Asymmetric Intramolecular Radical Vinylation Using Enantiopure Sulfoxides as Temporary Chiral Auxiliaries

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Abstract: A very diastereoselective addition−elimination sequence affords cyclopentane derivatives in high enantiomeric purities. The enantiopure sulfoxide unit serves as a very efficient temporary chiral auxiliary in this tandem reaction. Interestingly, the presence of the MAD Lewis acid totally reverses the stereochemical outcome of this reaction. Several determining parameters of this sequence have been investigated: the substitution of the vinyl sulfoxide moiety, the nature of the prochiral radical, the aromatic substituent of the sulfoxide group, the tether, and the role played by different Lewis acids.

For the past decade, radical reactions have occupied a prominent position in the realm of asymmetric synthesis.[1] This is due in part to the high compatibility of radical reactions with a large number of interesting functionalities, notably present on chiral auxiliaries, and to the possibility of optimizing the stereoselectivities on using Lewis acids.[2] For instance, the addition of a carbon-centered (alkyl or vinyl) radical to an alkene moiety bearing a chiral auxiliary has been well studied (Figure 1). Generally higher diastereoselectivities are obtained when the addition occurs in the position α to the chiral auxiliary.[3−6] Good to excellent β-diastereoselectivities could also be observed,[7−10] the use of Lewis acids being critical in the case of chiral acrylates[11,12] and *N*-enoyloxazolidinones.[13]

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,[9] while the pure carbon systems have so far led to poor results, even in the case of *N*-sulfinimines.[14] This failure is illustrated by the reaction of (*E*)-vinyl sulfoxide **1** (Scheme 1). When submitted to low-temperature radical reaction conditions (Bu_3SnH, Et_3B/O_2), two diastereomers of the methylene cyclopentane **2** were formed in an equimolar ratio. Running the same reaction at a lower temperature (−78 °C) does not yield any improvement. A rationale for this is the likely absence of control of the s-cis or s-trans vinyl sulfoxide conformation (Figure 2).[15−19] Since sulfoxides are known to be compatible with aluminum-based Lewis acids,[20,21] we ran this reaction in

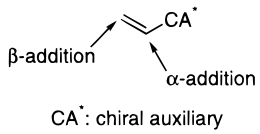
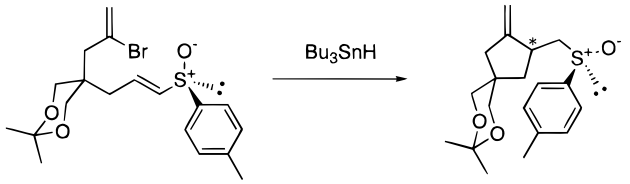


Figure 1.

Scheme 1



Conditions	Yield (%)	ds
Et_3B / O_2, rt	69	50 : 50
Et_3B / O_2, -78°C	89	50 : 50
Et_3B / O_2, -78°C, Al(*i*-Bu)$_3$	89	54 : 46
Et_3B / O_2, -78°C, MAD	90	61 : 39

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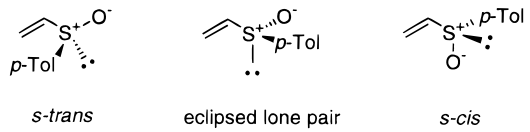
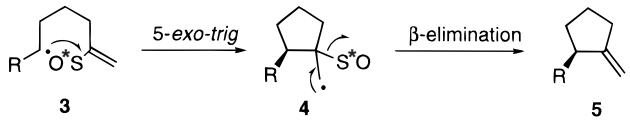


Figure 2.

Scheme 2



the presence of triisobutyl aluminum and MAD (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)), anticipating that we would freeze the reactive conformations and boost the stereoselectivity. The best result (22% de), though still quite mediocre, was obtained with the bulkier MAD. Obviously, no synthetic application could ensue from these findings. One could figure out that an acceptable level of diastereoselectivity could be attained on a more sophisticated reacting system, for instance by implementing a second Lewis base which would set the stage for a chelation in the presence of a Lewis acid. This was indeed achieved in an intermolecular version by Toru[10] who solved the diastereoselective intermolecular addition of alkyl radicals on 2-arylsulfinyl-2-cyclopentenones. In the presence of aluminum- or titanium-based Lewis acids, and by adjusting the size of the aromatic moiety on the sulfoxide (2,4,6-trimethylphenyl or 2,4,6-triisopropylphenyl), very high diastereomeric excesses were observed.

