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Stereoselective Reduction of Unsaturated 1,4-Diketones. A Practical Route to Chiral 1,4-Diols

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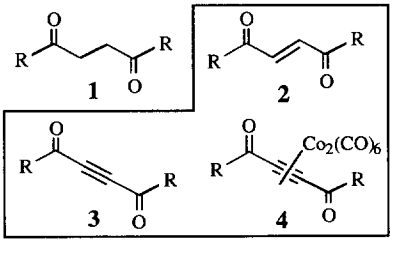
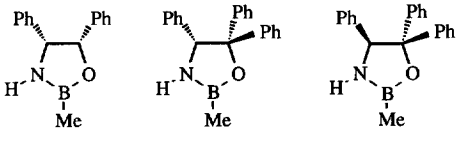
Abstract: A new synthetic route to C_2-symmetric chiral 1,4-diols based on the borane-mediated oxazaborolidine-catalysed reduction of 2-ene-1,4-diones (**2**), of 2-yne-1,4-diones (**3**), and/or of Co-complexed diketones **4** is described. Good to excellent enantio- and diastereoselectivities have been obtained in the reduction of diketones **3** and **4**, catalysed by oxazaborolidines **6** and **5**, respectively.

C_2-Symmetric 1,4-diols are valuable chiral building blocks for the preparation of 2,5-disubstituted pyrrolidines[1] and phosphine ligands of interest for asymmetric hydrogenation.[2] These 1,4-diols are currently obtained by enzymatic resolutions of mixtures of *meso* and racemic isomers[3] or by electrochemical Kolbe-type coupling of chiral β-hydroxy acids.[4] In this context, stereoselective reduction of symmetric 1,4-diketones could be an attractive approach to chiral 1,4-diols since one might expect multiplicative enantioselectivities due to the fact that most of the minor isomers derived from the first reduction becomes a diastereomer of the desired product after the second reduction. However, reports on efficient examples of such a process are scarce.[5,6]

During the past recent years, chiral oxazaborolidines have been successfully applied to the borane-mediated reduction of prochiral ketones.[7] As far as 1,4-diketones are concerned, Quallich et al. have reported[8] a few examples of reductions of saturated 1,4-diketones (**1**) by using (4*R*,5*S*)-4,5-diphenyl-1,3,2-oxazaborolidines (e.g. **5**) with good to excellent *dl*:*meso* ratios and enantioselectivities for aromatic and for hindered diketones. Nevertheless, reduction of hexane-2,5-dione (**1a**, R = Me) gave a poor stereoselectivity. Thus, the problem of having in hand a general and practical route to chiral 1,4-diols remains unsolved.

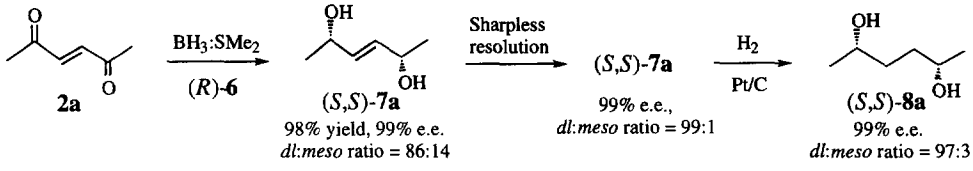




5 (*R*)-**6** (*S*)-**6**

Our previous experience on the reduction of α,β-unsaturated ketones catalysed by (*R*)- and (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidines, (*R*)- and (*S*)-**6**,[9] indicates that the presence of the double or triple bond could enhance the difference of steric requeriments at both sides of the carbonyl group, since the ethylenic moiety behaves as a group "larger" than a saturated chain in oxazaborolidine-mediated reductions, whereas an acetylenic moiety acts as a group "smaller". In this connection, we wish to report that the oxazaborolidine-mediated reduction of 2-ene-1,4-diones (**2**), of 2-yne-1,4-diones (**3**), and of Co-complexed diketones **4** is much more efficient en terms of stereoselectivity than the reduction of the corresponding saturated diketones **1**, and provides an attractive and general route to chiral 1,4-diols.

