Pergamon

Tetrahedron Letters 42 (2001) 5021–5023

TETRAHEDRON LETTERS

Racemization processes at a quaternary carbon center in the context of the asymmetric Michael reaction

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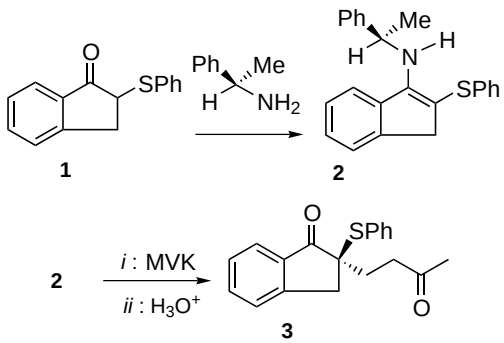
Received 17 May 2001; revised 18 May 2001; accepted 21 May 2001

Abstract—Several examples of racemization process at a quaternary carbon center affecting Michael adducts were reported. A brief statement to prevent the occurrence of the interfering retro-Michael reaction was also presented.

Since its discovery, in the mid 1880's, the Michael reaction has been extensively explored, and has played an amazing role in the area of synthetic organic chemistry. In the past two decades, much progress has been made in the development of asymmetric variants of this reaction, allowing the elaboration of Michael adducts of high enantiomeric purity. These efforts have culminated in the synthesis of a variety of adducts of paramount importance, which possess one stereocontrolled quaternary carbon center. However, although it is generally accepted that the configuration of a quaternary carbon center was definitively secured by the mechanism-based stereoselectivity (kinetic control), a subsequent racemization of adducts involving a transient retro-Michael process cannot be ruled out.

Here, we present several examples of the racemization process at a quaternary carbon center affecting Michael adducts. Although the reported cases deal with compounds which are prone to racemization, *one should keep in mind that this phenomenon might affect any Michael adduct*.

With the aim to extending the scope of the asymmetric Michael reaction using α-thiosubstituted secondary enamines,[1] we recently envisioned the utilization of α-sulfenylenamine (*R*)-**2** as a nucleophilic partner. This enamine resulted from the condensation between 2-phenylthio-1-indanone (**1**) and enantiomerically pure (*R*)-1-phenylethylamine (cat. *p*-TsOH, refluxing toluene). Addition of crude **2** to methyl vinyl ketone (MVK) (THF, 48 h at 20°C) gave, after hydrolytic workup (10% aqueous AcOH, 90 min at 20°C), Michael adduct **3** as a colorless solid in 81% yield. When freshly prepared, compound **3** exhibited a significant optical rotation ($[\alpha]_D = -87$, $c = 2.5$, MeOH), but, neither its absolute configuration (presumably *S*, as depicted, deduced from mechanistic considerations), nor its ee could be assigned at this stage. Conversely, addition of enamine (*ent*)-**2**, deriving from (*S*)-1-phenylethylamine, to MVK afforded adduct (*ent*)-**3** ($[\alpha]_D = +79$, $c = 2.5$, MeOH) (Scheme 1).



Scheme 1.

Keywords: asymmetric synthesis; Michael reaction; quaternary carbon center; racemization; X-ray crystallography.
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PII: S0040-4039(01)00926-1

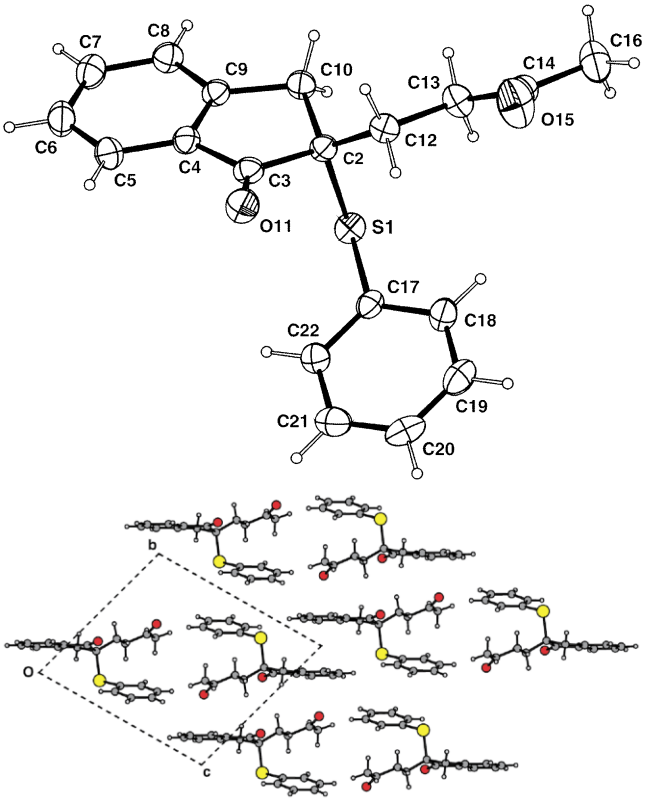
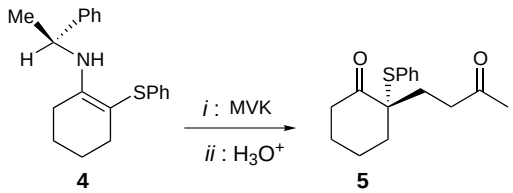
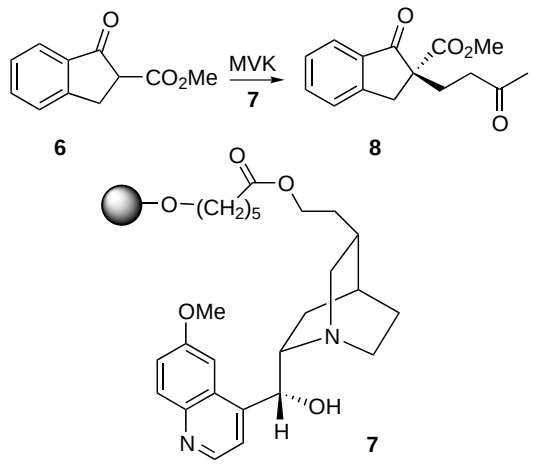