We preferred modifying our strategy according to the tandem reaction depicted in Scheme 2. The sequence would consist of a 5-exo-trig cyclization of a prochiral radical in an anti-Michael orientation, followed by the previously reported elimination of β-sulfinyl radicals[22−28] to furnish alkylidene cyclopentane **5**.[29] Implying an a priori quite favorable α-selectivity, this radical addition should be highly diastereoselective. To test this reaction, we synthesized precursors **19**−**33** (Scheme 3). The scope and the limitations are given in this article and we varied the following parameters: the substituents of the double bond, the nature of the prochiral radical, the role of Lewis acids, the sulfoxide moiety, and the tether.

Results and Discussions

1. Synthesis of Precursors. To prepare precursors **19**−**30**, we coupled allyl bromides **15**−**18**, easily prepared from the chemistry developed by Maignan,[30] with the sodium anion of selenylated malonates **6**−**14** (Scheme 3). Malonate **6** was obtained from the methoxyselenylation of the prenyldimethylmalonate.[31] The other selenylated malonates **7**−**14** were prepared through radical phenylselenyl group transfer according to the method of Byers.[32] The synthesis of the mesityl and the trisyl (*R*)-vinylsulfoxides was based on Kagan's procedure using chiral sulfate derivatives.[33] With these compounds in hand, precursors **31**−**33** were prepared by similar chemistry, albeit in lower yields (see Supporting Information). Finally, alkylation of the lithium anion of (*R*)-cyclohexylidene-*p*-tolyl sulfoxide **34**[34] with the iodide **35** gave a high yield of precursor **36**. Racemic precursors were synthesized from the commercially available phenylvinyl sulfoxide.

2. Radical Cyclizations. The radical cyclizations were generally conducted at low temperature from −78 to 0 °C in the presence of triethylborane and O_2 as an initiating system.[35] The racemic products were obtained by running the reaction in classical conditions: AIBN in refluxing benzene. In both cases an excess of initiator and tin hydride had to be used, since the process is not a chain reaction. Indeed, the resulting sulfinyl radical disproportionates rapidly and does not carry on the radical chain properly.[36]

3. Determination of Enantiomeric Excesses. The cyclization products **37**−**48** were reduced with $LiAlH_4$ to provide diols **49**−**58**. The ee determination was performed on these compounds using the chiral phosphorus derivatives NMR method of Alexakis and Mangeney,[37]which can be applied to 1,3-diols bearing a proximate stereogenic center. However, in our case, we sometimes faced some depreciated values and some problems of reproducibility. This may be attributed to the fact that the stereogenic center on diols **49**−**58** is too far away from the phosphorus atom. Fortunately, the enantiomeric diols could also be separated by chiral GC analysis, using a Chirasil-Dex CB column.

4. The Vinyl Sulfoxides Substituents (R_2 and R_3 Substituents). Our approach was initially tested with *E* precursor **19**, bearing an isopropyl group on the vinyl sulfoxide moiety (Scheme 6). Under low-temperature radical cyclization conditions, **19** underwent an exclusive 5-exo-trig radical cyclization to afford cyclopentyl derivative **37** in 60% yield (Table 1, entry 1). 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 **20** (entry 3). 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

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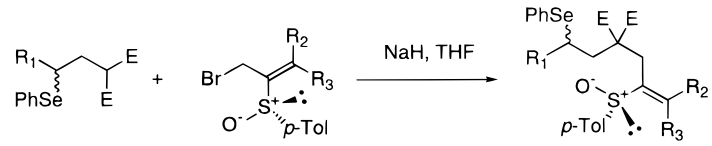
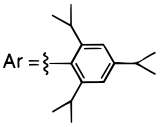
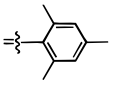
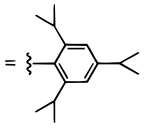
Scheme 3



