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Radical Cyclization/β-Elimination Tandem Reactions: Enantiopure Sulfoxides as Temporary Chiral Auxiliaries**

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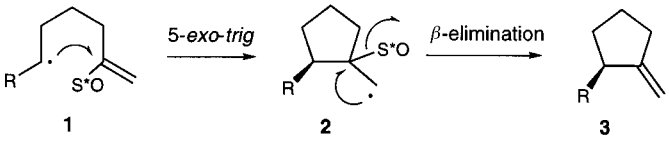
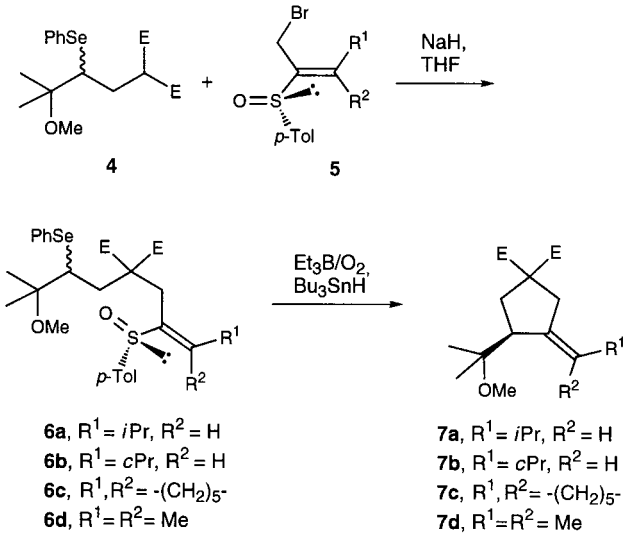
Owing to their compatibility with a large number of interesting functionalities and their occasionally high efficiency, diastereoselective radical cyclizations now represent a strategy of choice in the field of asymmetric synthesis.[1, 2] Notably, the addition of a carbon-centered (alkyl or vinyl) radical to an alkene moiety bearing a chiral auxiliary has been well studied, and generally higher diastereoselectivities are obtained when the addition occurs in the position α to the chiral auxiliary.[3] Nonetheless, good to excellent β-diastereoselectivities have also been observed,[4] the use of Lewis acids being critical in the case of chiral acrylates[5] and oxazolidinones amides.[6] Continuing our interest in chiral sulfur-based auxiliaries (sulfoxides[4c] and sulfinimines[7]), we have proposed the tandem reaction depicted in Scheme 1 as a new means for the preparation of enantiomerically enriched five-membered rings. We anticipated a highly diastereoselective radical cyclization (with an a priori quite favorable α-selectivity), followed by the well-documented elimination of β-sulfinyl radicals.[8]



1 2 3

Scheme 1. Proposed new tandem reaction. S*O = homochiral sulfoxide auxiliary

This approach, which relies on the easy introduction and the low cost of the homochiral sulfoxide unit, was first tested with **6a**, which is easily prepared by coupling of malonate **4**[9] and the known enantiopure *E* allylic bromide **5a** (Scheme 2).[10] Under low-temperature radical cyclization conditions (Et_3B/O_2),[11] **6a** underwent an exclusive *anti*-Michael 5-*exo-trig* radical cyclization to afford the cyclopentyl derivative **7a** in 60% yield (Table 1, entry 1). The substitution of 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 of this sequence (54% *ee*) was equally interesting.[12]



Scheme 2. Synthesis of the precursors **6** and the subsequent radical tandem reactions. E = CO_2Me

Table 1. Results of the tandem reaction (yields and stereoselectivity)

Entry	Precursor	T [°C]	Lewis acid	Product, yield [%][a]	*ee* [%],[12] abs. config.[b]
1	**6a**	−78	–	**7a**, 60	54, *S*
2	**6b**	−78	–	**7b**, 52[c]	48, *S*
3	**6b**	0	–	**7b**, 90	42, *S*
4	**6b**	0	MAD	**7b**, 46	64, *R*
5	**6c**	−40	–	**7c**, 62	88, *S*
6	**6c**	0	–	**7c**, 77	86, *S*
7	**6d**	−78	–	**7d**, 72	>96, *S*
8	**6d**	−40	–	**7d**, 70	>96, *S*
9	**6d**	0	–	**7d**, 93	>96, *S*
10	**6d**	0	Et_2AlCl	**7d**, 63	60, *S*
11	**6d**	0	MAD	**7d**, 52	92, *R*

[a] See the Experimental section. [b] The absolute configuration of **7d** was determined by a CD measurement.[16] Ozonolysis of **7a**–**c** afforded ketone **9** with positive specific rotations as found for **7d**, which also suggests a mainly *S* configuration for **7a**–**c**. [c] Starting material (38%) was recovered.

