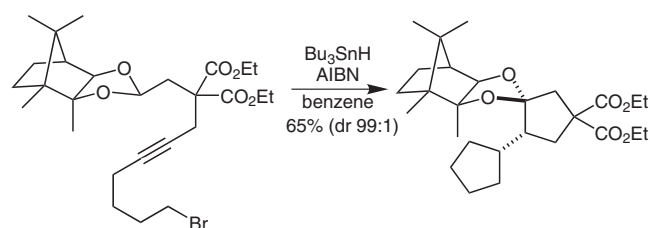
Crich and Bertrand and co-workers<sup>19,20</sup> developed a route to optically enriched ketones based on a hydrogen transfer of vinyl radicals using chiral acetals. The best results (dr <99:1) were obtained using a chiral auxiliary derived from camphor (Scheme 17). The vinyl radical required for the translocation process was generated from a primary bromoalkane via radical cyclization.<sup>20</sup>



**Scheme 15** Generation of alkoxyvinyl radicals by the addition of samarium ketyl radicals to alkoxyallenes

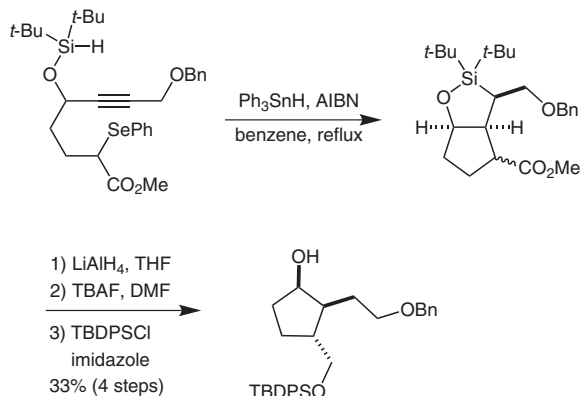


**Scheme 16** Vinyl radicals generated by the intramolecular addition of carbon-centered radicals



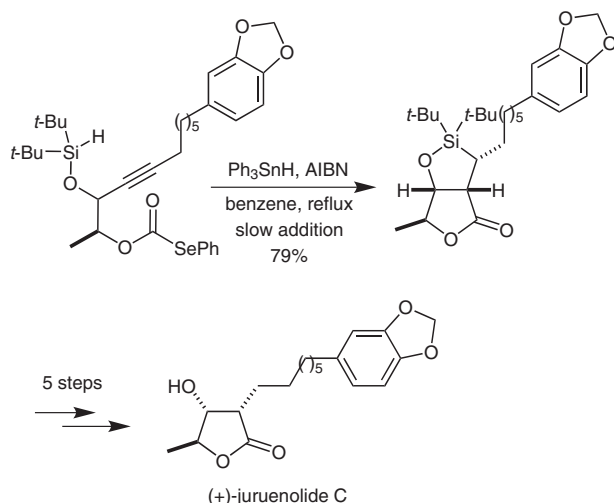
**Scheme 17** Chiral auxiliary controlled radical translocation–cyclization

Clive and co-workers developed a general procedure for making five-membered rings from alkoxyallenes bearing a phenyl selenide or xanthate moiety in the presence of tin hydride.<sup>21</sup> A sequence of a 5-*exo*-dig cyclization and an intramolecular hydrogen transfer leads to a silicon-centered radical intermediate. Under these conditions, the intermediate then cyclizes via a 5-*endo* mode with its alkene moiety. This translocation–cyclization process was used to prepare an intermediate for the synthesis of prostaglandins (Scheme 18).<sup>22,23</sup>



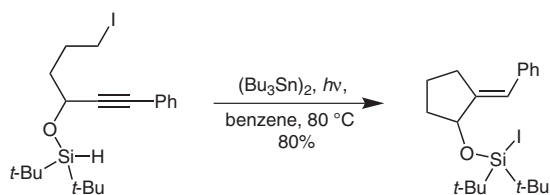
**Scheme 18** Elaboration of an intermediate for the synthesis of prostaglandins