When we carried out the reduction of **2a**[10] (1 mmol) with BH_3:SMe_2 (2.2 mmol) and (*R*)-**6** (2 mmol)[11] in THF at 0 °C, the allylic diol **7a** was obtained in essentially quantitative yield and better stereoselectivities (86:14 *dl:meso* ratio, 99% e.e.) than those obtained in reduction of saturated diketone **1a**[12] to diol **8a** (68:32 *dl:meso* ratio, 92% e.e.). In addition, the presence of the double bond in **7a** allowed us to improve its optical purity (up to 99:1 *dl:meso* ratio, 99% e.e.) by Sharpless epoxidation under controlled conditions.[13] Thus, the sequence outlined above, based on the reduction of **2a** emerges as a suitable choice to obtain highly enantioenriched (*R,R*) or (*S,S*)-hexane-2,5-diol by using (*S*)-**6** or (*R*)-**6**, respectively.



Unfortunately, when we tried to extend this process to the reduction of (*E*)-oct-4-ene-3,6-dione (**2b**, R = Et),[10] a poor stereoselectivity was noted (see Table 1, entry 2). Thus, we turned our attention to acetylenic diketones **3** and their $Co_2(CO)_6$ adducts, **4**, since the resulting diols **9** are versatile intermediates amenable to conversion into saturated diols **8** (catalytic hydrogenation) or allylic diols **7** ($LiAlH_4$ reduction):[14]

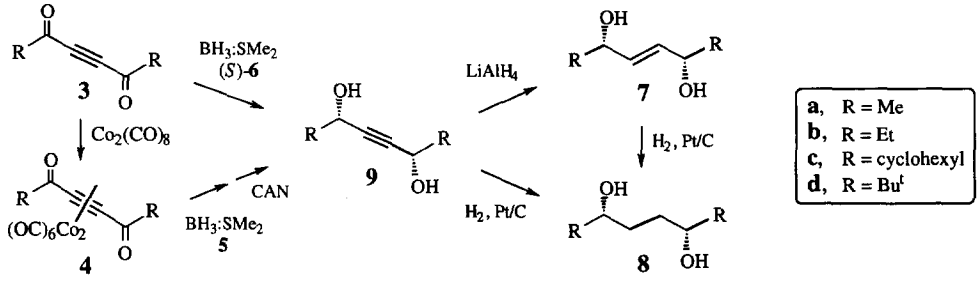
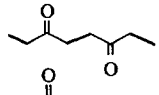
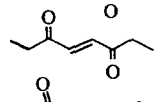
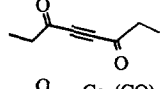
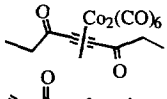
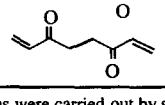
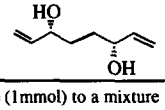


Table 1 summarises results regarding the reduction of acetylenic diketones **3b** and **4b**.[15] For the sake of comparison, results with saturated diketone **1b**[12] and vinyl diketones **2b** and **10** are also included.

Table 1. Reduction of Diketones to Diols (Precursors of **8b**) with BH_3:SMe_2[a]

entry	diketone	catalyst	diol	config.[b]	yield	*dl/meso* ratio[c]	e.e.[c]
1	 (**1b**)	(*S*)-**6**	**8b**	(*R,R*)	70%	59:41	46%
2	 (**2b**)	(*S*)-**6**	**7b**	(*R,R*)	67% (74%)[d]	72:28 (67:33)[d]	91% (88%)[d]
3	 (**3b**)	(*S*)-**6**	**9b**	(*S,S*)	82% (72%)[d]	81:19 (77:23)[d]	57% (50%)[d]
4[e]	 (**4b**)	**5**	**9b**	(*S,S*)	96%	98.6:1.4	97.8%
5	 (**10**)	(*S*)-**6**			65%	65:34	69%

[a] Reactions were carried out by slow addition of diketone (1mmol) to a mixture of BH_3:SMe_2 (2.2 mmol) and catalyst (2 mmol) in THF at 0 °C. [b] Determined by transformation of unsaturated diols into diol **8b** (H_2, Pt/C). The mixture of saturated diols (and their Mosher esters) were then compared with that given in the literature (ref. 2a). [c] Determined by HPLC and/or ^{19}F NMR analysis of the corresponding Mosher esters. [d] Within parentheses, values using 0.2 mmol of catalyst. [e] Yield and stereochemical results are referred to diol **9b** (after treatment with CAN/MeOH of the Co-complexed diol arising from the carbonyl reductions).