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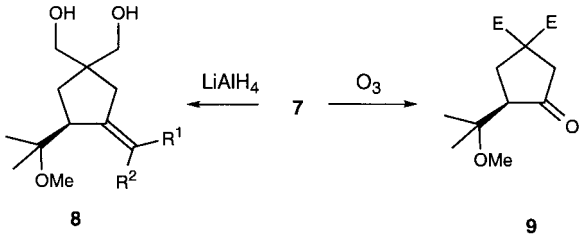
A similar result in terms of yield and stereoselectivity was obtained with **6b** (Table 1, entry 2). No sulfoxide adduct with cleavage of the cyclopropyl ring was isolated in this reaction, which suggests that the β-elimination of the sulfoxide moiety is faster than the rearrangement of the traditional radical clock, the α-cyclopropyl radical. This result is not surprising in view of the estimated rate of about $10^9\,s^{-1}$ for the β-elimination of the arylsulfinyl radical;[13] the generally recognized rate for the opening of related α-cyclopropyl radicals is $5.10^7\,s^{-1}$.[14] When the reaction was run at 0 °C, the yield of cyclization adduct **7b** dramatically increased (90%, Table 1, entry 3), but at the expense optical purity.

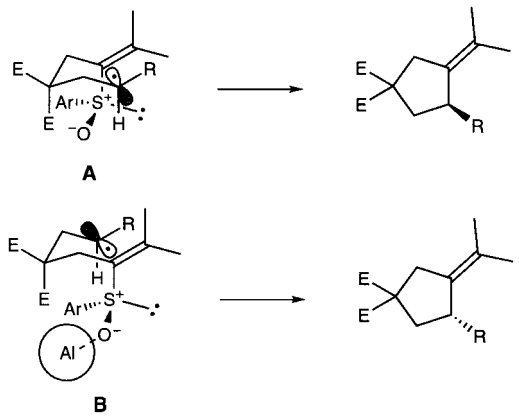
We thus decided to examine the behavior of terminally disubstituted vinyl sulfoxides. We anticipated that the addition of a substituent *cis* to the sulfoxide moiety would create additional allylic strain,[15] and thus freeze the reactive conformations and boost stereoselectivity. This proved correct, since terminally disubstituted vinyl sulfoxides **6c** and **6d** afforded much higher stereoselectivities (up to 96% *ee*; Table 1, entries 5 and 7). In both cases, no significant decrease in stereoselectivity was observed when the reaction was carried out at 0 °C, and the chemical yield was greatly improved. The high enantiomeric purity of **7d** led us to ozonolyze this compound to provide ketone **9**. A CD measurement on this product was performed to determine the absolute configuration of the stereogenic center. An intense positive Cotton effect was observed, from which the *S* configuration was inferred for **7d** (Scheme 3).[16]



Scheme 3. Derivatizations of the cyclization products **7**. See Scheme 2 for E, R^1, and R^2.

With a view to reverse the stereochemical outcome of the reaction, the effect of a Lewis acid was investigated next.[4d] While the use of Et_2AlCl promisingly diminished the optical yield (Table 1, entry 10), the addition of the very bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) to the reaction medium proved very rewarding, as the *R* enantiomer of **7d** was obtained with 92% *ee* (Table 1, entry 11). This confirmed the versatility of this process.[12] Interestingly, the same effect of inversion was still observed, although to a lesser extent, with the conformationally less constrained cyclopropyl precursor **6b** (Table 1, entry 4).

The stereoselectivities obtained with **6c** and **6d** may be rationalized by the following pseudo-chair transition state models (Scheme 4). When no Lewis acid is present the radical cyclization takes place through transition state **A**, in which the sulfoxide moiety in the lowest energy conformer is present with the lone pair electrons *s-cis* to the vinyl moiety.[15] The attack takes place *syn* to the sulfur–oxygen bond and *anti* to



Scheme 4. Transition state models.

