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A highly diastereoselective [2,3]-sigmatropic N,O rearrangement

Steven D. Bull,[a] Stephen G. Davies,*[a] Simon Jones,[a] Jacqueline V. A. Ouzman,[a] Anne J. Price[a] and David J. Watkin[b]

[a] *The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: steve.davies@chemistry.ox.ac.uk.*
[b] *Chemical Crystallography Laboratory, University of Oxford, 9 Parks Road, Oxford, UK, OX1 3PD*

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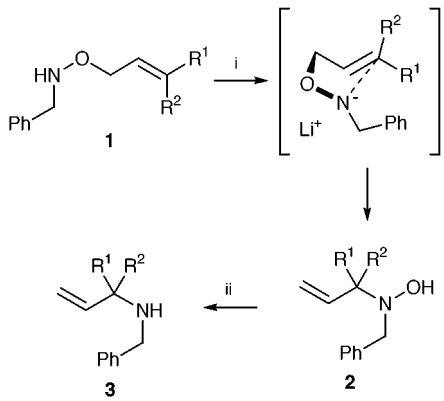
Lithium (*E*)-*N*-benzyl-*O*-(4-methoxy-4-phenylbut-2-enyl)-hydroxylamide undergoes a highly diastereoselective rearrangement *via* a chelated transition state, to afford after reduction, *syn*-3-benzylamino-4-methoxy-4-phenylbut-1-ene as a single diastereoisomer.

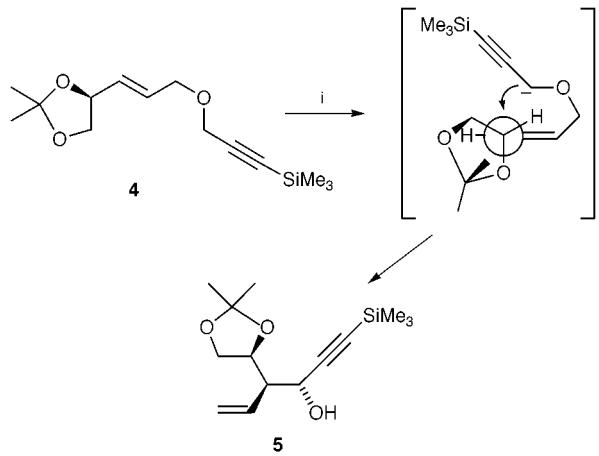
Intramolecular sigmatropic rearrangements have found widespread use in synthetic organic chemistry, primarily due to the high selectivities observed in these transformations.[1] We have recently reported on a novel intramolecular [2,3]-rearrangement of *N*-benzyl-*O*-allylic hydroxylamines **1** to afford *N*-benzyl-*N*-hydroxyallylamines **2**, which may be reduced to the corresponding *N*-benzyl-*N*-allylamines **3** in good yield (Scheme 1).[2] The transition state of this N,O rearrangement may be compared with that of the [2,3]-Wittig rearrangement;[3] deprotonation of **1** affords a lithium amide which rearranges through an envelope like transition state.



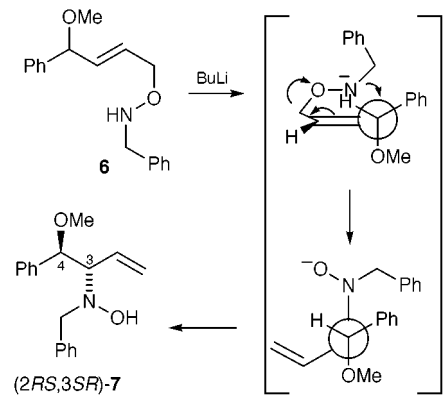
Scheme 1 *Reagents and conditions*: i BuLi, THF; ii, Zn, aq. HCl.

Previous investigations into the synthetic utility of the [2,3]-Wittig rearrangement[4] have revealed that allylic ethers with stereogenic centres bearing a heteroatom substituent adjacent to the migration terminus have the capacity to undergo diastereoselective rearrangement.[5] For example, deprotonation of allylic ether **4** with BuLi in THF at −78 °C affords the rearranged product **5**, containing two new stereogenic centres, in 66% de (Scheme 2)[6]. Facial selectivity in this case is controlled *via* a transition state where the carbanion attacks antiperiplanar to the heteroatom *via* a conformation which directs the allylic hydrogen on the original stereogenic centre to the 'inside' site.