Heterocycles such as pyrrolidines, pyrrolizidinones, tetrahydrofurans, and lactones have been prepared in high yields using this approach.<sup>23</sup> This process was also successfully applied to the synthesis of (+)-juruenolide C, a  $\gamma$ -lactone isolated from the seedlings and micropropagated leaves of *Virola surinamensis* (Scheme 19).<sup>24</sup>



**Scheme 19** Synthesis of (+)-juruenolide C

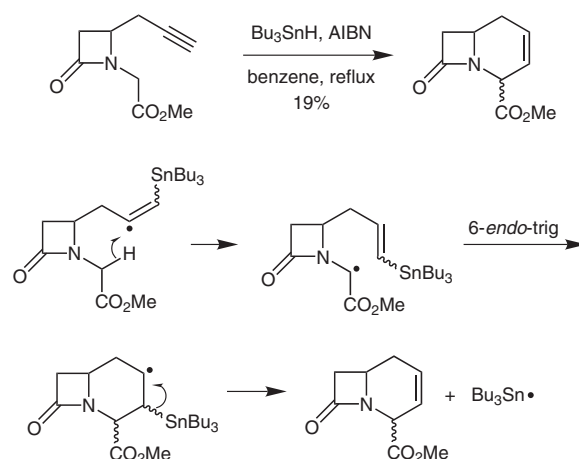
Interestingly, by replacing the phenyl selenide or xanthate moiety by an iodine atom, the bimolecular abstraction becomes faster than the 5-*endo* cyclization of the silicon-centered radical. This concept of ‘unimolecular chain transfer’ involving a silicon hydride for the translocation process was developed by Martinez-Grau and Curran (Scheme 20).<sup>25</sup>



**Scheme 20** The concept of ‘unimolecular chain transfer’

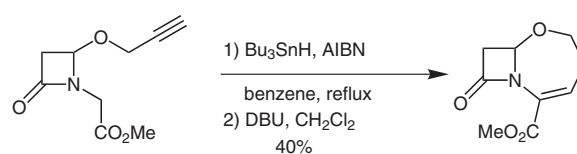
### 3.2 Addition of Tin-Centered Radicals

Bosch and Bachi developed an elegant synthesis of fused bicyclic  $\beta$ -lactams by the treatment of a terminal alkyne with tributyltin hydride. The reaction is catalytic in tin hydride and involves the addition of the stannyl radical to the alkyne followed by a radical translocation–cyclization–fragmentation process (Scheme 21).<sup>26</sup> In this particular case, the preferred cyclization is a 6-*endo*-trig process despite the bulkiness of the tributylstannyl group, suggesting that thermodynamic control may be involved in this process.



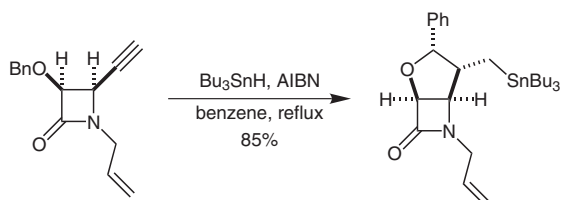
**Scheme 21** Translocation–cyclization cascade catalyzed by a tin hydride

Another  $\beta$ -lactam, substituted at the 4-position by a propargyloxy group, was converted into a fused  $\beta$ -lactam via a related radical cascade involving an initial 1,6-hydrogen transfer (favored because of the captodative stabilization of the formed glycynyl radical), a 7-*endo*-trig cyclization, and a fragmentation process (Scheme 22). The product was isolated after isomerization of the double bond to generate a conjugated enamido ester.