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 a priori more difficult approach could partly explain the lower yield observed with MAD. 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.

In conclusion, a new radical cyclization/β-elimination tandem reaction has been designed which affords alkylidenecyclopentyl derivatives in high optical purities. The absolute configuration of the products can be controlled simply by the presence or the absence of the MAD Lewis acid in the reaction mixture. The efficient β-elimination of the chiral sulfoxide auxiliary augurs well for the synthesis of useful enantiopure cyclopropyl and cyclobutyl derivatives. This and applications to the synthesis of compounds of biological relevance are currently under active investigation in our laboratory.

Experimental Section

General procedure for the cyclization: To a solution of vinyl sulfoxide **6d** (530 mg, 0.89 mmol) in toluene (18 μL) at 0 °C were added under argon *n*-tributyltin hydride (360 μL, 1.3 μmol, 1.5 equiv) and triethylborane (4.5 mL, 4.5 mmol, 5 equiv). Air was injected through the solution every 30 min. After 1.5 h the same quantities of tributyltin hydride and triethylborane were added, and air was again injected. The reaction mixture was stirred at 0 °C for 3 h, diluted with diethyl ether (50 mL), and washed twice with brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography to afford 248 mg of **7d** (93%) as a yellow oil. $R_f = 0.30$ (petroleum ether:diethyl ether, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.72 (s, 3H), 3.67 (s, 3H), 3.10 (s, 3H), 2.94 (d, $J = 14.7$ Hz, 1H), 2.82–2.85 (m, 2H), 2.48 (dd, $J = 13.9$, 8.7 Hz, 1H), 2.38 (dd, $J = 13.9$, 4.2 Hz, 1H), 1.66 (s, 3H), 1.64 (d, $J = 2$ Hz, 3H), 1.15 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 173.4$, 172.6, 133.6, 126.5, 78.7, 59.1, 52.7, 52.6, 49.2, 48.9, 39.3, 34.7, 23.5, 22.9, 22.7, 21.7; IR (film) $\tilde{\nu} = 2920$, 1730, 1070, 730 cm^{-1}; elemental analysis for $C_{16}H_{26}O_5$: found (calcd): C 64.50 (64.41), H 8.83 (8.78); $[\alpha]_D^{25} = -34.0°$ ($c = 1.32$, $CHCl_3$).

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Regioselective Synthesis of *trans*-1 Fullerene Bis-Adducts Directed by a Crown Ether Tether: Alkali Metal Cation Modulated Redox Properties of Fullerene – Crown Ether Conjugates**

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Since the introduction of the tether-directed remote functionalization of fullerenes,[1–3] a variety of bis(cyclopropanated) [60]fullerene derivatives have been synthesized both regio- and stereoselectively[2] by macrocyclization of the carbon sphere by a double Bingel addition.[4] This reaction has provided ready access to bis(methano)fullerenes with *cis*-2, *cis*-3, *e*, *trans*-4, and *trans*-3 addition patterns (Figure 1).[5]

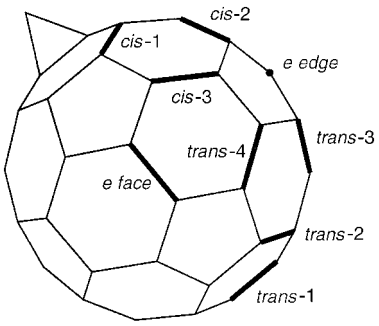

Figure 1. Position notation for bis-adducts of C_{60}.

However, it has proven quite challenging to develop extended tethers with a suitable degree of conformational homogeneity that would span the carbon sphere and direct the second addend into the *trans*-2 and, in particular, the *trans*-1 positions on the opposite pole.[6] Among the up to eight regioisomeric C_{60} bis-adducts isolated from various sequential (nontethered) double additions,[7, 8] the *trans*-1 derivative is almost always the least abundant for both kinetic and statistical reasons. Thus, the stepwise Bingel reaction with diethyl 2-bromomalonate, reported by Hirsch and co-workers,[5, 7] gave the *trans*-1 bis-adduct in only 0.8 – 2% yield after tedious regioisomer separation. Regioselective access to a *trans*-1 bis-adduct was achieved by Kräutler et al. in a most elegant topochemical reaction in which anthracenes are added by cycloaddition to the two poles of the fullerene.[9]

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