Diastereoselective Reductions of β-Substituted-γ-Keto Sulfoximines and a Novel Palladium(0)-catalysed Allylic Sulfoximine to Allylic Sulfinamide Rearrangement

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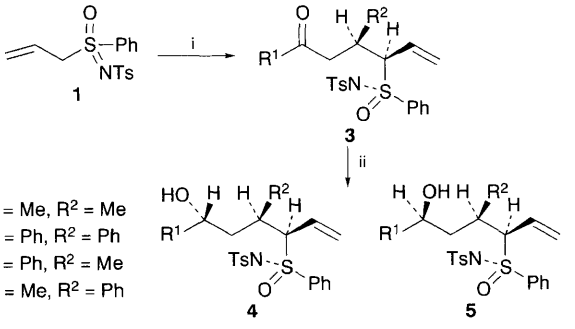
The reduction of β-substituted-γ-keto *N*-tosyl sulfoximines is highly diastereoselective and the allylic sulfoximines products undergo a facile rearrangement to allylic sulfinamides in the presence of a palladium(0) catalyst.

The diastereoselective reduction of β-keto sulfoxides to β-hydroxy sulfoxides[1] is a method that has been extensively exploited in the asymmetric synthesis of bioactive natural products.[2] In contrast, reduction of the related β-keto sulfoximines proceeds with only modest diastereoselection.[3] We report here that the reduction of β-substituted-γ-keto *N*-tosyl sulfoximines is highly diastereoselective and that the stereochemical outcome of these reactions can be understood in terms of the solid- and solution-state conformation of the γ-keto sulfoximine.

The β-substituted-γ-keto sulfoximines **3** (Scheme 1) were prepared from the diastereoselective 1,4-conjugate addition of racemic lithiated allylic sulfoximine **1** to acyclic enones **2** as described previously.[4] Diastereomerically pure γ-keto sulfoximines **3** were reduced by treatment with diisobutylaluminium hydride (DIBAL-H, 1.2 molar equiv.) in THF–CH_2Cl_2 (1 : 1) at −78 °C for 2 h. The reactions were quenched at −78 °C and the product diastereoselections were determined on the crude reaction mixtures by ^{1}H NMR (400 MHz) analysis. Diastereomerically pure carbinol products **4** could be obtained by purification of the crude reaction products by column chromatography or recrystallization. The results of this investigation are summarised in Table 1.

In three of the four cases studied the reduction reactions were highly diastereoselective giving alcohol **4** in favour of its diastereostereomeric alcohol **5**. The structures of the alcohols **4a** and **4b** were determined by single-crystal X-ray structural analysis.† To understand the stereochemical outcome of these reductions ^{1}H NMR experiments were performed on the γ-keto sulfoximines **3a** and **3b**, together with an X-ray study of **3a**.



Scheme 1 *Reagents and conditions*: i, Bu^{n}Li, THF, −78 °C then R′C(O)CH=CHR^2 **2**; ii, DIBAL-H, THF–CH_2Cl_2, −78 °C

Table 1 Reduction of ketones **3** with DIBAL-H

Ketone	Yield (%)[a]	Diastereoselectivity[b] 4 : 5
3a	87	93 : 7
b	79	93 : 7
c	49[c]	95 : 5
d	79[d]	70 : 30

[a] Yield of diastereomerically pure product after column chromatography. [b] From analysis of the crude reaction product by ^{1}H NMR. [c] Recrystallized yield of diastereomerically pure product. [d] Yield of mixture of **4d** and **5d**.

In the solid state, the X-ray studies of **3b**[4] and **3a** (Fig. 1) show that these molecules have a hairpin structure and that the *N*-tosyl of the sulfoximine group lies under one face of the keto group. ^{1}H NMR studies indicated that in solution, **3a** and **3b** adopt a similar hairpin conformation to that found in the solid state. The dihedral angles estimated from an examination of the vicinal coupling constants in the ^{1}H NMR spectra of **3a** and **3b** were consistent with those obtained from the solid-state structure. NOESY experiments on **3a** and **3b** showed NOE cross peaks that indicated the *N*-tosyl group was close in space to the protons α to the keto group (Scheme 2). The preference for a hairpin conformation may be a consequence of the prefered *anti* orientation of the sterically demanding *S*-phenyl group and the β-substituted keto alkyl side chain. From the X-ray study of **3a**, the C(3)–C(4)–S(4)–C(41) torsion angle is 162.7(3), 157(2)° (two independent molecules).

