

Diastereoselective Addition of Metal-coordinated and 'Naked' Tri-*sec*-butylborohydrides to a Norephedrine-derived 2-Acetyloxazolidine

Leonardo Manzoni,^a Tullio Pilati,^b Giovanni Poli*^a and Carlo Scolastico*^a

^a Dipartimento di Chimica Organica e Industriale, Università di Milano, Centro CNR per lo Studio delle Sostanze Organiche Naturali, via Venezian 21, 20133, Milano, Italy

^b Centro per lo Studio delle Relazioni tra Struttura e Reattività Chimica, Via Golgi 19, 20124, Milano, Italy

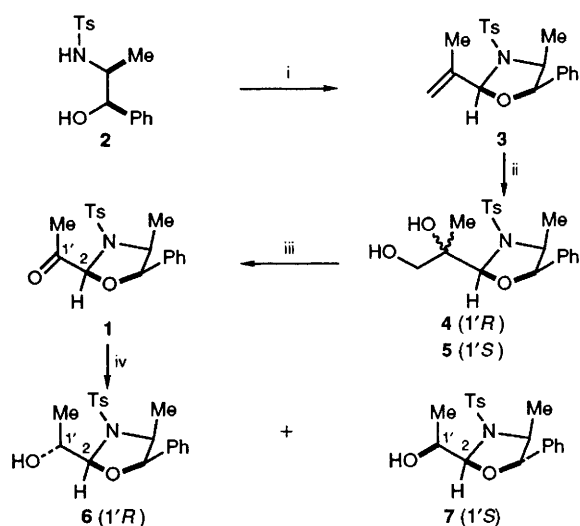
The addition of tri-*sec*-butylborohydrides to the 2-acetyl-1,3-oxazolidine **1** can be directed with high selectivity to either the *Si* or the *Re* π -carbonyl face under chelating or non-coordinating conditions, respectively.

The diastereoface differentiating addition of nucleophilic reagents to chiral carbonyl compounds is an important topic in organic synthesis and has led to a considerable amount of experimental¹ as well as theoretical² work. Following our recent results in the asymmetric transformation of alk-2-enyl-substituted oxazolidines³ we were prompted to investigate how such a chiral template could bias the hydride addition⁴ to the carbonyl moiety of a 2-acetyl derivative.

Our model substrate **1** has been synthesized† *via* a three-step procedure (Scheme 1). Acid-promoted condensation of methacrolein with *N*-tosylnorephedrine **2** gave 2-(prop-2-enyl)oxazolidine **3** as the only isomer. Catalytic osmylation gave diols **4** and **5** in a 60:40 mixture, which upon oxidative cleavage of the crude product, afforded ketone **1**.

In order to be able to determine directly the steric outcome of the planned reduction, an authentic sample of one epimeric carbinol (of the two possible) was first synthesized (Scheme 2).

Osmylation⁵ of 2-vinyloxazolidine **8**‡ gave the diols **9** and **10** as a chromatographically separable 75:25 epimeric mixture. The absolute configuration of the former diol was easily assessed by conversion into the known (*S*)-dithiane **11**.⁶ Reductive removal of the primary hydroxy group in **9**, according to a monotosylation–iodination–reduction sequence, gave the carbinol **7** of known (1'*S*) absolute configuration.



Scheme 1 Ts = *p*-MeC₆H₄SO₂ Reagents and conditions: i, H₂CCMe-CHO, HC(OMe)₃, pyridinium toluene-*p*-sulfonate, PhH, reflux, (55%); ii, OsCl₃ (0.05 equiv.), Me₃NO·2H₂O, aq. acetone, 25°C, (80%); iii, NaIO₄, aq. dioxane, 25°C, (85%); iv, see Table 1

† Satisfactory analytical data were obtained for all new compounds.

‡ **8** was prepared in 89% yield as the only C₂-epimer *via* pyridinium tosylate-mediated condensation between **2** and acrolein diethyl acetal.

