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New developments in radical chemistry. Applications to total synthesis and asymmetric processes*

Christophe Aïssa, Bénédicte Delouvrié, Anne-Lise Dhimane,
Louis Fensterbank, and Max Malacria†

Université Pierre et Marie Curie, Laboratoire de Chimie Organique de Synthèse, Tour 44-54, B. 229, 4, Place Jussieu, 75252 Paris Cedex 05 France

Abstract: This article reviews our contribution in the field of radical synthetic chemistry, focusing on cascades relying on the use of propargylic BMDMS ethers and asymmetric synthesis using enantiopure vinylsulfoxides.

THE 5-*EXO-DIG* CYCLIZATION OF BMDMS PROPARGYLIC ETHERS: AN EFFICIENT TRIGGER FOR RADICAL CASCADES

The vinyl radical, a precious tool

The vinyl radical of type **3** resulting from the highly efficient and regioselective 5-*exo-dig* cyclization of α-silyl radical **2**, generated from bromomethyldimethylsilyl (BMDMS) propargyl ethers of type **1** has been revealed as a very versatile synthetic tool [1]. Scheme 1 illustrates different processes we have worked out over the past years. A simple stannane reduction on **3** provides heterocycles **4**, which upon further addition of MeLi, give trimethylenemethane (TMM) precursors [2]. Alternatively, an oxidative treatment with H_2O_2 (Tamao oxidation), or Bu_4NF (protodesilylation) yields valuable trisubstituted olefins [3].

All sorts of intramolecular trapping of the vinyl radical have been envisaged. The simplest is naturally a 5-*exo-trig* radical cyclization from **5**, giving birth to a variety of cyclopentenes **6** [4]. This process is completely diastereoselective, setting the resulting methyl group and the C–O bond *syn* to each other. When a methallyl group, instead of an allyl group, is present, a competition between the 5-*exo-trig* and 6-*endo-trig* modes of cyclization occurs. The 6-*endo-trig* cyclization becomes major when the vinyl radical is substituted by a phenyl group (cyclohexene **8**). A final diastereoselective reduction of the methine radical installs a *syn* relationship between the methyl group and the C–O bond [4b]. Vinyl radicals are also very prone to engage into hydrogen transfers. A rare 1,4-H transfer (from **9**) has been for instance discovered [5]. However, our most useful approaches in this domain have relied on 1,5-H transfers. An X activating group, such as a dioxolane, suitably located on the propargyl chain, promotes a 1,5-(π-*exo*)-H transfer from the vinyl radical **11**. The translocated radical then cyclizes back in a 5-*exo-trig* manner to provide α-functionalized cyclopentanone derivatives **12**. We have studied the diastereoselectivity of the reduction of the final β-silyl radical [6], and also investigated the possibility of developing an asymmetric version of this process, by introducing a homochiral dioxolane moiety. The best de obtained reached 50% [4c]. With highly sterically encumbered (gem-diisopropyl) substrates, vinyl radical **13** ungergoes a diasteroselective 1,5-(π-*endo*)-H transfer with an unactivated methyl group. The resulting methylene radical then cyclizes according to the disfavored 5-*endo-trig* mode of cyclization, placing the R group *syn* to the methyl group and to the C–O bond. A diastereoselective stannane reduction of the β-silyl radical installs a *cis* ring junction and terminates the sequence