**Scheme 22** A 1,6-hydrogen transfer followed by a 7-*endo*-trig cyclization and a fragmentation process

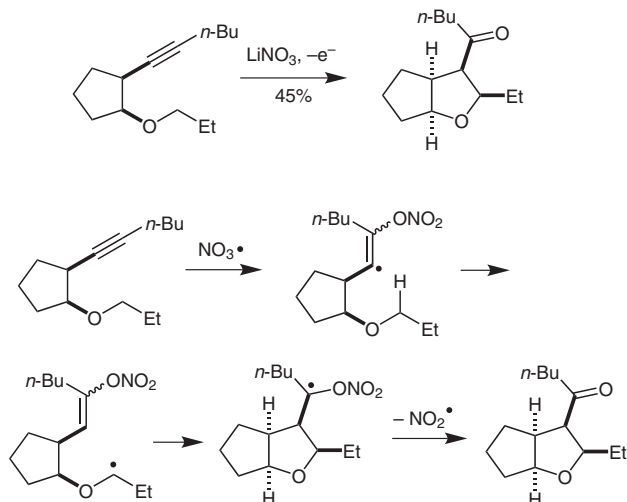
Alcaide et al. observed an unexpected 1,5-hydrogen transfer during the preparation of fused bicyclic  $\beta$ -lactams.<sup>27</sup> For the reaction shown in Scheme 23, the vinyl radical generated by the addition of the tributyltin radical to the alkyne moiety of the substrate underwent a fast translocation process at the benzylic position instead of the anticipated cyclization with its allyl moiety. The reaction afforded the corresponding fused tetrahydrofuran in 85% yield as a single diastereomer.



**Scheme 23** An unpredicated, but efficient 1,5-hydrogen transfer–cyclization process

### 3.3 Addition of Oxygen-Centered Radicals

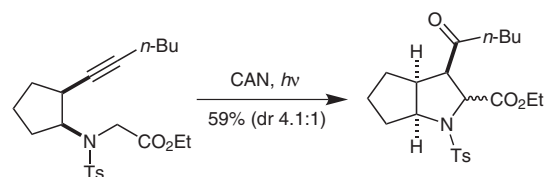
The use of inorganic oxygen-centered radicals in organic synthesis has been included in a review.<sup>28</sup> Wille and co-workers reported the formation of fused tetrahydrofurans using a nitrate radical induced, oxidative, self-terminating cyclization cascade (Scheme 24).<sup>29</sup> The inorganic oxygen-centered radical is generated by the anodic oxidation of lithium nitrate.<sup>30</sup> The termination of this cyclization cascade is kinetically controlled and determined by the ease of the final homolytic cleavage of the oxygen–heteroatom bond.<sup>31</sup> Linear alkynes and alkynones failed to cyclize under these conditions.



**Scheme 24** Nitrate radical induced, oxidative, self-terminating cyclization cascade used for the preparation of fused tetrahydrofurans

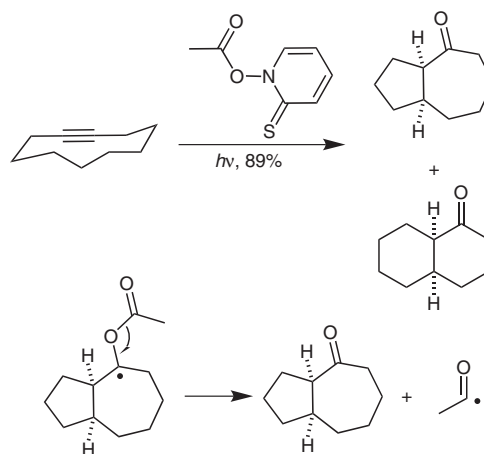
The reaction proceeds via the initial addition of the oxygen-centered nitrate radical ( $\text{NO}_3$ ) to the less-hindered site of the alkyne, generating an alkenyl radical. This radical undergoes a 1,5-hydrogen transfer and a subsequent 5-*exo*-trig cyclization. Finally, homolytic cleavage of the weak O– $\text{NO}_2$  bond terminates the sequence to yield the tetrahydrofuran with the concomitant release of the nitrite radical ( $\text{NO}_2$ ). The final nitrite radical is far less reactive than the nitrate radical and does not propagate a radical chain process. This sequence can be considered as a *self-terminating radical oxygenation* in which  $\text{NO}_3$  acts formally as an O-atom synthon, thus converting alkynes into carbonyl compounds under very mild conditions. Different inorganic, organic, uncharged, and even charged oxygen-centered radicals can act as O-donors in their