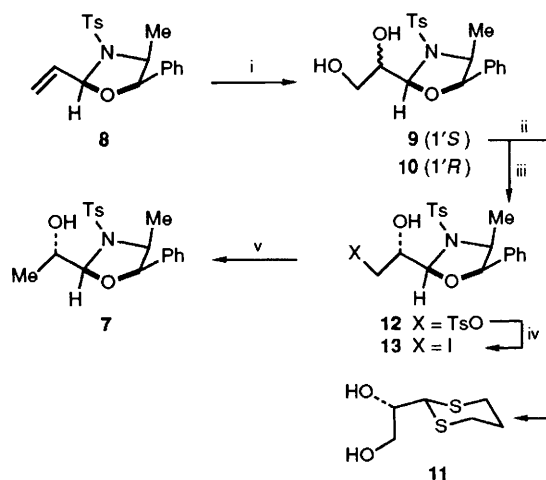
In a first set of reductions (Table 1, entries 1–6) the tested hydrides gave the carbinols **6** and **7** (Scheme 1) with poor stereocontrol ranging from 63:35 to 37:63. However, more useful results were obtained with the bulky metal tri-*sec*-butylborohydrides,⁷ (Table 1, entries 7–9) which gave an increasing **6**:**7** ratio in the order: Li < K < Na. Such dramatic stereochemical changes must depend on the different geometric requirements in the interactions between the metal cations and the available oxygen atoms [carbonyl-, sulfone-, oxazolidine-, and tetrahydrofuran (THF)-oxygen].

In order to gain more information on the role of the cation, the model reduction was then studied in the presence of cation complexing agents such as crown ethers and cryptands.⁸

These polyethers were expected to generate 'naked' trialkylborohydrides the reducing behaviour of which could have been different, in terms of reactivity and selectivity, from the parent hydrides. Pioneering work in this field was done by Pierre and Handel⁹ who observed total inhibition of the reducing power of LiAlH₄ in the presence of cryptands. The reduction of a chiral 2-acyl-1,3-oxathiane with tri-*sec*-butylborohydride in the presence and absence of crown ethers was reported by Eliel.¹⁰ In that case, no noticeable stereochemical change was noted.

However, in the present study the 'naked' borohydrides behaved quite differently from the parent ones. The first apparent trend was the dramatic reversal of π -face discrimination upon cation complexation. In keeping with the less effective complexing power of crown ethers with respect to cryptands, such a trend was moderate in the former case and maximum in the latter.

The above results appear to be consistent with a preferred *Si* face hydride addition on a chelated SO₂/OC^{11,12} intermediate in the case of the metal-coordinated trialkylborohydrides [Fig. 1(a)]. Such a chelated form is expected to be more favoured and/or reactive¹¹ than a 'non-chelated' or an 'O_{ring}-chelated'



Scheme 2 Reagents and conditions: i, OsCl₃ (0.05 equiv.), Me₃NO·2H₂O, aq. acetone, 25°C, (80%); ii, HS(CH₂)₃SH, BF₃·Et₂O, CH₂Cl₂, 25°C, (41%); iii TsCl, pyridine, 25°C, (51%); iv, NaI, acetone, reflux, (53%); v, Bu₃SnH, α,α' -azoisobutyronitrile (0.01 equiv.), toluene, reflux, (56%)

Table 1 Hydride reduction of **1**

Entry	Hydride	Additive	Solvent	6:7 ^b	Yield (%)
1	NaBH ₄	—	MeOH	50:50	81
2	ZnBH ₄	—	Et ₂ O	50:50	78
3	LiAlH ₄	—	Et ₂ O	60:40	7 ^c
4	Li(Bu ^c O) ₃ AlH	—	THF	42:58	75
5	Bu ⁱ ₂ AlH	—	CH ₂ Cl ₂	37:63	88
6	[MeO(CH ₂) ₂ O] ₂ AlH	—	Tol	65:35	97
7 ^a	LiBu ^s ₃ BH	—	THF	55:45	96
8 ^a	KBu ^s ₃ BH	—	THF	83:17	88
9 ^a	NaBu ^s ₃ BH	—	THF	93:7	98
10 ^a	LiBu ^s ₃ BH	18-Crown-6	THF	52:48	79
11 ^a	LiBu ^s ₃ BH	Kriptofix 211	THF	≤1:≥99	98
12 ^a	KBu ^s ₃ BH	18-Crown-6	THF	21:79	70
13 ^a	KBu ^s ₃ BH	Kriptofix 222D	THF	≤1:≥99	83
14 ^a	NaBu ^s ₃ BH	12-Crown-4	THF	55:45	80
15 ^a	LiBu ^s ₃ BH	MgBr ₂ ·Et ₂ O	CH ₂ Cl ₂ -THF	96:4	90

^a Reactions performed at -78 °C. ^b Determined by ¹H NMR on the crude products.