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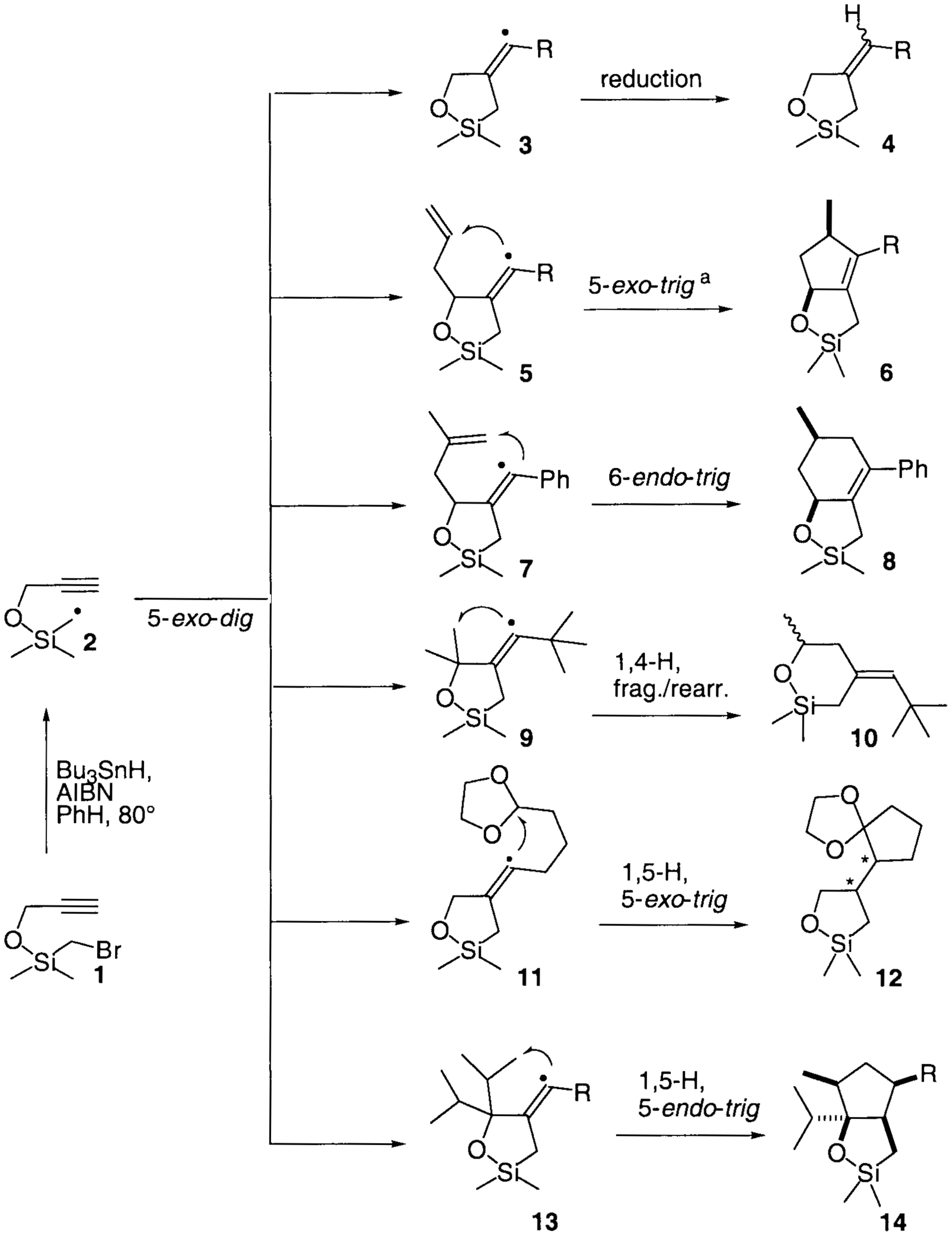
†Corresponding author: E-mail: malacria@ccr.jussieu.fr

[7]. This sequence has proven quite general for the synthesis of cyclopentanes **14**, and has constituted so far the most efficient case of 5-*endo-trig* cyclization in an all-carbon system [8]. 1,6-H Transfers from the vinyl radical have also been disclosed in transannular series [9] and acyclic series [10], but their synthetic versatility has not been completely exploited.