reactions with alkynes.<sup>31–33</sup> Fused pyrrolidines are also obtained through this self-terminating, oxidative radical cyclization cascade. For example, the treatment of a *cis*-alkynylcyclopentyl-substituted amine with photochemically generated nitrate radicals affords the corresponding fused pyrrolidine (Scheme 25).<sup>34</sup>



**Scheme 25** Nitrate radical mediated preparation of a fused pyrrolidine

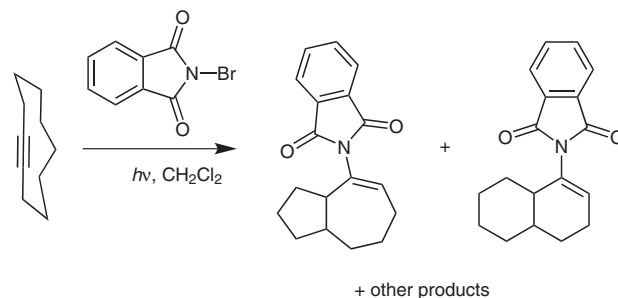
Medium-sized cycloalkynes react with various oxygen-centered radical precursors to yield fused bicyclic structures.<sup>32,33,35</sup> A typical example using a Barton ester as a source of the acetyloxy radical is shown in Scheme 26. In this process, the final fragmentation liberates an acetyl radical.<sup>33</sup>



**Scheme 26** Transannular translocation–cyclization reactions with acetyloxy radicals

### 3.4 Addition of Nitrogen-Centered Radicals

The addition of an imido radical to medium-sized cycloalkynes affords a mixture of products arising from transannular translocation–cyclization and simple addi-

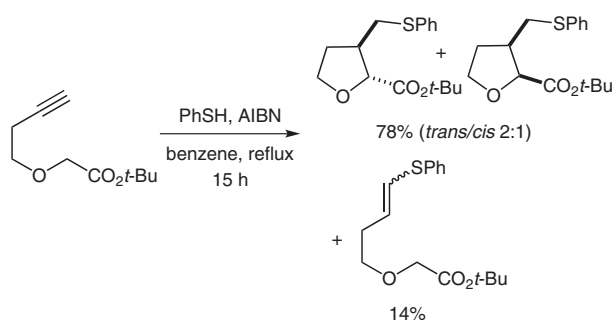


**Scheme 27** Transannular hydrogen transfers initiated by the addition of imido radicals to alkynes

tion reactions (Scheme 27).<sup>36</sup> The formation of the unsaturated bicyclic compounds may be rationalized as occurring by the final transfer of a bromine atom from *N*-bromophthalimide to the cyclized radicals followed by the loss of hydrogen bromide.

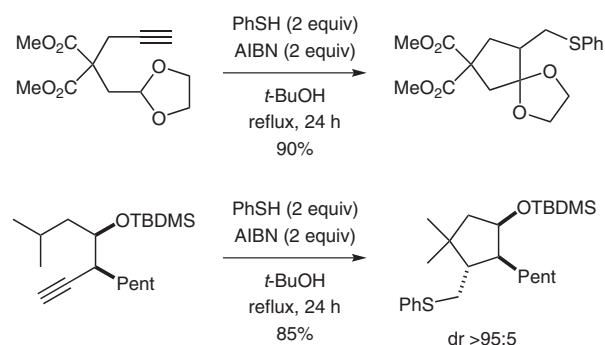
### 3.5 Addition of Sulfur-Centered Radicals

In 1994, Burke and Jung reported the preparation of tetrahydrofurans from linear homopropargyl ethers using thiophenol to achieve the radical cascade (Scheme 28).<sup>37</sup> The tetrahydrofuran derivatives were obtained in fair yields, but the formation of the noncyclized adduct could not be suppressed, despite the fact that the hydrogen transfer step is highly favored because of the stabilization of the intermediate radical.



