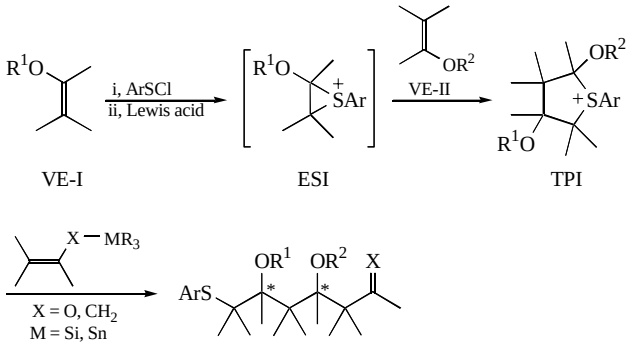
# Highly diastereoselective one-pot four-component coupling of *p*-TolSCl, 1-methoxycycloalkene, methyl vinyl ether and a carbon nucleophile leading to the synthesis of polyfunctional compounds

**Margarita I. Lazareva,[a,b] Yury K. Kryschenko,[a,c] Ron Caple,*[a] Victor G. Young, Jr.[d] and William A. Smit*[b]**

[a] *Chemistry Department, University of Minnesota-Duluth, MN 55812 Duluth, USA. Fax: +218 726 7394*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: +7 095 135 5328*
[c] *Higher Chemical College, Russian Academy of Sciences, 125819 Moscow, Russian Federation. Fax: +7 095 135 8860*
[d] *X-Ray Crystallographic Laboratory, Chemistry Department, University of Minnesota, MN 55455 Minneapolis, USA*

An one-pot $TiCl_4$ initiated assemblage of polyfunctional compounds *via* a sequential coupling of *p*-TolSCl, 1-methoxycycloalkene, methyl vinyl ether and Sn- or Si-capped carbon nucleophile is shown to proceed with high diastereoselectivity at all newly created chiral centres.

The sequence of three kinetically independent intermolecular $Ad_E$ reactions mediated by sulfur-stabilized reagents and intermediates has been recently developed as a versatile method for the one-pot synthesis of polyfunctional compounds from simple precursors in accordance with Scheme 1.[1–3]




**Scheme 1**

At the first step of this sequence, electrophilic addition of ArSCl to the initial alkyl vinyl ether (VE-I) followed by the treatment of the formed adduct with a Lewis acid produced an episulfonium ion-like intermediate (ESI), which reacted further as an electrophile with another alkyl vinyl ether (VE-II) to give a sulfur-stabilized intermediate of the next generation, namely, the five-membered thiophanium ion (TPI). The third step involved electrophilic addition of the TPI at the double bond of the $Alk_3Si/Sn$-capped π-donors with the concomitant removal of the respective $Alk_3Si/Sn^+$ moiety. Various carbon nucleophiles such as allylsilanes and -stannanes, siloxyalkenes and -dienes, cyclic and acyclic silyl ketene acetals were shown to be active as the quenchers at this final step. These data taken together with the previously documented variability of the VE components used for the generation of the TPI-like intermediates well-attested to the generality and preparative promise of the developed procedure.[3]