Figure 1. X-Ray crystal structure of adduct (±)-**3**. Top: ORTEP drawing of the molecule (shown in the *S* configuration) with displacement ellipsoids at the 30% probability level. Bottom: Crystal packing viewed along the **a** axis (color code: sulfur, yellow; oxygen, red).



Scheme 2.



Scheme 3.

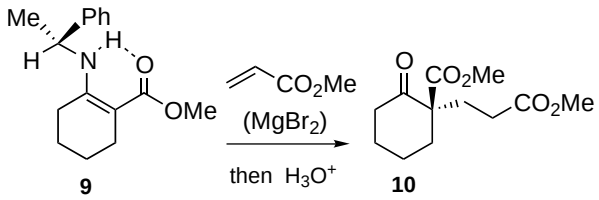
Unexpectedly, when the above enantiomeric adducts were kept *in the solid state at room temperature*, their optical rotations progressively faded, and vanished within a few weeks.[2] That compounds **3** and (*ent*)-**3** suffer racemization on standing without destruction of the crystal lattice, was highlighted by X-ray diffraction analysis. Indeed, the 'aged', optically inactive crystals of both origins displayed the same diffraction pattern, revealing a centrosymmetric space group ($P\bar{1}$), and the presence of a pair of enantiomers per cell unit (Fig. 1).[3]

On the other hand, we have established that a sample of Michael adduct (*S*)-**5**, of 95% ee, resulting from the addition of α-sulfenylenamine (*S*)-**4** to MVK, remained unaltered on standing at room temperature.[1] Therefore, the unusually facile racemization of adducts **3** and (*ent*)-**3** should be clearly attributed to the presence of a fused aromatic nucleus which enhances the acidity of the starting α-phenylthiocyclanone, the retro-Michael process thus being favored (Scheme 2).

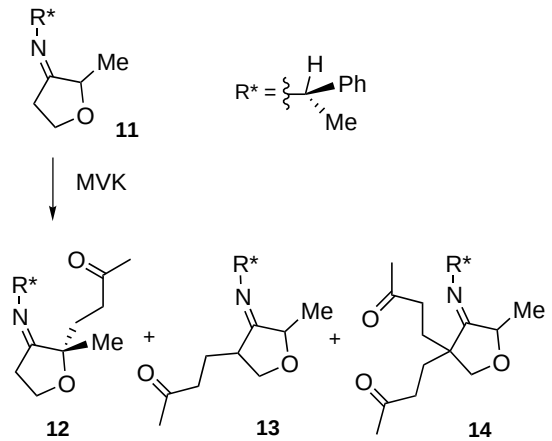
A closely related racemization process has been observed with adduct (*R*)-**8**, issuing from the conjugate addition of 2-carbomethoxy-1-indanone (**6**) to MVK, in the presence of polymer-supported quinine (**7**) as a catalyst.[4] We have indeed proved that a freshly prepared sample of (*R*)-**8**, of 87% ee, completely racemized within a few weeks, when kept in the solid state at room temperature. Noteworthy, it was also established that adduct **8** racemizes during liquid chromatography on a chiral stationary phase, as well as during NMR experiments, when a chiral lanthanide shift reagent was added (Scheme 3).