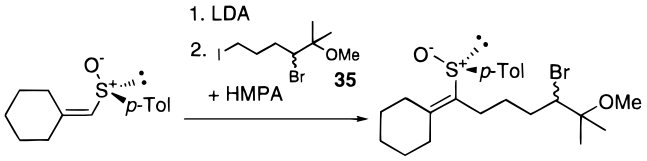
6, R_1 = 
7, R_1 = OEt
8, R_1 = CH_2OH
9, R_1 = CH_2OTBS
10, R_1 = CH_2OEt
11, R_1 = *n*-Bu
12, R_1 = *c*-Hex
13, R_1 = $CH(OMe)_2$
14, R_1 = *t*-Bu

15, R_2 = *i*-Pr, R_3 = H
16, R_2 = *c*-Pr, R_3 = H
17, $R_2 = R_3 = -(CH_2)_5-$
18, $R_2 = R_3$ = Me

19, R_1 =  , R_2 = *i*-Pr, R_3 = H
20, R_1 =  , R_2 = *c*-Pr, R_3 = H
21, R_1 =  , $R_2 = R_3 = -(CH_2)_5-$
22, R_1 =  , $R_2 = R_3$ = Me
23, R_1 = OEt, $R_2 = R_3$ = Me
24, R_1 = CH_2OH, $R_2 = R_3$ = Me
25, R_1 = CH_2OTBS, $R_2 = R_3$ = Me
26, R_1 = CH_2OEt, $R_2 = R_3$ = Me
27, R_1 = *n*-Bu, $R_2 = R_3$ = Me
28, R_1 = *c*-Hex, $R_2 = R_3$ = Me
29, R_1 = $CH(OMe)_2$, $R_2 = R_3$ = Me
30, R_1 = *t*-Bu, $R_2 = R_3$ = Me

31, R_1 = CH_2OEt, Ar = 
32, R_1 = *c*-Hex, Ar = 
33, R_1 = *c*-Hex, Ar = 

Scheme 4



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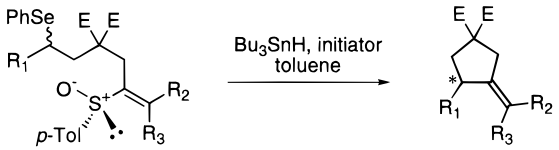

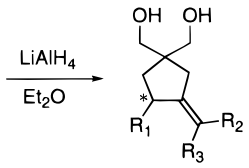

49, R_1 =  , R_2 = *i*-Pr, R_3 = H
50, R_1 =  , R_2 = *c*-Pr, R_3 = H
51, R_1 =  , $R_2 = R_3 = -(CH_2)_5-$
52, R_1 =  , $R_2 = R_3$ = Me
53, R_1 = OEt, $R_2 = R_3$ = Me
54, R_1 = CH_2OEt, $R_2 = R_3$ = Me
55, R_1 = *n*-Bu, $R_2 = R_3$ = Me
56, R_1 = *c*-Hex, $R_2 = R_3$ = Me
57, R_1 = $CH(OMe)_2$, $R_2 = R_3$ = Me
58, R_1 = *t*-Bu, $R_2 = R_3$ = Me

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,[38] compared to the generally admitted rate of 5×10^7 s^{-1} for the opening of related α-cyclopropyl radicals.[39] When the reaction

Scheme 6

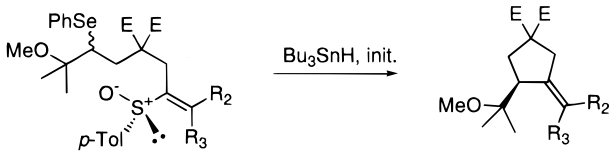

Table 1. Results of the Tandem Reaction (yields and stereoselectivity) with Variation of the R_2 and the R_3 Groups

entry	precursor	R_2, R_3	*T*, °C	product; yield, %[a]	ee, %[b] (abs config)
1	**19**	R_2 = *i*-Pr, R_3 = H	−78	**37**; 60	73 (*S*)
1	**19**	R_2 = *i*-Pr, R_3 = H	0	**37**; 74	65 (*S*)
3	**20**	R_2 = *c*-Pr, R_3 = H	−78	**38**; 52[c]	73 (*S*)
4	**20**	R_2 = *c*-Pr, R_3 = H	0	**38**; 90	42[d] (*S*)
5	**21**	$R_2 = R_3 = -(CH_2)_5-$	−40	**39**; 62	88 (*S*)
6	**21**	$R_2 = R_3 = -(CH_2)_5-$	0	**39**; 77	86 (*S*)
7	**22**	$R_2 = R_3$ = Me	−78	**40**; 54	>98 (*S*)
8	**22**	$R_2 = R_3$ = Me	−40	**40**; 67	>98 (*S*)
9	**22**	$R_2 = R_3$ = Me	0	**40**; 93	98 (*S*)
10	**22**	$R_2 = R_3$ = Me	10[e]	**40**; 89	92 (*S*)