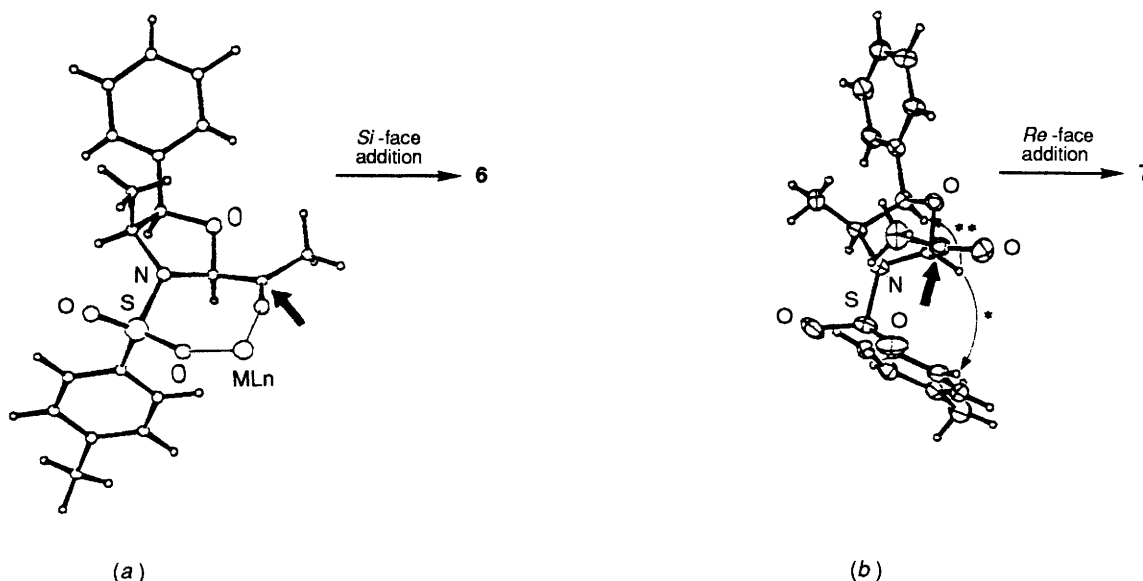


Fig. 1 Stereochemical models for the addition of *tri-sec-butyl* borohydrides to ketone **1**. (a) chelated form; (b) X-ray crystal structure and diagnostic nuclear Overhauser effects of **1** (*, 6.4% NOE; **, 4.5% NOE). ORTEP drawing with 20% probability ellipsoid. Selected dihedral angles (°): O(1)-C(2)-C(1')-O -90.5(4), N(3)-C(2)-C(1')-O 156.0(3), H-C(2)-C(1')-O 26(2).

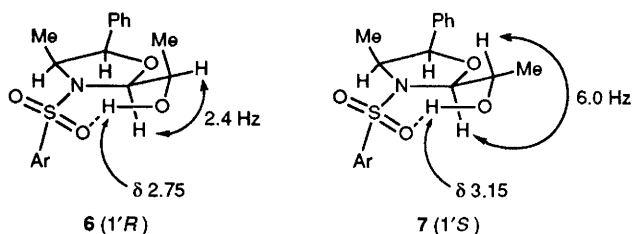


Fig. 2 Postulated conformations of carbinols **6** and **7** and their relevant spectroscopic features

one in the following decreasing order: Na > K > Li. In agreement with the above hypothesis, the presence of a bicoordinating Lewis acid such as MgBr₂·Et₂O dramatically improved the selectivity of LiBu^s₃BH from 55:45 to 96:4 (Table 1, entries 7 and 15).