A misguided experimental protocol, source of retro-Michael process, can affect the reliability of an asymmetric Michael reaction. Thus, in the early 1990's, Guingant et al. disclosed the conjugate addition of chiral β-enamino esters, derived from 1-phenylethylamine, to electron-deficient alkenes (alkyl acrylates, α,β-ethylenic ketones, acrylonitrile).[5] Ees in the range of 55–90% were reported. However, the purification procedures of the Michael adducts having always included a distillation step, we hypothesized a competing thermal racemization, decreasing the ees. Correctness of this assertion was proved as follows. Addition of β-enamino ester (*R*)-**9** to methyl acrylate furnished the Michael adduct (*R*)-**10** with a 95% ee.[6a] As expected, after careful distillation under reduced pressure, the ee of this adduct was significantly lowered. The fact that a retro-Michael process occurs during distillation was emphasized by the concomitant formation of a noticeable amount of methyl acrylate. Thereafter, several cyclic or acyclic β-enamino esters of the type **9** were condensed with various electrophilic alkenes.[6a–g] *Ees of the resulting Michael adducts were invariably = 95%* (Scheme 4).

The retro-Michael process can also modify the regiochemical features of an asymmetric Michael reaction. Thus, we have shown that the addition of chiral imine **11**, deriving from 2-methyldihydrofuran-3-one and (*R*)-1-phenylethylamine, to MVK afforded a mixture of



Scheme 4.



Scheme 5.

adducts (**12**+**13**+**14**).[7] Incidentally, it was observed that the conjunction of an excess of MVK and an extended reaction time results in the gradual disappearance of the monoalkylated regioisomers **12** and **13**, for the benefit of the *gem*-dialkylated adduct **14**. The unexpected conversion [**12**→**14**] firstly requires the isomerization of quaternary adduct **12** into regioisomer **13**, a rearrangement which involves the migration of the incoming butanone appendage from the more substituted α-side of the imine function to the less substituted position. Finally, the regioselective addition of a second molecule of MVK to compound **13** furnishes the dialkylated adduct **14** (Scheme 5).

In conclusion, we have demonstrated that an interfering retro-Michael process can affect the stereochemical/regiochemical features of Michael adducts bearing a stereocontrolled quaternary carbon center. *Neglect of reversibility in the area of asymmetric synthesis results in the collection of senseless data and the drawing of misleading conclusions*. Some of the most important guides to prevent the occurrence of retro-Michael process are listed below.

1. Select the mildest possible way for synthesizing Michael adducts.
2. Avoid any strongly basic/acidic workup.
3. Restrict the use of purification procedures demanding prolonged heat exposure (e.g. distillation step), and shorten the contact of adducts with highly polar chromatographic media (e.g. silica gel).
4. Be careful in utilizing chromatographic methods for the determination of ees, particularly the chiral GC.

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2. For a remarkable study of the crystalline-state racemization, see: Ohashi, Y. *Acc. Chem. Res.* **1988**, *21*, 268–274.
3. Compound (±)-**3**: colorless solid; mp 88°C. Crystallographic data (one example given): colorless crystal of 0.05×0.15×0.30 mm. $C_{19}H_{18}O_2S$, $M_w=310.39$. Triclinic system, racemic space group $P\bar{1}$. Two enantiomeric molecules in the cell, $Z=2$, $a=6.829$ (4), $b=10.623(6)$, $c=11.755(6)$ Å, $\alpha=73.66$ (3), $\beta=83.79$ (3), $\gamma=83.31$ (3)°, $V=810.20$ Å^3, $d_c=1.272$ g cm^{-3}, $F(000)=328$, λ(Mo-Kα)$=0.71073$ Å, $\mu=0.20$ mm^{-1}; 8644 data measured ($-8\le h\le 8$, $-14\le k\le 14$, $-11\le l\le 13$) with a Nonius Kappa-CCD area-detector diffractometer, of which 2462 reflections were unique and 1974 observed having $I\ge 2\sigma(I)$. The structure was solved by direct methods using program SHELXS86[8] and refined by full-matrix least-squares based upon unique F^2 with program SHELXL93.[9] The hydrogen atoms located in difference Fourier maps were fitted at theoretical positions and assigned an isotropic displacement parameter equivalent to that of the bonded atom, plus 20%. Thus, refinement converged to $R_1(F)=0.0498$ for the 1974 observed reflections and $wR_2(F^2)=0.1173$ for all the 2462 data, goodness-of-fit, $S=1.035$. Residual electron density between −0.18 and 0.31 e Å^{-3}. The indane system is planar, except for the C-2 atom, deviated from the mean plane of the other eight atoms by −0.260 (3) Å. The dihedral angle between the indane nucleus and the phenyl ring is 22.5°. In the crystal packing, the centrosymmetric molecules are stacked, facing each other the aromatic ring of the indane systems or the phenyl attached to the sulfur atoms at about 3.5 Å, along the **b** axis direction. Fully crystallographic results have been deposited as Supplementary Material (CIF file), at the Cambridge Crystallographic Data Centre, UK.
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