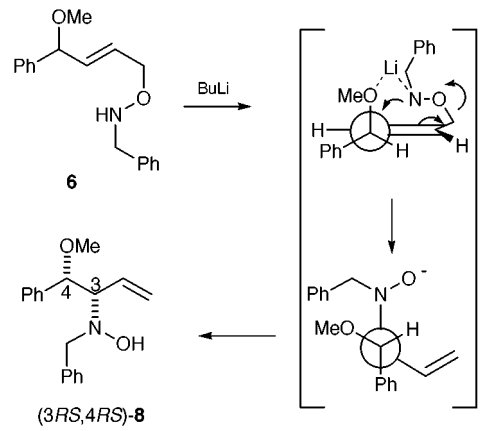
This type of stereoelectronic effect might also operate to control facial selectivity during the [2,3]-N,O rearrangement of the lithium anion of (*E*)-*N*-benzyl-*O*-(4-methoxy-4-phenylbut-2-enyl)hydroxylamine **6**, however in contrast to the Wittig rearrangement, in this case the possibility of chelation control is also present. If N,O rearrangement of the lithium anion of **6** proceeds *via* a transition state where facial selectivity is determined by stereoelectronic effects, then the *anti*-diastereoisomer **7** will be formed (Scheme 3), while a rearrangement pathway which proceeds *via* a chelated transition state would result in the *syn*-diastereoisomer **8** (Scheme 4).



Scheme 2 *Reagents and conditions*: i, BuLi, THF, −78 °C.

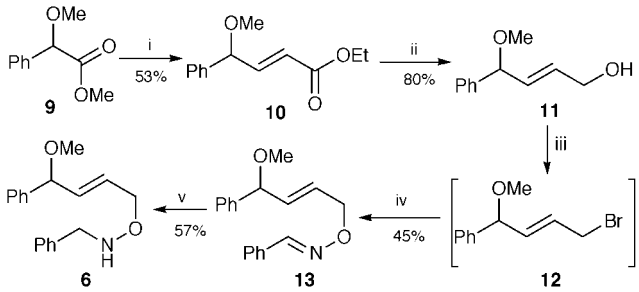


Scheme 3



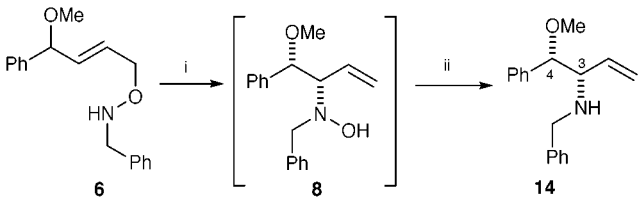
Scheme 4

Thus (*E*)-*N*-benzyl-*O*-(4-methoxy-4-phenylbut-2-enyl)hydroxylamine **6** was prepared from racemic methyl *O*-methylmandelate **9** *via* our previously described synthetic protocol for this class of hydroxylamine.[2] Methyl *O*-methylmandelate **9** was reduced with DIBAL-H in toluene at −78 °C and the resulting aldehyde treated *in situ* with ethoxycarbonylmethylene(triphenyl)phosphorane to afford the α,β-unsaturated ester **10** in an unoptimised 53% yield. Reduction of ester **10** with DIBAL-H in toluene gave allylic alcohol **11** in 80% yield, which was treated with NBS in the presence of PPh_3 to afford an unstable allylic bromide **12**. Subsequently, the crude reaction product of the bromination reaction was treated with the potassium anion of *syn*-benzaldehyde oxime to afford oxime **13** in an overall 45% yield from allylic alcohol **11**. Reduction of oxime **13** with pyridine·borane/HCl gave the desired rearrangement substrate (±)-(*E*)-*N*-benzyl-*O*-(4-methoxy-4-phenylbut-2-enyl)hydroxylamine **6** in 57% yield (Scheme 5).



Scheme 5 *Reagents and conditions*: i, DIBAL-H, toluene, −78 °C, then $Ph_3P{=}CHCO_2Et$; ii, DIBAL-H, toluene, −78 °C; iii, NBS, PPh_3, CH_2Cl_2; iv, PhCH=NOK, THF; v, pyridine·BH_3, EtOH, HCl.

Treatment of hydroxylamine **6** with 1.1 equiv. of BuLi in THF at −78 °C, followed by warming to room temperature over 1 h resulted in complete [2,3]-rearrangement to afford a single diastereoisomer of 3-benzyl(hydroxy)amino-4-methoxy-4-phenylbut-1-ene **8** in 94% conversion as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Subsequent reduction of the unstable *N*-hydroxy compound **8** to *syn*-3-benzylamino-4-methoxy-4-phenylbut-1-ene **14** with zinc in aqueous hydrochloric acid was achieved in 63% isolated yield (Scheme 6).†



Scheme 6 *Reagents and conditions*: i BuLi, THF, −78 to 25 °C; ii, Zn, aq. HCl.

X-Ray crystallographic analysis of the crystalline HCl salt of *syn*-3-benzylamino-4-phenylbut-1-ene **14** clearly revealed that [2,3]-rearrangement of **6** had occurred to afford *syn*-**8** where the relative stereochemistry of the two newly formed stereogenic centres was (3*RS*,4*RS*) (*vide infra*) (Fig. 1).‡

The *syn*-selectivity of diastereoisomer **14** found during rearrangement of **6** is clearly in accord with the chelation control transition state model described in Scheme 4, rather than the stereoelectronic model described in Scheme 3.