[a] See Experimental Section. [b] Determined by chiral GC analysis. [c] Starting material (38%) was recovered. [d] Determined by ^{31}P NMR, see ref 37. [e] AIBN, sun lamp initiation.

was run at 0 °C, the yield of cyclization adduct **38** dramatically increased (90%, entry 4). The given ee (42%) does not really mean a loss of stereoselectivity. More likely, it just illustrates the depreciation of ee that we sometimes observed with the phosphorus method (see above). To probe this, at −78 °C (entry 3), the phosphorus method gave a ee of 48% instead of 73% by GC. It should also be pointed out that in both cases, as determined by NOE measurements, the *E* configuration of the alkene moiety of **37** and **38** was maintained.

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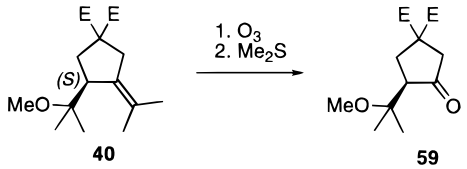
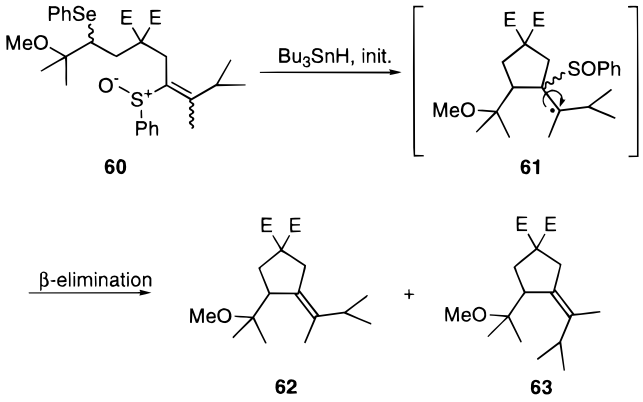
Scheme 7



We thus decided to examine the behavior of terminally disubstituted vinyl sulfoxides, 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 vinyl sulfoxides **21** and **22** afforded much higher stereoselectivities, up to 98% ee (Table 1, entries 5 to 9). In both cases, no significant decrease of stereoselectivity was observed when running the reaction at 0 °C and the chemical yield was greatly improved. With a sunlamp and AIBN initiation, the stereoselectivity remained very high (Table 1, entry 10), thus discarding any role played by the triethylborane in the stereoselectivity of the reaction. The high enantiomeric purity of **40** led us to ozonolyze this compound, to provide ketone **59**, on which a CD measurement was performed to determine the absolute configuration of the stereogenic center (Scheme 7). An intense positive Cotton effect was observed, and the configuration was deduced to be (*S*) on **40**.[40−42] Ozonolysis of **37**−**39** also afforded ketone **59** with specific rotations of positive sign as in the case of **40**, thus suggesting a similar major (*S*) absolute configuration for **37**−**39**.