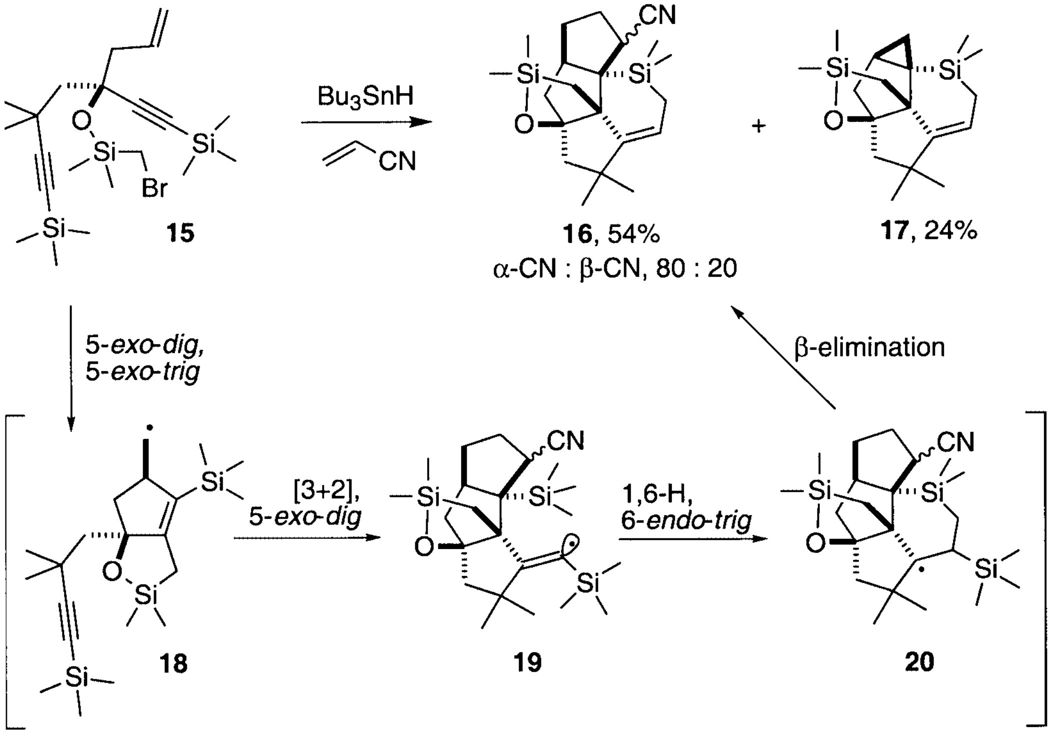
[a] From this equation, the final Bu_3SnH is not indicated.

Scheme 1

Our utilization of the propargylic BMDMS ethers has recently culminated in two cascade sequences leading to linear triquinanes and the total synthesis of *epi*-illudol. These are developed below.