**Scheme 28** Burke and Jung's thiophenol-mediated 1,5-hydrogen transfer

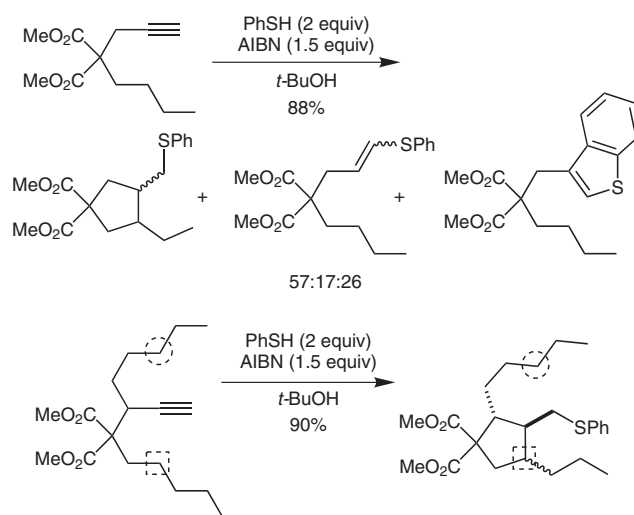
This process was further investigated and reaction conditions allowing the efficient preparation of five-membered rings were found.<sup>38,39</sup> Indeed, when the reaction is run in *t*-BuOH as a solvent and a stoichiometric amount of 2,2'-azobis(isobutyronitrile) is slowly added, excellent yields of the translocation–cyclization products are obtained. The modified conditions are applicable to a wide range of substrates. In most cases, the formation of the noncyclized adduct is not observed (Scheme 29).



**Scheme 29** Optimized thiophenol-mediated translocation–cyclization reaction

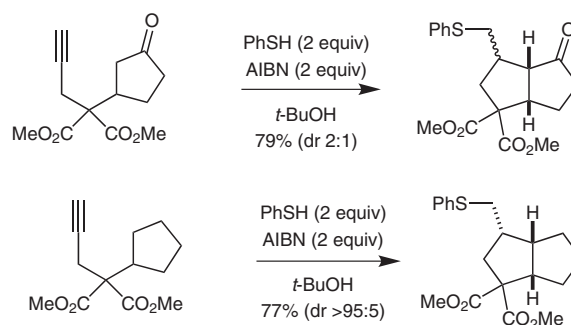
An interesting substituent effect was noted when the translocation process led to acyclic secondary radicals (Scheme 30). In the absence of a substituent at the propargylic position, the reaction affords a mixture of the cyclized and noncyclized adducts, and a benzothiophene derivative resulting from homolytic aromatic substitution by the intermediate vinyl radical. In contrast, the presence of a propargylic substituent dramatically changes the course of the reaction and gives exclusively the cyclized product in high yield. This disparity was attributed to the vicinal disubstituent effect, akin to the well-established geminal disubstituent effect (Thorpe–Ingold effect).<sup>40</sup> The regioselectivity of the 1,5-hydrogen transfer (square vs circle in Scheme 30) is controlled by the *gem*-diester effect.