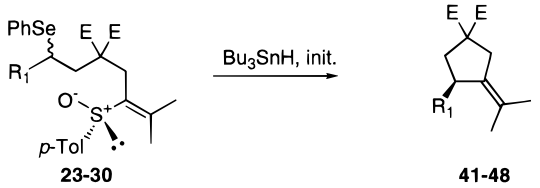
The results obtained with the cyclopropyl precursor **20** intimate that the β-elimination of the sulfinyl radical is faster than the opening of the α-cyclopropyl radical. We wanted to gain a better insight into this β-elimination, namely: does it occur with inversion or retention of chemistry of the alkene moiety? The cyclizations of **19** and **20** brought the first elements of information, since, as previously mentioned, they proceeded with a complete retention of configuration. We may wonder whether this β-elimination is not under kinetic control, implying that it is the more favorable pathway at any temperature. This would corroborate the findings of Boothe,[23] who reported that the radical β-elimination of diastereomeric 2-bromo-3-phenylsulfinylbutanes to give but-2-ene "occurs before rotation about the C−C bond and consequent equilibration of radical conformations can occur". However, we could not synthesize the *Z* isomers of **19** and **20**, because of the *E* configuration of the obtained allyl bromides,[30] and this forbids any firm conclusion. We thus decided to prepare precursor **60**, isolated as a *E*:*Z* 1:1 mixture of diastereomers. The stereochemical outcome of the radical cyclization of **60** proved to be temperature dependent (Scheme 8). At low temperature, the reaction is highly diastereoselective in favor of the *E* isomer **62**, while raising the temperature significantly increases the amount of the *Z* isomer **63**. This finding suggested to us that in this case, the β-elimination of the sulfinyl radical is under thermodynamic control. The formation of a tetrasubstituted double bond is probably less favorable than the formation of a trisubstituted one and at low temperature the relative rates (rotation vs β-elimination) must change, mainly because of a less contributing $-T\Delta S^{\#}$ term for

Scheme 8



Conditions	Yield (%)	*E*-**62** : *Z*-**63**
AIBN, PhH, Δ	75	70 : 30
Et_3B / O_2, PhH, rt	74	77 : 23
AIBN, PhH, hν, 10°C	61	83 : 17
Et_3B / O_2, Tol., -78°C	60	97 : 3

Scheme 9



the β-elimination process. Consequently, the bond rotation would be more favorable from **61** in a cold medium, resulting in the formation of the more stable diastereomer **62**. At higher temperature, the β-elimination would augment, thus preventing the thermodynamic equilibrium to be completely reached and giving the **62**−**63** mixture.

5. The Prochiral Radical (R_1 group). To have an insight into the synthetic potential associated with this reaction, we altered the nature of the prochiral radical, by varying the R_1 substituent (Scheme 9). The obtained results call for several comments. First, as previously observed, there is no significant loss of stereoselectivity on changing the reaction temperature from −78 to 0 °C or from −20 to 0 °C (entry 3 vs 4, 7 vs 8, and 10 vs 11); however, a substantial gain in yield is generally recorded. Second, on a general basis, the bulkier the R_1 substituent, the higher the stereoselectivity. Notably, high ee values were obtained with bulky secondary or tertiary substituents (R_1 = cyclohexyl, *t*-Bu).

All these data can be rationalized by the following model (Scheme 10). We presumed that the preferred conformation for the sulfoxide when R_2 and R_3 are alkyl groups is the one that eclipses the lone pair and the C−R_3 bond.[16,19] The radical then cyclizes in the pseudochair **65**, anti to the bulky aromatic group, and placing the R_1 group in pseudoequatorial position, to avoid 1,3-diaxial interactions with the sulfoxide moiety and an ester group. This produces the major enantiomer **67**, consistent with our experimental results of Tables 1 and 2. However, for R_3 = H (precursors **19** and **20**), the s-cis conformation becomes more accessible[17] and radical cyclization through transition state **64**, anti to the *p*-tolyl group, is now possible. This would explain why we obtained cyclization products **37** and **38** with a lower enantioselectivity.

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Scheme 10

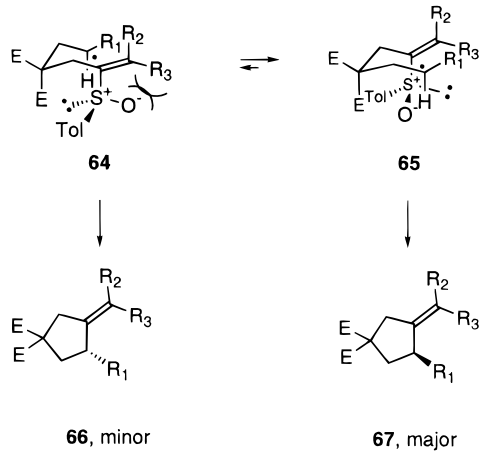


Table 2. Effect of the Prochiral Radical (R_1 Group)