Thus the high diastereoselectivity and the stereochemical outcome of these reduction reactions can be attributed to the sulfoximine group which effectively hinders the α-face of the γ-

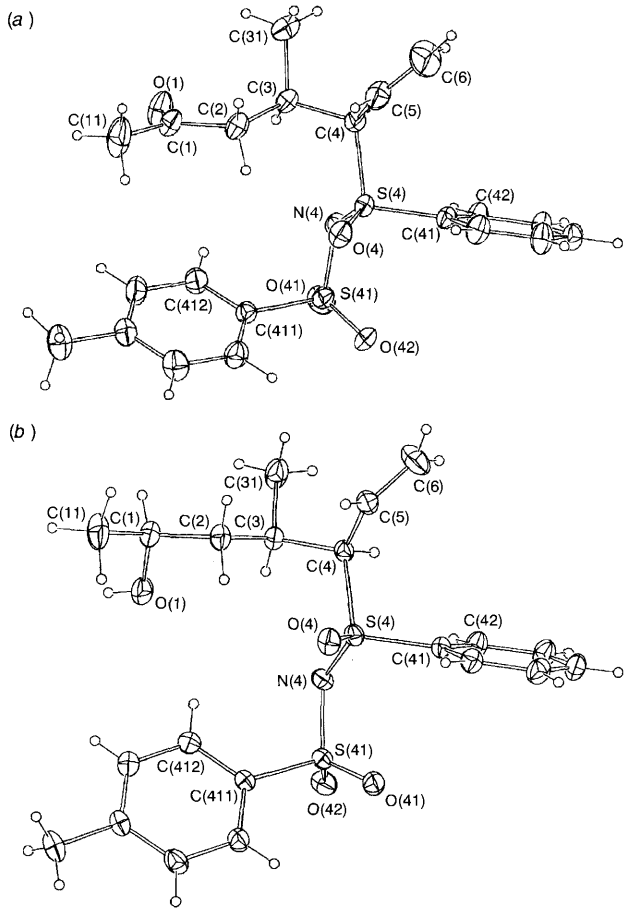


Fig. 1 Molecular projections of (*a*) **3a** (one of the two similar independent molecules in the asymmetric unit) and (*b*) **4a**. 20% Thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have arbitrary radii of 0.1 Å.

keto group to hydride addition (Scheme 2). While the β-substituent in **3** may also influence the degree of diastereoselection in these reductions it would seem unlikely since the reduction of chiral β-non-chelating-substituted ketones proceeds with only modest diastereoselection.[5] The reasons for the poor diastereoselection in the case of α-keto sulfoximine **3d** are not clear, especially when ^{1}H NMR studies suggest that **3d** has a similar conformation to that of **3a–c**.

To further demonstrate the synthetic versatility of allylic sulfoximines we have found that allylic sulfoximines undergo a facile rearrangement to allylic sulfinamides in the presence of a palladium(0) catalyst. For example, treatment of **4b** with freshly prepared tetrakis(triphenylphosphine)palladium(0) (5 mol%) in THF solution at room temperature for 10 min gave a mixture (76:24) of the isomeric allylic sulfinamide **7**, as a single diastereoisomer, and the sulfonamide **8** in 90% yield after chromatographic purification (Scheme 3). No rearrangement occurred in the absence of the palladium catalyst in THF at reflux for 2 h. Mild base hydrolysis of this mixture gave pure sulfonamide **8** in 81% overall yield. As far as we are aware this is the first example of a synthetically useful method for the conversion of allylic sulfoximines to allylic sulfinamides. While the thermal rearrangement of allylic sulfoximines to their allylic sulfinamides has been predicted from MNDO calculations by Harmata and Claasen[6] and by us[7] such a rearrangement could not be demonstrated in the laboratory. During the preparation of this manuscript Gais *et al.*[8] reported the thermolysis of some enantiomerically pure allylic sulfoximines lead to partial rearrangement to their isomeric allylic sulfinamides. However these reactions required harsh conditions (80–110 °C, 15–120 h) and significant amounts (26–95%) of starting sulfoximine was always present. By analogy with the known chemistry of allylic sulfones[9] we assume the above facile and efficient palladium-catalysed rearrangement occurs *via* the allylpalladium cation complex intermediate **6**. Interestingly, reductive removal of the sulfoximidoyl group on **4b** could be readily achieved with sodium borohydride in methanol in the presence of a catalytic amount of $Pd(PPh_3)_4$. The alkene **9** was obtained in 59% yield as a 52:48 mixture of geometric isomers. The generality of these palladium-catalysed rearrangements will be reported elsewhere.