Linear triquinanes from acyclic precursors

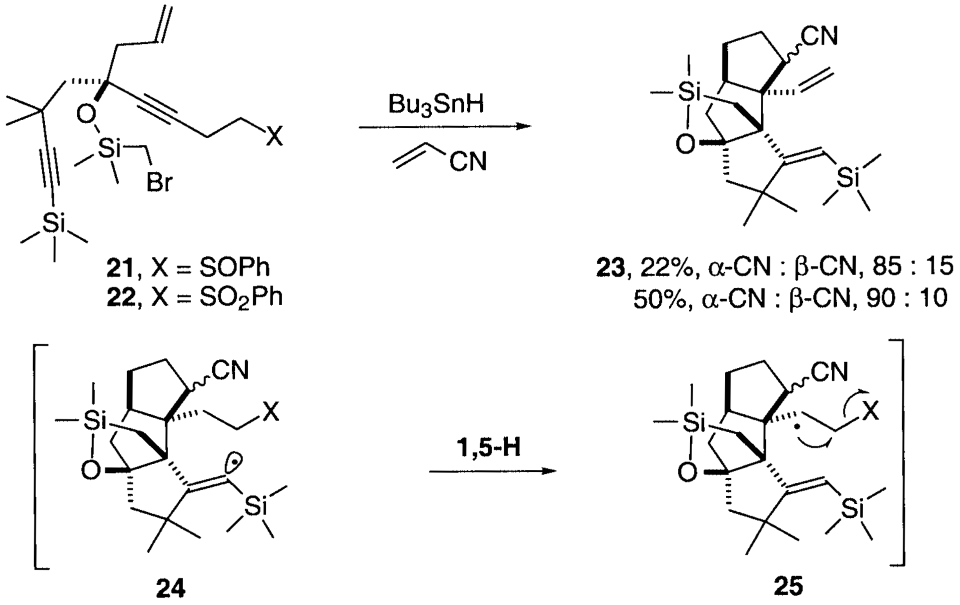
Previous studies in our laboratory established that the homoallyl radical, resulting from the 5-*exo-dig*, 5-*exo-trig* tandem as in the formation of cyclopentenes **6**, could readily engage into a radical [3+2] cycloaddition, with a Michael acceptor like acrylonitrile [11]. By this methodology, a diquinane could be obtained as a single diastereomer. We next focused on the possibility of constructing triquinanes [12]. This action would necessitate the addition of one more unsaturation. Our initial attempts, however, were thwarted by hydrogen transfers from the initial vinyl radical [4b]. In view of the linear triquinane skeleton, we had to quaternarize the second propargylic position. Therefore, we concentrated on precursor **15** [13], bearing a gem-dimethyl group, whose cyclization in presence of acrylonitrile furnished the two adducts **16** and **17** in good overall yield (Scheme 2).



Scheme 2

Both compounds originate from the initial and usual 5-*exo-dig*, 5-*exo-trig* tandem. The resulting homoallyl radical **18** has two options. The first and major one, to provide triquinane **16**, is a Michael condensation on acrylonitrile followed by a 5-*exo-trig* closure. The resulting β-silyl radical then cyclizes in a 5-*exo-dig* fashion to give vinyl radical **19**. Because of the very large surrounding steric hindrance, this radical intermediate is particularly protected from any intermolecular reaction. Instead, it engages into a 1,6-H transfer with a methylsilane group to give an α-silyl radical which then undergoes a 6-*endo-trig* cyclization. This yields doubly neopentylic radical **20**, whose only way out is an unprecedented β-elimination of a trimethylsilyl radical, setting the vinylsilane function of **16**. The second option, to provide cyclopropyl adduct **17**, is a competing 3-*exo-trig* cyclization from **18**, whose driving force is the subsequent 5-*exo-dig* cyclization. From this, an identical sequence as for the construction of **16**, takes place. The outcome of the sequence leading to the triquinane **16** is remarkable: 11 elementary steps, 6 new C–C bonds, 3 contiguous quaternary centers, and 4 new stereogenic centers almost totally controlled. Only incomplete stereocontrol during the [3+2] annulation step is responsible for the formation of the minor β-CN epimer of **16**.

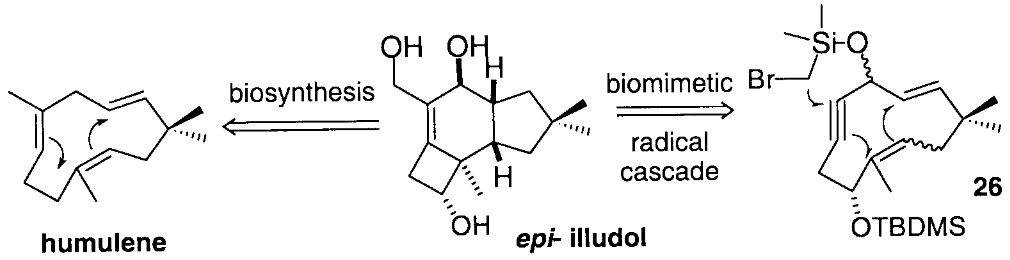
We next sought to obtain the linear triquinane framework without any supplementary ring [13]. To achieve this, we relied on an approach ending with a favorable 1,5-H transfer from vinyl radical of type **24** and followed by the β-elimination of a suitable leaving group, thus avoiding any telomerization of the final radical species (Scheme 3). We prepared sulfoxide **21** and sulfone **22** because of the reported very fast β-elimination of the arylsulfinyl and -sulfonyl group. Both substrates allowed the synthesis of vinyltriquinane **23**, with a distereoselectivity consistent with previous findings. The difference of yield between the cyclization of **21** and **22** simply reflects the poorer ability of the sulfinyl radical to propagate the radical chain.