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**Scheme 30** Effect of the vicinal substituents on the translocation rate

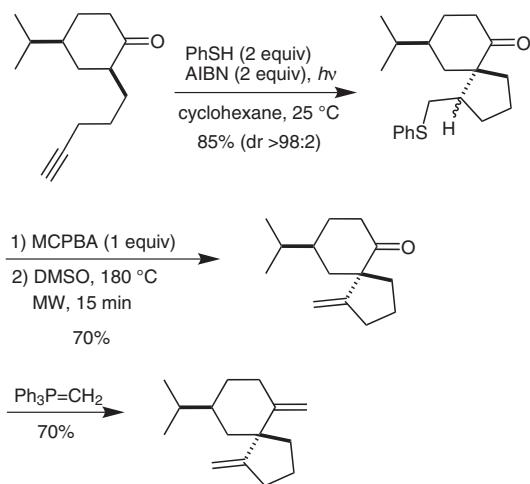
The thiophenol method has been extended to the preparation of fused bicyclic structures from readily available cycloalkane and cycloalkane derivatives (Scheme 31).<sup>39</sup>



**Scheme 31** Thiophenol-mediated 1,5-hydrogen transfer applied to the preparation of bicyclic skeletons

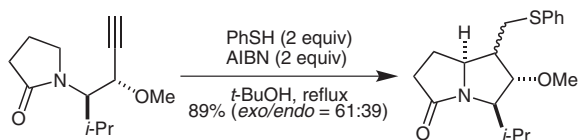
The incorporation of the phenylsulfanyl group in the final product is very useful for its further functionalization as illustrated by the total synthesis of optically pure (–)-erythrodiene, a marine sesquiterpenoid isolated from the Caribbean gorgonian octocoral *Erythropodium caribaeorum* (Scheme 32). Interestingly, the translocation–cyclization process takes place with high diaste-

reoselectivity at the spirocyclic center. The subsequent oxidation of the sulfide to give the corresponding sulfoxide followed by thermal elimination allows the efficient generation of the 5-*exo*-methylenecyclopentane ring.<sup>41</sup> Finally, methylenation of the cyclohexanone according to the procedure of Huang and Forsyth<sup>42</sup> provides (–)-erythrodiene.



**Scheme 32** Synthesis of (–)-erythrodiene

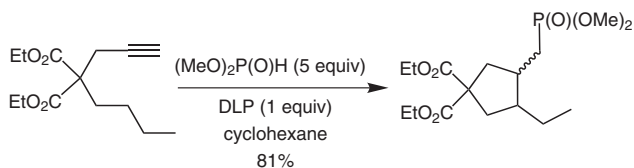
Highly functionalized 1-azabicycloalkanes are prepared in a concise manner using the above tin-free 1,5-hydrogen transfer–cyclization process (e.g., Scheme 33).<sup>43</sup> The precursors for the radical reactions are readily assembled either from pyrrolidine, piperidine, or hexahydro-1*H*-azepine, or via the condensation of a properly designed *N*-alkylimine with an allenylzinc species.



**Scheme 33** Preparation of a pyrrolizidine derivative

### 3.6 Addition of Phosphorus-Centered Radicals

Phosphorus-centered radicals generated from dialkyl phosphonates are suitable for translocation–cyclization cascade processes to prepare cyclic phosphonates in high yields from terminal alkynes (e.g., Scheme 34).<sup>44</sup> This method is particularly efficient for slow hydrogen transfers and is attractive because the reaction can be run under relatively concentrated conditions (0.1 M). The reagents