entry	precursor	R_1	*T*, °C	product; yield, %[a]	ee, %[b] (abs config)
1	**23**	OEt	0	**41**; 95	66[c] (*S*)
2	**24**	CH_2OH	0	**42**; 100	4[d] (*R*)
3	**25**	CH_2OTBS	−20	**43**, 42	26[e] (*R*)
4	**25**	CH_2OTBS	0	**43**; 77	26[e] (*R*)
5	**26**	CH_2OEt	0	**44**; 89	22 (*R*)
6	**27**	*n*-Bu	0	**45**; 88	47 (*S*)
7	**28**	cyclohexyl	−78	**46**; 43	84 (*R*)
8	**28**	cyclohexyl	0	**46**; 72	85 (*R*)
9	**29**	$CH(OMe)_2$	0	**47**; 100	31[f] (*S*)
10	**30**	*t*-Bu	−20	**48**; 95	94 (*R*)
11	**30**	*t*-Bu	0	**48**; 94	89 (*R*)

[a] See Experimental Section. [b] Determined by chiral GC analysis. [c] Determined by ^{31}P NMR. [d] Determined directly on 42. [e] Determined on **42** after desilylation of **43**. [f] Determined by transacetalisation with (*R*,*R*)-(+)-diphenyl-1,2-ethanediol.

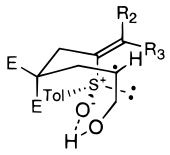


Figure 3.

Two examples of Table 2 are worthy of further discussion. We studied the behavior of alcohol **24**, anticipating that we could lock the transition state through hydrogen bonding between the hydroxy group and the sulfoxide moiety.[43] In comparison to the ether precursors **25** and **26**, a notable drop of selectivity was recorded (Table 2, entry 2 vs. 4 and 5), as if to a slight extent some hydrogen bonding setting the CH_2OH group in pseudoaxial position (see Figure 3) indeed intervened and would balance out the usual pseudoequatorial attack. This too weak effect for a reversal of stereoselectivity could be rationalized by a relatively loose ten-membered-ring chelate.

Another striking piece of data is the cyclization of **23**. A fair selectivity is obtained (66% ee) with this compound, especially when compared to R_1 groups of similar size (precursors **26** and **27**). Complexation of the ethoxy group with surrounding triethylborane molecules, resulting overall in a larger group, probably implies a more pronounced pseudoequatorial orientation.

6. Effect of Lewis Acids. Reexamining Scheme 10 drove us to the utilization of aluminum-based Lewis acids. The complexation of the sulfoxide moiety should modify the steric environment, and possibly reverse the group priorities (Scheme 11). We initially focused on precursor **22** which offered the best results. The addition of 4 equiv of diethylaluminum chloride proved to be encouraging, since a notable decrease of selectivity was obtained, suggesting (Table 3, entry 1) that the two antagonist attacks **68** and **69** (Scheme 12) took place. Presumably, by using a very bulky Lewis acid like MAD, we should be able to restrict the cyclization through approach **68**, and indeed, we obtained the (*R*) antipode of **40** with a ee of 92% (Table 3, entry 2). Furthermore, on a general basis, the addition of MAD allowed a reversal of the stereochemical outcome of the reaction, with higher enantioselectivities than the reactions without MAD (up to 62% for precursor **26**).

We also examined the behavior of other Lewis acids developped by Yamamoto and Maruoka, such as MAPH and ATPH[44,45] (Figure 4). In most cases, we also witnessed an inversion of the stereoselectivity (Table 3, entries 6, 12, and 13); however, the outcome was not as satisfactory as the one obtained with MAD. The ATPH Lewis acid is an extremely bulky one; moreover, it possesses three oxygenated ligands so that the Lewis acidity is decreased. This presumably could result in a less tight complexation of the oxygen of the sulfinyl moiety,

Scheme 11

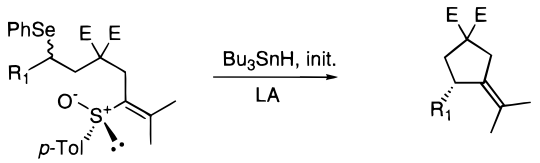
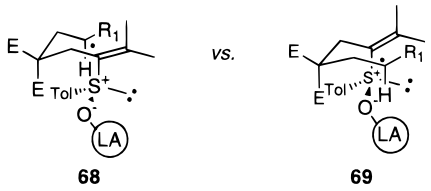