On the other hand, with 'naked' borohydrides tight coordination or chelation phenomena should be absent. A reactive conformation§ akin to that found in the crystal

structure of **1** [Fig. 1(b)]¶ is thus likely to be involved in this case. A 6.4% NOE effect between HC₂ and the aromatic proton *ortho* to the sulfonamide, in combination with the absence of that between MeC₁ and HC₂, confirms a similar conformation in solution. Given the above assumption, hydride addition antiperiplanar¹³ to the electronegative oxaz-

¶ Crystal data for **1**: C₁₉H₂₁NO₄S, orthorhombic, space group P2₁2₁2₁, *a* = 9.738(1), *b* = 11.059(1), *c* = 17.630(1) Å, *V* = 1898.6(3) Å³, *Z* = 4, *D_c* = 1.258 g cm⁻³, Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 1.83 cm⁻¹ a crystal of 0.30 × 0.28 × 0.24 mm³ was sealed in a glass capillary tube to avoid intensity decay. Nonius CAD4 diffractometer; 2473 reflection collected up to 2θ = 55°, 1373 observed [*I* > σ(*I*)]. The structure is MULTAN-resistant; it was solved by using the program RISCON (A. Bianchi, C. N. Gramaccioli, T. Pilati and M. Simonetta, *Acta Crystallogr. Sect. A.*, 1981, **37**, 65); a molecular model for **1**, requested by this routine, was derived from **4** (T. Pilati, unpublished work); refinement by full-matrix least-squares analysis with weights *w* = 1/σ²(*F_o*); *R* = 0.042, *R_w* = 0.040; hydrogen atoms of two methyls are disordered; they were introduced in calculated positions but not refined. S, O, N, C, atoms anisotropic, H isotropic; no particular residue on the last Δ Fourier map. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ Theoretical studies¹³ predict transition states with rather obtuse angles of attack in the absence of electrophilic activation.

olidine oxygen atom rationalizes the observed *Re* face selectivity well.

The intrinsic coordinating ability of the sulfonamide group was also apparent in the carbinols **6** and **7**, as deduced from their ¹H NMR spectra in CDCl₃. In fact, the dilution-independent chemical shifts of the hydroxy protons and the relative values of their *J*_{C-2,C-1'} are only consistent with an intramolecular SO...HO interaction^{||} (Fig. 2). Such a feature should prove useful in the configuration assignment of other carbinol analogues.

In conclusion, addition of tri-*sec*-butylborohydrides to the acetyloxazolidine **1** may be conveniently directed to either of the carbonyl π-faces with exceptionally high selectivity and high yield. Locking of the acetyl moiety through metal chelation allows a virtually exclusive *Si* face selectivity, whereas removal of the electrophilic activation by making the borohydrides 'naked', affords the alternative *Re* topicity. Comparison of these data with those reported for the related 2-acyl-1,3-oxatianes¹⁰ indicates the peculiar behaviour of oxazolidine **1**.

We believe that the present study confirms norephedrine-derived oxazolidines as effective chiral templates for asymmetric synthesis, and stimulates interest in new ways of selectivity control with trialkylborohydrides.

We thank the Consiglio Nazionale delle Ricerche (Progetto Chimica Fine II) and Ministero dell'Università e della Ricerca Scientifica for financial support.