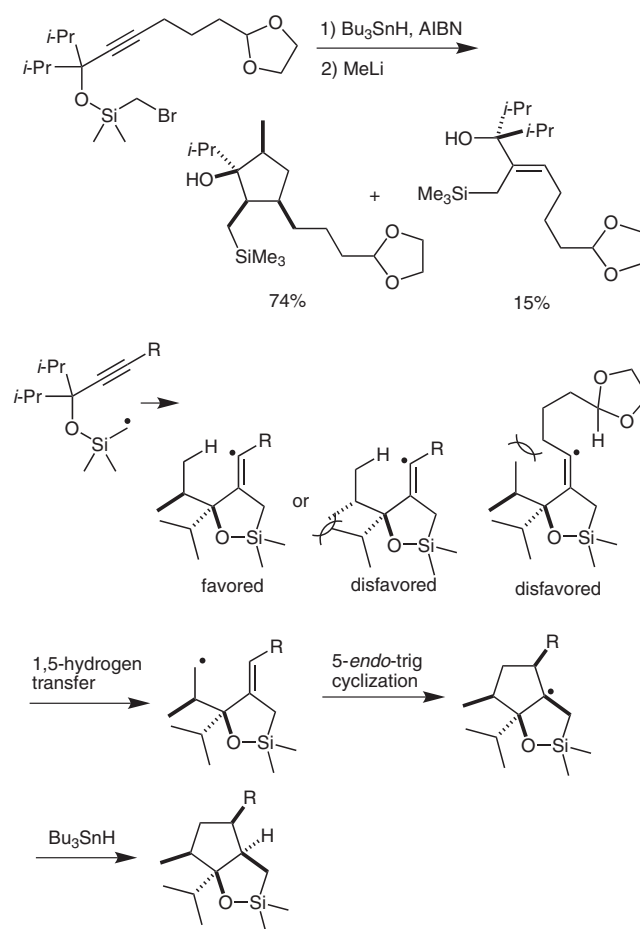


**Scheme 34** Dialkyl phosphonate mediated translocation–cyclization reaction (DLP = dilaunoyl peroxide)

are mixed together at once at the beginning of the reaction, thereby obviating the need for the slow addition technique. Moreover, a simple aqueous workup removes the excess of the dialkyl phosphonate.

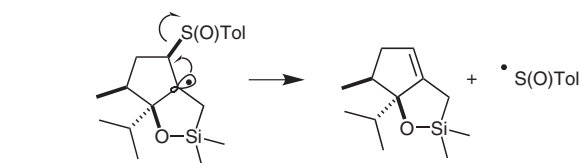
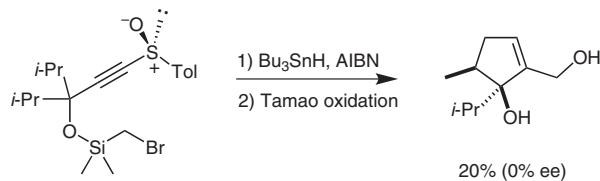
## 4 Translocation–Cyclization Processes Involving a Stereoselective Hydrogen Atom Transfer

Recent advances in stereoselective radical translocations have also been reviewed.<sup>45</sup> Malacria and co-workers reported the first example of the translocation–cyclization process of a vinyl radical involving a stereoselective 1,5-hydrogen transfer (Scheme 35). In this example, the 5-*exo*-dig cyclization of a (bromomethyl)silyl propargyl ether affords a vinyl radical that stereoselectively abstracts a hydrogen from one of the two diastereotopic methyl groups of an isopropyl substituent.<sup>46</sup> After treatment of the crude product with methyllithium, a cyclopentanol was obtained in 74% yield as a single diastereomer. A second product was obtained in 15% yield resulting from the reduction of the vinyl radical before hydrogen atom abstraction. Interestingly, no product resulting from the 1,5-hydrogen transfer from the activated acetal carbon–hydrogen bond was observed.



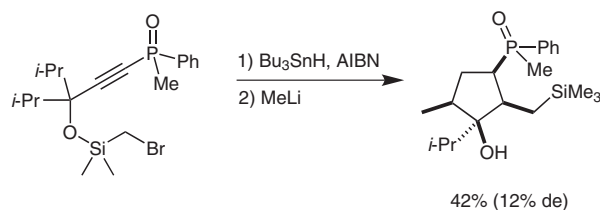
**Scheme 35** Diastereoselective 1,5-hydrogen transfer

Attempts to control the absolute and relative stereochemistry of the hydrogen atom transfer step using chiral auxiliaries have been reported.<sup>46</sup> An optically pure alkynyl sulfoxide afforded the product resulting from a translocation–cyclization–fragmentation process in low yield (Scheme 36). However, the product was racemic resulting from a lack of facial selectivity during the hydrogen abstraction process.