In summary, we have demonstrated that β-substituted-γ-keto sulfoximines undergo highly diastereoselective keto-reductions with DIBAL-H. The corresponding carbinol adduct **4b** underwent a novel and efficient palladium-catalysed allylic sulfoximine to allylic sulfinamide rearrangement which further extends the synthetic utility of these compounds in diastereoselective and potentially enantioselective synthesis.[10]

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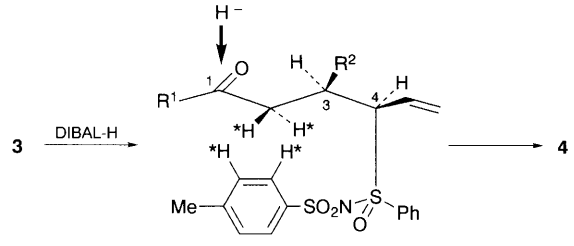
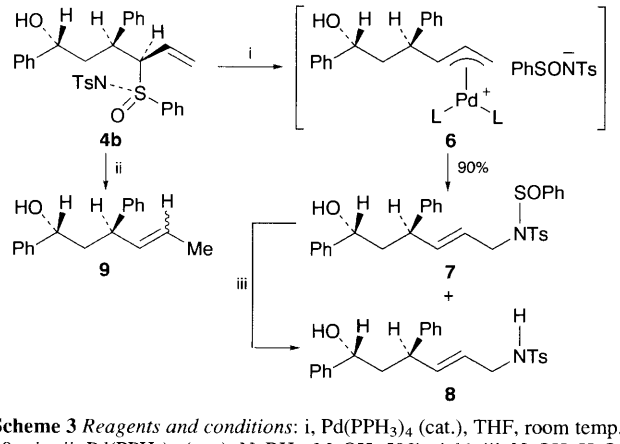


Scheme 2 NOESY cross peaks observed between asterisked protons



Scheme 3 *Reagents and conditions*: i, $Pd(PPH_3)_4$ (cat.), THF, room temp., 10 min; ii, $Pd(PPH_3)_4$ (cat.), $NaBH_4$, MeOH, 59% yield, iii, NaOH, H_2O–MeOH, room temp.; Ts = *p*-$MeC_6H_4SO_2$

Footnote

† *Crystal/refinement data:* **3a**· $C_{21}H_{25}NO_4S$·≈0.25 $CH_3CO_2C_2H_5$, M ≈441.6, triclinic, space group $P\bar{1}$, a = 16.619(4), b = 13.624(4), c = 12.544(10) Å, α = 64.57(5), β = 88.85(4), γ = 67.89(2)°, V = 2342 Å^3. $D_c(Z = 4)$ ≈ 1.25 g cm^{-3}. N_0 = 5374 'observed' [$I > 3\sigma(I)$] diffractometer data out of N = 7701 independent absorption corrected reflections refined to conventional R (on $|F|$) = 0.055, R_w (statistical weights) = 0.061. Difference map artefacts modelled as ethyl acetate solvent molecule, disordered about an inversion centre, and refined with geometrical constraints. **4a**. $C_{21}H_{27}NO_4S_2$, M = 421.6, monoclinic, space group $P2_1/n$, a = 12.744(4), b = 13.663(6), c = 13.104(3) Å, β = 100.72(3)°, V = 2242 Å^3. D_c (Z = 4) = 1.25 g cm^{-3}. R, R_w = 0.034, 0.043 for N, N_0 = 3914, 3244. For both structures, $2\theta_{max}$ = 50°, θ–2θ scan mode, monochromatic Mo-Kα radiation (λ = 0.7107$_3$ Å); full-matrix–large-block least-squares refinement, non-hydrogen atom thermal parameter form anisotropic, (x, y, z, $U_{iso})_H$ constrained in **3a**, refined in **4a**. Atom coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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