Received, 13th April 1992; Com. 2/01911F

References

- 1 Leading references: L. A. Paquette, T. L. Underiner and G. C. Gallucci, *J. Org. Chem.*, 1992, **57**, 86; D. C. Wigfield, *Tetrahedron*, 1979, **35**, 449; R. R. Fraser and M. Stanculescu, *J. Am. Chem. Soc.*, 1987, **109**, 1580; E. P. Lodge and C. H. Heathcock, *J. Am. Chem. Soc.*, 1987, **109**, 3353; A. S. Cieplak, B. D. Tait and C. R. Johnson, *J. Am. Chem. Soc.*, 1989, **111**, 8447; Y. Kurita and C. Takayama, *Tetrahedron*, 1990, **46**, 6633.
- 2 Leading references: D. Mukherjee, Y.-D. Wu, F. R. Fronczek and K. N. Houk, *J. Am. Chem. Soc.*, 1988, **110**, 3328; K. N. Houk and Y.-D. Wu, *Stereochemistry of Organic and Bioorganic Transformations*, ed. W. Bartmann and K. B. Sharpless, VCH, New York, 1987, pp. 247-260; S. S. Wong and M. N. Paddon-Row, *J. Chem. Soc., Chem. Commun.*, 1990, 456; S. S. Wong and M. N. Paddon-Row, *J. Chem. Soc., Chem. Commun.*, 1991, 327; Y.-D. Wu, J. A. Tucker and K. N. Houk, *J. Am. Chem. Soc.*, 1991, **113**, 5018; A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540.
- 3 See for example: A. Bernardi, S. Cardani, T. Pilati, G. Poli, C. Scolastico and R. Villa, *J. Org. Chem.*, 1988, **53**, 1600; S. Cardani, G. Poli, C. Scolastico and R. Villa, *Tetrahedron*, 1988, **44**, 5929.
- 4 N. Greeves, in *Comprehensive Organic Chemistry*, ed. B. M. Trost, Pergamon Press, 1991, vol. 8, ch. 1.1.
- 5 L. Colombo, C. Gennari, G. Poli, C. Scolastico and S. De Munari, *Tetrahedron Lett.*, 1985, **26**, 5459.
- 6 H. Redlich and B. Schneider, *Liebigs Ann. Chem.*, 1983, 412; A. Bernardi, G. Poli, C. Scolastico and M. Zanda, *J. Org. Chem.*, 1991, **56**, 6961.
- 7 For a recent use of LiBu₃BH in the stereoselective reduction of a ketone see: D. P. Curran and J. Zhang, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2613.
- 8 B. Dietrich, in *Inclusion Compounds*, ed. J. L. Atwood, J. E. D. Davies and D. D. McNicol, Academic Press, 1984, ch. 10, pp. 392-393.
- 9 J. L. Pierre and H. Handel, *Tetrahedron Lett.*, 1974, **15**, 2317; A. Loupy, J. Seyden-Penne and B. Tchoubar, *Tetrahedron Lett.*, 1976, **17**, 1677.
- 10 K.-J. Ko, W. J. Frazee and E. L. Eliel, *Tetrahedron*, 1984, **40**, 1333; see also: S. V. Frye and E. L. Eliel, *J. Am. Chem. Soc.*, 1988, **110**, 484.
- 11 X. Chen, E. R. Hortelano, E. L. Eliel and S. V. Frye, *J. Am. Chem. Soc.*, 1992, **114**, 1778.
- 12 Chelation between bicoordinating Lewis acids and carbonyl oxygens is well documented: M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 556; S. Shambayati, S. L. Schreiber, in *Comprehensive Organic Chemistry*, ed. B. M. Trost, Pergamon, 1991, vol. 1, ch. 10. On the other hand, only a few known precedents involve sulfonamides: W. Oppolzer, I. Rodriguez, J. Blagg and G. Bernardinelli, *Helv. Chim. Acta*, 1989, **72**, 123; W. Oppolzer, G. Poli, A. J. Kingma, C. Starkemann and G. Bernardinelli, *Helv. Chim. Acta*, 1987, **70**, 2201.
- 13 K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li and R. J. Loncharich, *Science*, 1986, **231**, 1108.
- 14 See for example: S. G. Pyne, P. Bloem and R. Griffith, *Tetrahedron*, 1989, **45**, 7013; G. Delogu, O. De Lucchi, P. Maglioli, *Synlett*, 1989, 28; A. Bernardi, L. Colombo, C. Gennari and L. Prati, *Tetrahedron*, 1984, **40**, 3775.
- 15 C. A. Hasnoot, F. A. DeLeeuw and C. Altona, *Tetrahedron*, 1980, **36**, 2783.

^{||} Examples of intramolecular SO...HO chelation are known.¹⁴ A similar hydrogen-bonded conformation has been observed in the crystal structure of **4** (T. Pilati, unpublished work). Estimation¹⁵ of *J*_{C-2,C-1'} on models of **6** and **7**, obtained by incorporating the carbinols into the crystal structure of **4**, afforded the following values: **6**, *J*_{C-2,C-1'} 2.8; **7**, *J*_{C-2,C-1'} 7.7 Hz.