**Scheme 36** An attempt to control the stereoselectivity of the hydrogen transfer using a sulfoxide

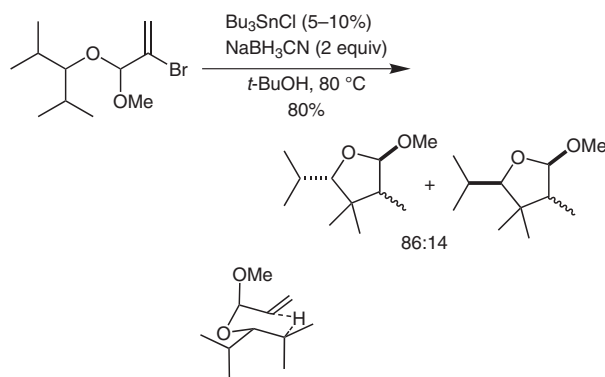
A second attempt with a chiral phosphine oxide gave a modest level of stereocontrol (Scheme 37).<sup>46</sup>



**Scheme 37** An attempt to control the stereoselectivity of the hydrogen transfer using a phosphine oxide

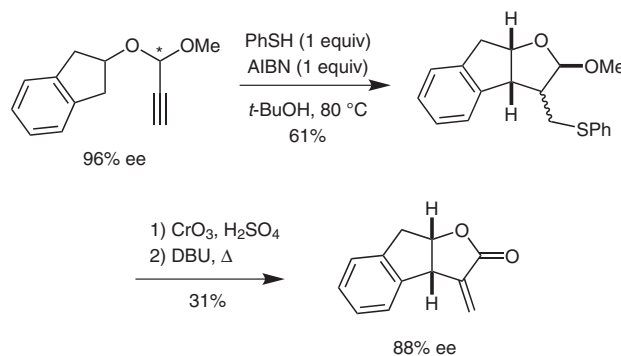
The diastereoselectivity of the hydrogen transfer during the translocation step involving chiral acetals was investigated in depth.<sup>47</sup> The abstraction proceeds with good stereochemical control and is easily rationalized as occurring via a chair-like transition state in which the 2-methoxy group occupies an axial position as a result of the anomeric effect, and the nonreacting group at C-5 is in a pseudo-equatorial position (Scheme 38). This model is closely related to that reported for the cyclization of chiral acetals.<sup>48</sup>

The preparation of a nonracemic  $\alpha$ -methylene-substituted lactone using a diastereoselective hydrogen atom abstraction has been described (Scheme 39). For this purpose, an optically enriched propynal acetal (96% ee) was isolated by high-performance liquid chromatography on a chiral column. The reaction of the acetal using the thiophenol method, followed by the oxidation of the resulting cyclic



**Scheme 38** Diastereoselective hydrogen transfer of chiral acetals

acetal with an excess of Jones reagent and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene, afforded the diastereomerically pure  $\alpha$ -methylene-substituted lactone with 88% enantiomeric excess. The diastereoselectivity of the hydrogen atom abstraction step is greater than 95:5.<sup>47</sup>



**Scheme 39** Synthesis of an optically enriched  $\alpha$ -methylene-substituted lactone

## 5 Conclusion

Highly regioselective, and sometimes even stereoselective, hydrogen transfers can be coupled with highly predictable 5-*exo*-trig cyclizations. Such reaction sequences may serve as a unique tool for the construction of five-membered ring systems. The appeal of this strategy is further enhanced by the availability of the precursors and the possibility of running the reactions under tin-free conditions. Finally, because of the unique functional group compatibility of radical reactions, the translocation–cyclization process represents a useful tool for the synthesis of complex and functionalized structures, such as those found in biologically active natural products.

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