Scheme 3

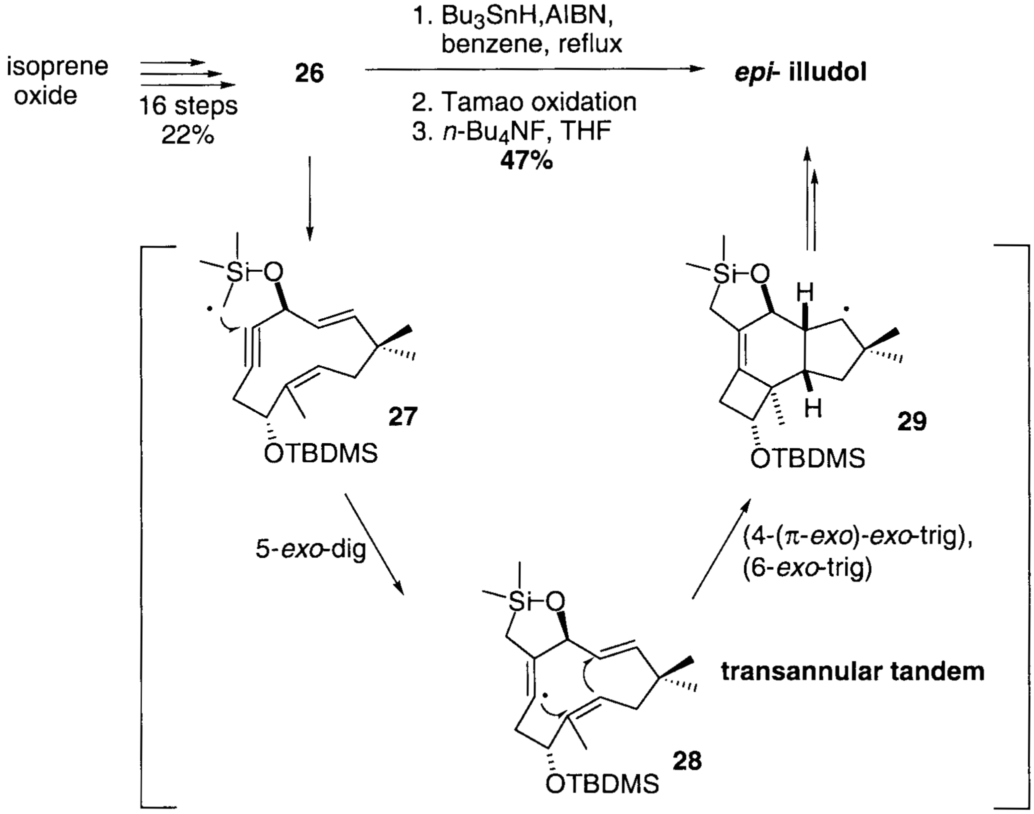
First total synthesis of natural protoilludane, *epi*-illudol

The unusual angular 4,6,5-tricyclic framework of protoilludanes family is built biosynthetically from humulene by a transannular carbocationic tandem cyclization (Scheme 4). These antibacterial natural products (e.g., illudols, armillols, tsugicolines), therefore, possess a *bis*-allylic diol moiety, easily accessible from the corresponding BMDMS propargylic ether. For these reasons, we have designed a biomimetic radical transannular cascade strategy from an adequately substituted cycloundecadienyne [14].