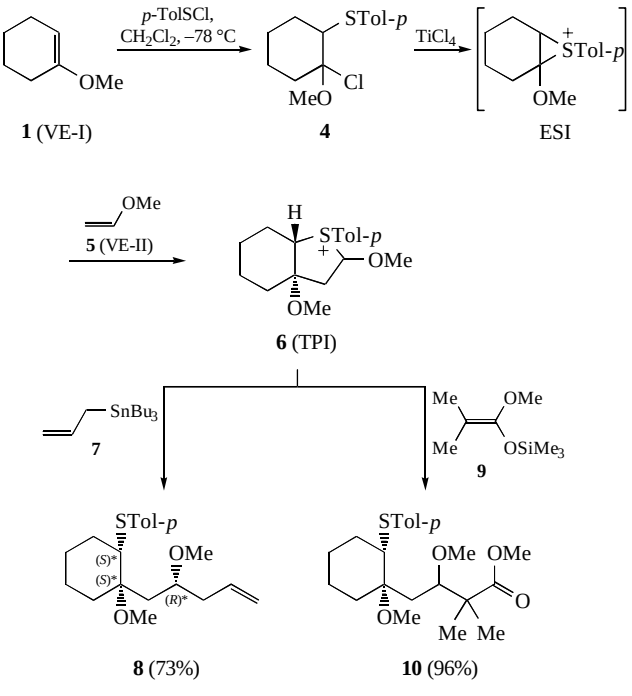
However, it was also found that this coupling, when executed with acyclic vinyl ethers employed as both VE-I and VE-II components, exhibits rather low diastereoselectivity at the newly created 1,3-chiral centres. As a rule, in these cases, nearly 1:1 mixtures of diastereomers are formed, and this ratio was found to be only slightly affected by variations in the reaction parameters (the Lewis acid, the temperature, the solvent and the nature of the ArS substituent).[2,3]

Here we demonstrate that the utilization of 1-methoxycycloalkenes as VE-I component affects dramatically the stereochemical outcome of the described reaction sequence, and highly stereoselective formation of a single diastereomer can be achieved.

1-Methoxycyclohexene **1**, 4-*tert*-butyl-1-methoxycyclohexene **2** and 1-methoxycyclopentene **3** were used as the starting alkene components. The reaction between equimolar amounts of **1** and *p*-TolSCl in $CH_2Cl_2$ solution proceeded almost instantaneously at –78 °C to give corresponding 1,2-adduct **4** (Scheme 2). No attempts were made to isolate this product, and the latter was immediately treated with 1.2 equiv. of methyl vinyl ether **5** in the presence of 1.2 equiv. of $TiCl_4$. The formation of a cationoid complex, presumably TPI salt **6**, was completed within 30 min at –78 °C (TLC monitoring data). After that 2 equiv. of allyltri-*n*-butyltin **7** was added to the reaction mixture, and it was stirred for 1 h at –78 °C. Subsequent treatment of the resulting solution with an aqueous $NaHCO_3$–diethyl ether mixture followed by the standard work-up and column chromatography furnished *Z*-1-methoxy-1-(2′-methoxypent-4′-enyl)-2-(*p*-tolylthio)cyclohexane **8** as a single diastereomer isolated in 73% yield.† The utilization of 1-methoxy-2-methyl-1-trimethylsilylpropene **9** as the quencher for TPI **6** afforded stereochemically pure adduct **10** isolated in 96% yield.

Under essentially the same conditions, alkene **2** was converted to adduct **11** isolated as an individual diastereomer (yield 60%) (Scheme 3).

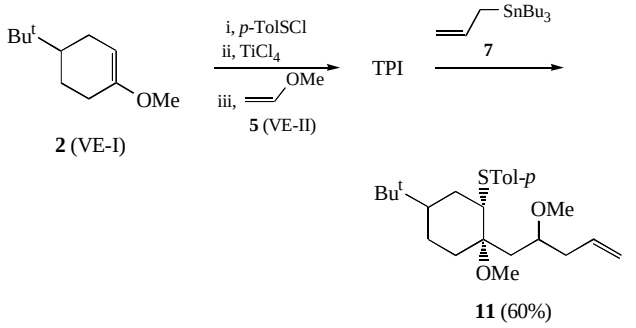
The relative structure of adduct **8** was unambiguously established by single-crystal X-ray analysis of the corresponding sulfone **8a** (prepared by the oxidation of **8** with OXONE®,[4] yield 70%)‡ (Figure 1). It seems reasonable to assume that adducts **8** and **11** belong to the same stereochemical series.