Table 3. Effect of Lewis Acids

entry	precursor	additive	product; yield, %[a]	ee, %[b] (abs config)
1	**22**	Et_2AlCl	**40**; 63	60 (*S*)
2	**22**	MAD	**40**; 52	92 (*R*)
3	**20**	MAD	**38**; 46	82 (*R*)
4	**23**	MAD	**41**; 35	52 (*R*)
5	**24**	MAD	**42**; 65	76 (*R*)
6	**24**	ATPH	**42**; 23	38 (*R*)
7	**25**	MAD	**43**; 66	84 (*R*)
8	**26**	MAD	**44**; 84	84 (*R*)
9	**29**	MAD	**47**; 89	92 (*R*)
10	**27**	MAD	**45**; 70	95 (*S*)
11	**28**	MAD	**46**; 88	93 (*R*)[d]
12	**28**	MAPH	**46**; 75	34 (*R*)
13	**28**	ATPH	**46**; 56	86 (*R*)
14	**30**	MAD	—[c]	
15	**30**	MAPH	**48**; 55	57 (*R*)

[a] All reactions were run at 0 °C, see Experimental Section. [b] Determined by chiral GC analysis. [c] Reduced starting material was isolated (80%). [d] A CD measurement on the corresponding ketone **70** showed an intense negative Cotton effect, suggesting a (*R*) configuration for **46**.

Scheme 12



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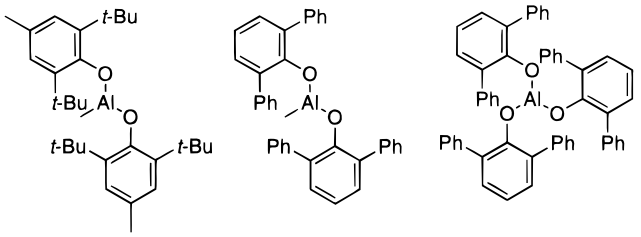

Figure 4.

Table 4. Effect of the Arysulfinyl Group

entry	precursor	aromatic substituent	product; yield, %[a]	ee, %[b] (abs config)
1	**31**	trisyl	**44**; 52	49 (*S*)
2	**32**	mesityl	**46**; 80	68 (*R*)
3	**33**	trisyl	**46**; 69	66 (*R*)

[a] All reactions were run at 0 °C, see Experimental Section. [b] Determined by chiral GC analysis.

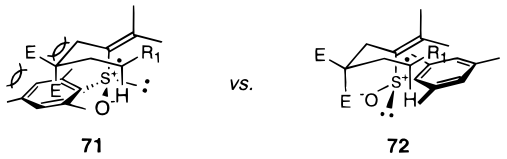

Figure 5.

and consequently in a drop of the selectivity. The MAPH is less sterically demanding than ATPH and MAD and this would be directly reflected by the weaker enantiomeric excesses we obtained (entries 12 and 15). The *t*-Bu precursor **30** displayed a rather peculiar behavior with Lewis acids certainly because of steric effects. No cyclization in the presence of MAD could be achieved, as if the approach syn to the *p*-tolyl group as of the bulky radical **68** was completely impeded. No inversion of the enantioselectivity was observed with MAPH, instead a decrease of selectivity (Table 3, entry 15), which suggests a poor complexation and recalls the result of precursor **22** in the presence of Et_2AlCl (entry 1) occurred.