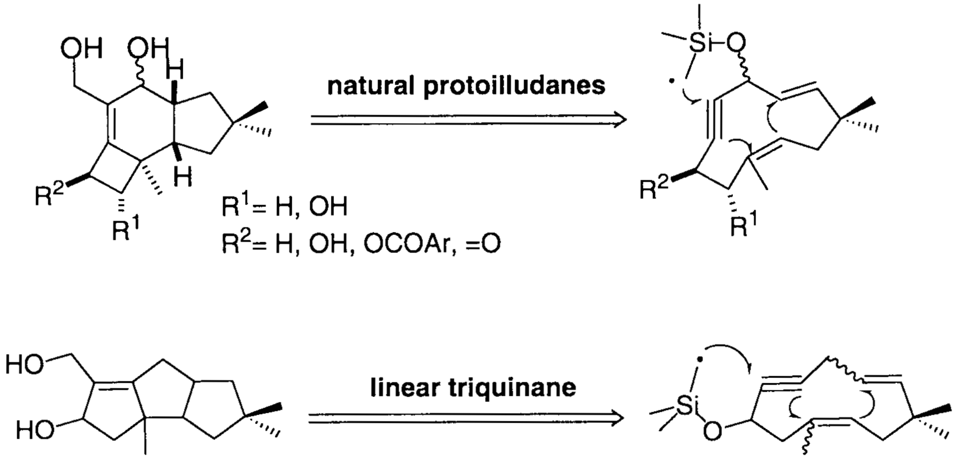
Scheme 4

Thus, precursor **26**, submitted to classical Bu_3SnH-AIBN conditions, provides the expected α-silyl radical **27** which cyclizes regioselectively [9] in a 5-*exo-dig* manner (Scheme 5). The resulting vinyl radical **28** undergoes a challenging 4-(π-*exo*)-*exo-trig* transannular closure to a new radical species, which is directly involved in a second more favorable transannular 6-*exo-trig* process. This final process serves as a driving force for the complete diastereoselective construction of tetracycle **29**. A final Tamao oxidation and subsequent desilylation generate the expected *epi*-illudol.



Scheme 5

This versatile strategy should allow a general access to the above-mentioned natural protoilludanes possessing this intriguing *exo*-methylene cyclobutane entity [15]. We now focus on how to open a new route to linear triquinane skeletons through a similar transannular strategy from an eleven-membered-ring with three judiciously positioned unsaturations (Scheme 6).

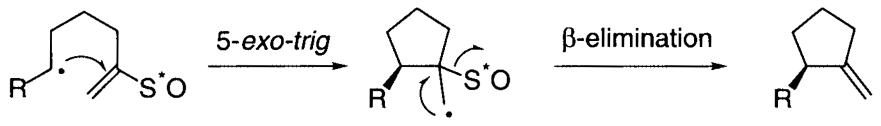


Scheme 6

These new developments in radical cascades starting from BMDMS propargylic ethers and leading to natural skeletons, indubitably show the efficiency and the great potentialities of such a trigger [16].