**Scheme 2**

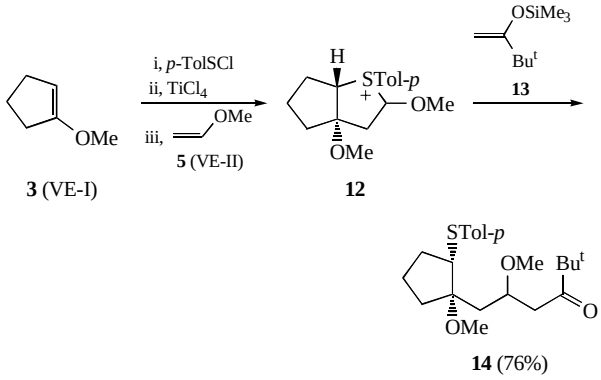
A similar reaction sequence was applied to convert vinyl ethers **3** and **5** into the cationoid complex, presumably TPI salt **12**. Treatment of this intermediate with pinacolone trimethylsilyl enol ether afforded the expected product also isolated as the only diastereomer (yield 76%), its stereochemistry being tentatively assigned as structure **14** (Scheme 4).

It is certainly premature to discuss the steric course of the described reactions in the absence of reliable data on the structure of TPI intermediates **6** and **12**. A comparison of the above result on the nearly complete stereoselectivity of the formation of the three stereogenic centres in adducts **8**, **10**, **11** and **14** with the previously reported non-diastereoselectivity of the similar couplings carried out with acyclic vinyl ethers[2,3] enables us to




**2** (VE-I) **11** (60%)

**Scheme 3**




**3** (VE-I) **12** **14** (76%)

**Scheme 4**

suggest that the conformational rigidity of the bicyclic TPI-like intermediate derived from methoxycycloalkenes is the main factor that controls the steric outcome of the entire coupling. The observed high diastereoselectivity of the multicomponent coupling greatly enhances the potential of the suggested procedure based on the controlled sequence of $Ad_E$ reactions as a novel approach to the convergent synthesis of polyfunctional compounds.

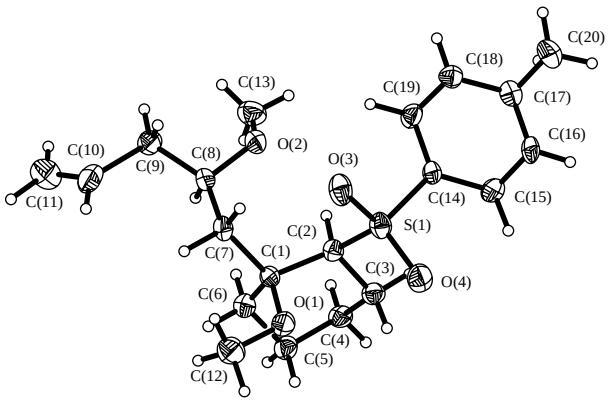



**Figure 1** Molecular structure of sulfone **8a**.

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† Consistent analytical and spectral data ($^1$H and $^{13}$C NMR, HRMS and/or elemental analysis) were obtained for all new products. Diastereomeric purity was ascertained by the careful analysis of $^1$H NMR data. For the reactions leading to the formation of adducts **8**, **11** and **14**, the $^1$H NMR data of the minor chromatographic fractions revealed the presence of trace amounts of the diastereomeric products (less than 10%), but we were unable to isolate these products from the mixtures containing other impurities.