In conclusion, (*E*)-*N*-benzyl-*O*-(4-methoxy-4-phenylbut-2-enyl)hydroxylamine **6** undergoes a highly diastereoselective rearrangement to afford, after reduction, *syn*-3-benzylamino-4-methoxy-4-phenylbut-1-ene **14** containing two new stereogenic centres with complete diastereoselectivity *via* a chelated transition state.

Notes and references

† *Selected data* for **14**: mp 41–43 °C; δ_H (400 MHz, $CDCl_3$) 3.21 (3H, s, OCH_3), 3.31 (1H, t, *J* 8.2, $CHCH{=}CH_2$), 3.62 (1H, d, *J* 13.2, $NHCH_2$), 3.87 (1H, d, *J* 13.2, $NHCH_2$), 4.07 (1H, d, *J* 8.2, MeOC*H*), 4.93 (1H, d, *J* 17.2, $CH{=}CH_2$), 5.03 (1H, d, *J* 10.4, $CH{=}CH_2$), 5.48–5.56 (1H, m, $CH{=}CH_2$), 7.23–7.35 (10H, m, ArC*H*); δ_C(100 MHz, $CDCl_3$) 51.2 ($NHCH_2Ph$), 56.8 (OCH_3), 66.9 ($NHCHCH{=}CH_2$), 86.6 (PhCHOMe), 118.6 ($CH{=}CH_2$), 126.7, 127.8, 127.9, 128.0, 128.1, 128.3 (10 × ArCH), 136.7 ($CH{=}CH_2$), 138.9 (*ipso*-ArC), 140.5 (*ipso*-ArC); *m/z* (APCI+) 323 (13%), 269 (12), 268 (100, MH^+), 237 (13), 236 (82, $M^+ - OMe$) (HRMS: calc. for $C_{18}H_{21}NO$, 268.1701; Found, 268.1706).

‡ *Crystal data* for **14**·HCl·H_2O: $C_{18}H_{24}ClNO_2$, *M* = 321.84, monoclinic, space group *P*1 2_1/n 1, *a* = 6.403(1), *b* = 27.046(1), *c* = 10.252(1) Å, β = 97.85(2)°, *V* = 1758.8 Å^3, *T* = 180 K, *Z* = 4, D_c = 1.21 g cm^{-3}, *T* = 180 K, μ(Mo-*K*α) = 0.22 mm^{-1}, 3109 independent reflections were measured, of which 2050 were used, *R* = 0.11, R_W = 0.16. Rint = 0.08. The sample was one of many pieces cut from clear plate-like crystals. Although the cut samples remained clear, the diffraction patterns showed that they were always severely damaged by shearing parallel to the large face during the cutting. The final sample was obtained by repeatedly shaving very thin slices away from the edges of the original large crystal. The best obtainable diffraction pattern did not represent a simple single crystalline sample. Data extraction from the 90 images (180 degrees) collected on a Nonius DIP2000 diffractometer were complicated by the presence of more than one reciprocal lattice. Reflections from the strongest lattice were used as the basis for the structure analysis, but were inevitably contaminated by data from the weaker lattice. We could not determine a valid twin law relating the two lattices—the sample was probably polycrystalline. The weakest data showed the greatest discrepancy between F_o and F_c, presumably because the accidental overlap of a strong component of the minor lattice on a weak component of the strong lattice had a more damaging effect than the inverse. Data with $I < 6\,\sigma(I)$ were therefore excluded from the refinement. The value of '6' is subjective, but was chosen by looking at the residual distribution so as to preserve as many 'fair' reflections as possible, and at the same time reject as many 'suspect' reflections as possible. Only one of the water hydrogen atoms could be located. CCDC 182/1415. See http://www.rsc.org/suppdata/cc/1999/2079/ for crystallographic data in .cif format.

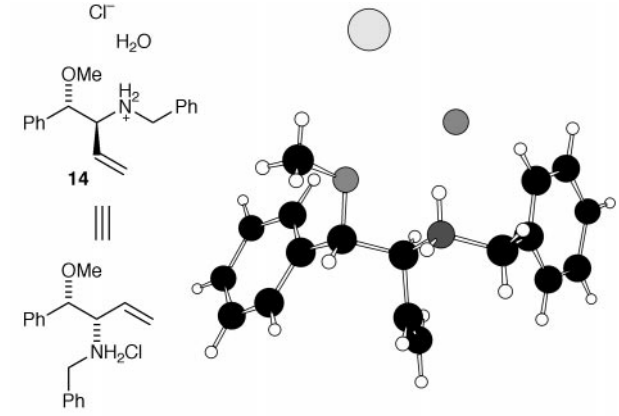


Fig. 1 X-Ray crystal structure of the hydrated HCl salt of *syn*-(3*RS*,4*RS*)-**14**.

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7 For an example where the diastereoselectivity observed for a [2,3]-Wittig rearrangement has been rationalised *via* a chelated transition state, see S. W. Scheuplein, A. Kusche, R. Brückner and K. Harms, *Chem. Ber.*, 1990, **123**, 917.

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