7. The Arylsulfinyl Groups. The recent work of Toru illustrates the important role played by the aromatic substituents of the sulfoxide auxiliary. In our case, we could anticipate that a bulky substituent would lock the reacting conformations and notably force the pseudoequatorial orientation of the R_1 group. The results obtained with the OEt precursor **31** were encouraging in this sense, since an increase of ee of 27% was observed (Table 4, entry 1 vs Table 2, entry 5). We next wanted to check if we could render the total stereoselectivity of the reaction with R_1 = cyclohexyl (Table 2, entries 7 and 8). However, with the cyclohexyl precursors **32** and **33**, the stereoselectivity confusingly dropped by 20%. Reinspecting the models showed us that conformation **71**, which eclipses the lone pair, is no longer the best one (Figure 5). Interactions involving the bulky aromatic moieties (trisyl or mesityl) with the axial ester group and the nearby methylene take place. In contrast, the s-trans conformation **72**[15,18] appears more plausible. The R_1 group would still be placed in pseudoequatorial position. However, in the case of the bulky cyclohexyl group, the pseudoequatorial approach is also hampered by the substituent of the aromatic ring at the 2- or 6-position. This additional constraint would result in a larger amount of pseudoaxial attack and thus justify the erosion of the ee (Table 4, entry 3). In comparison, the smaller CH_2-OEt group would still fit for a major pseudoequatorial orientation. Moreover, this orientation could be enhanced by some dipolar repulsions between the ethoxy and the sulfinyl groups.

Scheme 13

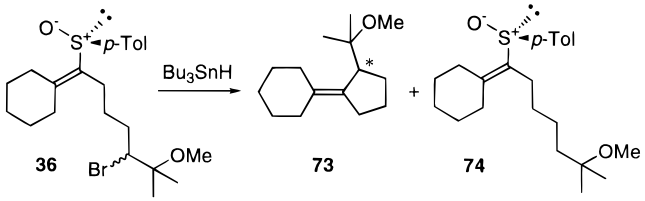

Table 5. Reactivity and Stereoselectivity of a Precursor with No *gem*-Dicarboxyl Groups

entry	precursor	conditions	yield of **73**, %	ee, %[a]	yield of **74**, %
1	**36**	Et_3B/O_2, 0 °C	0	−	90
2	**36**	AIBN, toluene, Δ, 4×10^{-4} mol·h^{-1}	65	0	35
3	**36**	AIBN, toluene, 10 °C, $h\nu$, 13×10^{-4} mol·h^{-1}	15	30	80
4	**36**	Et_3B/O_2, 0 °C, MAD	0		90

[a] Determined by chiral GC analysis.

8. The Tether. The radical cyclization of **36** is a nice illustration of the *gem*-dicarboalkoxy effect evidenced by Jung in cycloadditions (Scheme 13).[46] No cyclization adduct **73** can be obtained at low temperature (Table 5, entry 1), the reduction product **74** being isolated in high yield. Only in refluxing toluene and with a slow addition of tin hydride could we isolate **73**, albeit in average yield. As expected, in these conditions, no stereoselectivity was detected. At 10 °C, the radical cyclization proceeded slugglishly (15% of **73**) and with a quite mediocre stereoselectivity (Table 5, entry 3), compared to the product **40**. Therefore, the malonate moiety, presumably because of possible 1,3-diaxial interactions, not only favors the cyclization by restricting the number of reacting conformations, but also appears to play a key role in the stereoselectivity of the sequence. The presence of MAD in the reaction medium did not bring any amelioration in terms of reactivity.

9. Conclusion. An efficient 5-exo-trig radical cyclization in an anti-Michael orientation followed by the β-elimination of a homochiral sulfinyl moiety opens a new access to enantiopure alkylidenecyclopentanes. This sequence relies on the use of a temporary chiral auxiliary. Very high enantioselectivities can be reached, up to 98% ee. The β-elimination process was shown to be faster than the opening of a cyclopropyl ring in the case of a trisubstituted alkene and competitive with bond rotation in the case of a tetrasubstituted alkene. Gratifyingly, the enantioselectivity can be reversed and improved by introducing the bulky MAD Lewis acid in the reaction medium, giving a new illustration of the versatile use of Lewis acids for stereoselective radical reactions. Applications of this methodology in the synthesis of enantiopure heterocyclic compounds are underway.

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Supporting Information Available: All experimental procedures and spectral data for new compounds, as well as ^{1}H NMR spectra for **7**, **10**, **13**, **19**, **20**, **21**, **24**, **25**, **26**, **27**, **28**, **30**, **A**, **B**, **31**, **32**, **33**, **36**, **41**, **45**, **53**, **57**, **60**, **70**, **73**, and **74** and ^{13}C NMR spectra for **23**, **29**, **39**, and **59**; chiral GC spectra of diols **52** showing all experiments with precursor **22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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