**8**: $R_f$ = 0.30 (hexane–EtOAc = 8:1). $^1$H NMR ($CDCl_3$) $\delta$: 1.45–1.55 and 1.69–1.78 (2m, 8H, 4$CH_2$ in ring), 1.80 (dd, 1H, $CH_A$, $^1J$ 2.4 Hz, $^2J$ 15.3 Hz), 2.14 (dd, 1H, $CH_B$, $^1J$ 8.7 Hz, $^2J$ 15.3 Hz), 2.28 (s, 3H, *Me*Ph), 2.34 (m, 2H, C$H_2$CH=), 3.20 (s, 3H, MeO), 3.27–3.35 (m, 1H, CHS), 3.29 (s, 3H, MeO), 3.42 (m, 1H, C*H*OMe), 5.08 (m, 2H, $CH_2$=), 5.81 (ddt, 1H, CH=, $^1J$ 7.2 Hz, $^2J$ 10.1 Hz, $^3J$ 17.2 Hz), 7.06 and 7.31 (2d, 4$H_{arom}$, $J$ 8.2 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$: 20.86 (*Me*Ph), 21.58, 24.13, 29.36 and 31.47 (4$CH_2$ in ring), 37.55 and 38.19 (2$CH_2$ in chain), 48.43 (CHS), 55.65 and 56.16 (2MeO), 77.02 and 77.27 (*C*HOMe, *C*OMe), 117.25 ($CH_2$=), 129.30 (2$CH_{arom}$), 132.03 (2$CH_{arom}$), 132.86 and 136.08 (2$C_{arom}$), 134.39 (CH=). MS, *m*/*z*: 334 [M$^+$]. Found (%): C, 71.90; H, 9.09; S, 10.01. Calc. for $C_{20}H_{30}O_2S$ (%): C, 71.81; H, 9.04; S, 9.59.

‡ **8a**: mp 85–87 °C (hexane–diethyl ether). $^1$H NMR ($CDCl_3$) $\delta$: 1.10–2.04 (4m, 10H, 4$CH_2$ in ring, $CH_2$ in chain), 2.37 (m, 2H, C$H_2$CH=), 2.42 (s, 3H, *Me*Ph), 2.83 (dd, 1H, $CHSO_2$, $^1J$ 10.0 Hz, $^2J$ 14.4 Hz), 3.11 (s, 3H, MeO), 3.31 (s, 3H, MeO), 3.59 (dd, 1H, CHOMe, $^1J$ 5.1 Hz, $^2J$ 11.2 Hz), 5.16 (m, 2H, $CH_2$=), 5.86 (m, 1H, CH=), 7.30 and 7.80 (2d, 4$H_{arom}$, $J$ 8.0 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$: 21.69 (*Me*Ph), 20.99, 24.58, 24.64 and 31.59 (4$CH_2$ in ring), 37.50 and 38.20 (2$CH_2$ in chain), 48.30 ($CHSO_2$), 56.10 and 69.31 (2MeO), 77.82 (*C*HOMe, *C*OMe), 117.63 ($CH_2$=), 128.85 (2$CH_{arom}$), 129.15 (2$CH_{arom}$), 134.42 (CH=), 138.80 and 143.20 (2$C_{arom}$).

*X-Ray crystallographic data for sulfone* **8a**. $C_{20}H_{30}O_4S$, $M$ = 366.50, monoclinic, space group $P2_1$, $a$ = 7.9421(5) Å, $b$ = 14.6954(9) Å, $c$ = = 8.5892(5) Å, $\alpha$ = 90°, $\beta$ = 107.985(1)°, $\gamma$ = 90°, $V$ = 953.48(10) Å$^3$, $Z$ = 2, $D_c$ = 1.277 g cm$^{-3}$, $\mu$ = 0.191 mm$^{-1}$, $F$(000) = 396, $2\theta_{max}$ < 50°. Unit cell parameters and intensities of 2895 ($R_{int}$ = 0.0286) independent reflections were measured with a Siemens SMART Platform CCD diffractometer, monochromated MoK$\alpha$ ($\lambda$ = 0.71073 Å) radiation at 173(2) K, crystal size 0.22×0.22×0.08 mm. The structure was solved by the direct methods and refined by the full-matrix least-squares procedure on $F^2$ in the anisotropic approximation for non-hydrogen atoms. Refinement converged to $R_1$ = 0.0480 for 2491 reflections with $I > 2\sigma(I)$ based on $F$; and $wR_2$ = = 0.1083, GOF = 1.061 for all independent reflections. All calculations were carried out using the system SHELXTL-V5.2. Atomic coordinates, thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see *Mendeleev Commun.*, Issue 1, 1999. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/38.