ASYMMETRIC INTRAMOLECULAR RADICAL VINYLATION USING ENANTIOPURE SULFOXIDES AS TEMPORARY CHIRAL AUXILIARIES

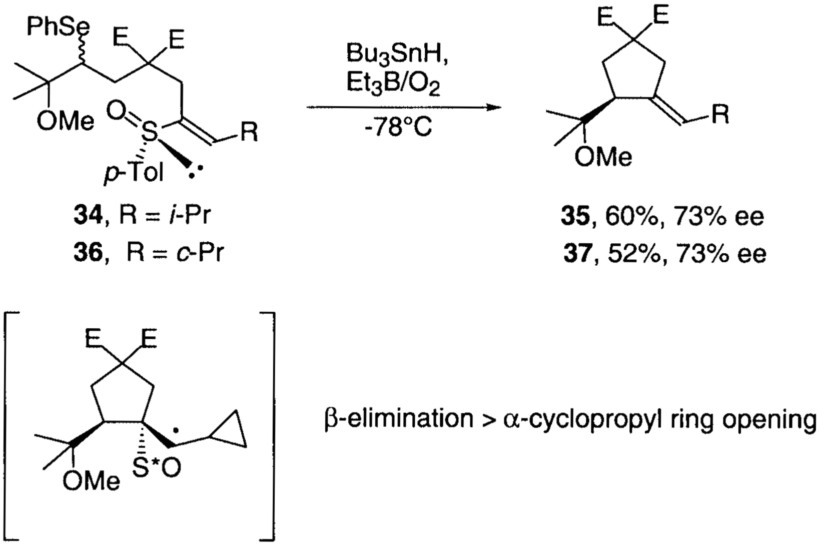
We have focused for some years on the use of chiral sulfur-based auxiliaries, mainly sulfoxides, because of their easy introduction, their low cost, and their versatile final functionalization. Our initial approach, based on the Michael addition of a vinyl radical onto vinyl sulfoxides gave mixed results. Very high diastereoselectivities were obtained for β-alkoxy vinyl sulfoxides [17], while the pure carbon systems have so far led to poor results, even in the case of *N*-sulfinimines [18]. We preferred modifying our strategy according to the tandem reaction depicted in Scheme 7. The sequence would consist in a 5-*exo*-*trig* cyclization of a prochiral radical **30** in an anti-Michael orientation, followed by the previously reported elimination of β-sulfinyl radicals to furnish alkylidene cyclopentane **32**. Implying an *a priori* quite favorable α-selectivity, this radical addition should be highly diastereoselective.



30 **31** **32**

Scheme 7

To test this reaction, we synthesized *E*-precursor **34**, bearing an isopropyl group on the vinylsulfoxyde moiety (Scheme 8). Under low-temperature, radical cyclization conditions, **34** underwent an exclusive 5-*exo-trig* radical cyclization to afford cyclopentyl derivative **35** in 60% yield [19]. One substituent on the vinyl sulfoxide at the β-position is sufficient here to preclude the 6-*endo-trig* mode of cyclization. Moreover, no cyclopentyl derivative incorporating the sulfoxide moiety was observed, which confirmed the efficiency of the β-elimination of the sulfoxide auxiliary. The promising stereoselectivity (73% ee) of this sequence was equally interesting. A similar result in terms of yield and stereoselectivity was obtained with cyclopropyl precursor **36**.



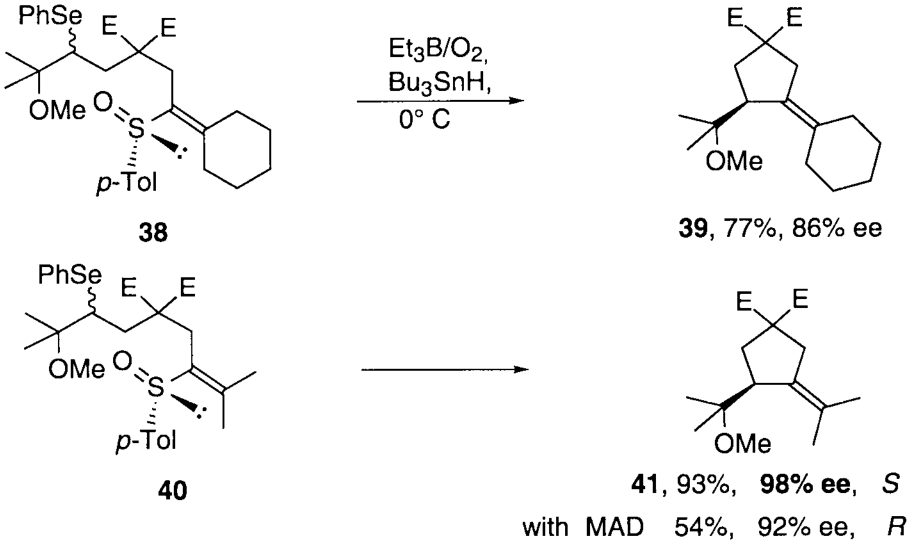
Scheme 8

No sulfoxide adduct showing the opening of the cyclopropyl ring was isolated in this reaction, presumably suggesting that the β-elimination of the sulfoxide moiety is even faster than the rearrangement of the traditional radical clock, the α-cyclopropyl radical. This result is not so surprising in view of the estimated rate of about $10^9 s^{-1}$ for the β-elimination of the arylsulfinyl radical [20] compared to the generally admitted rate of $5.10^7 s^{-1}$ for the opening of related α-cyclopropyl radicals [21].

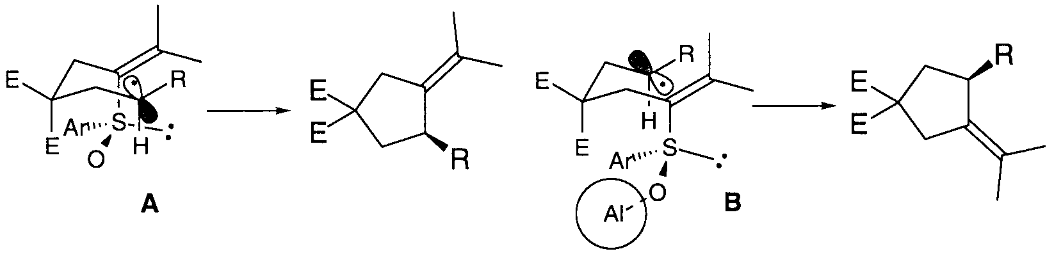
We thus decided to examine the behavior of terminally disubstituted vinylsulfoxides, anticipating that the addition of a substituent *cis* to the sulfoxide moiety should create some additional allylic strain and thus should freeze the reactive conformations and enhance the stereoselectivity. This proved correct since terminally disubstituted vinylsulfoxides **38** and **40** afforded much higher stereoselectivities, up to 98% ee [19]. In both cases, no significant decrease of stereoselectivity was observed when running the reaction at 0 °C and the chemical yield was greatly improved (Scheme 9).

The compatibility of sulfoxides with aluminum-based Lewis acids [22] drove us to the utilization of methylaluminum-bis-2,6-di-tert-butyl-4-methylphenoxide (MAD) in this cyclization. The complexation of the sulfoxide moiety should modify the steric environment, and possibly reverse the group priorities. This hypothesis proved correct since an almost complete inversion of induction was observed in presence of MAD (Scheme 10).

The above model allows a rationalization of these data. When no Lewis acid is present, the radical cyclization takes place through pseudo-chair **A**, in which the sulfoxide in the lowest energy conformer is present with the lone pair *s-cis* to the vinyl moiety. The attack takes place *syn* to the S–O bond



Scheme 9



Scheme 10

and *anti* to the *p*-tolyl group; the bulky alkyl group is thus forced into a pseudo-equatorial position. In the presence of the very bulky MAD Lewis acid, which complexes to the oxygen atom of the sulfoxide group, the radical cyclization would occur as depicted in transition state **B**, *syn* to the bulky *p*-tolyl group. This model also applies to a large extent to monosubstituted alkenes. However, these less-rigid systems easily assume other reactive conformations, which decreases the overall selectivity of the process. We have studied many other precursors and have notably noticed that the enantioselectivity drops, with a less sterically demanding R group, and that MAD is the most satisfactory Lewis acid.

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