Whereas **3b** is efficiently reduced in the presence of oxazaborolidine (*R*)-**6** (entry 3), its $Co_2(CO)_6$ complex **4b** does not react under the same conditions, apparently because its hindrance prevents the complexation with the catalyst. This problem was solved by using less sterically demanding catalyst **5** (entry 4), where the lack of a phenyl in the α-face makes it more available for complexation.[10b] Finally, treatment of Co-complexed diol with CAN in MeOH readily liberates highly enantioenriched **9b**. Reduction of **9b** with $LiAlH_4$ in refluxing THF yielded allylic diol **7b** without appreciable loss of optical purity.[16] Alternatively, catalytic hydrogenation of **9b** (H_2, Pt/C) afforded saturated diol **8b**.

Despite the moderate stereoselectivity achieved with **3b** (R = Et), we undertook a study on the scope and limitations of the reduction of acetylenic diketones (**3a**, R = Me to **3d**, R = Bu^t)[17] assuming that the stereoselectivity could be enhanced as far as the steric hindrance increased.

Table 2. Reduction of Acetylenic Diketones **3** and **4** with BH_3:SMe_2[a]

entry	diketone	catalyst	diol[b]	*dl/meso* ratio[c,d]	e.e.[c,d]	yield[d]
1	**3a**	(*R*)-**6**	(*R,R*)-**9a**	72:22 (62:38)	85% (80%)	85% (65%)
2	**3c**	(*R*)-**6**	(*R,R*)-**9c**	88:12 (84:16)	97% (96%)	90% (90%)
3	**3d**	(*R*)-**6**	(*R,R*)-**9d**	>99.9:0.1 (97:3)	>99.9% (99.8%)	98% (95%)
4	**4a**	**5**	(*S,S*)-**9a**	90:10	98%	72%
5[e]	**4c**	**5**	(*S,S*)-**9c**	95:5	96%	71%
6	**4d**	**5**	----------	no reaction	----------	

[a] Reactions were carried out by slow addition of diketone (1 mmol) to a mixture of BH_3:SMe_2 (2.2 mmol) and catalyst (2 mmol) in THF at 0 °C. Yields and stereochemical results for diketones **4** are referred to diols **9** (after treatment with CAN/MeOH of the diols arising from the carbonyl reduction). [b] Absolute configuration was established by comparison of the sign of specific rotations of diols after hydrogenation (H_2, Pt/C) with that given in the literature (ref. 2a). [c] Determined by HPLC and/or ^{19}F NMR analysis of the corresponding Mosher diesters. [d] Within parentheses, values using 0.2 mmol of catalyst. [e] Excesses of BH_3:SMe_2 (3 mmol) and **5** (4 mmol) were needed to complete the reduction.

As shown in Table 2, compound **3c** and even the relatively hindered diketone **3d** were readily reduced with excellent enantio- and diastereoselectivities. Similar behaviour was observed for $Co_2(CO)_6$ complexes **4a** and **4c**. Instead, the sterically more demanding **4d** remained unchanged under similar conditions.

In summary, the borane-mediated reduction of acetylenic 1,4-diketones catalysed by oxazaborolidines **6** and **5** appears to be a general and efficient synthetic route to chiral saturated and 2-unsaturated 1,4-diols.

Acknowledgements

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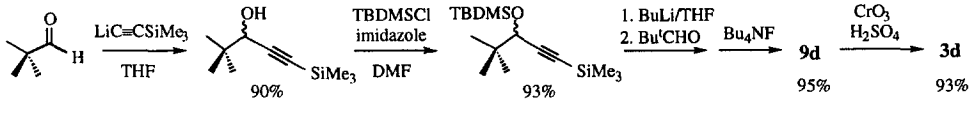
2. (a) Burk, M.J.; Feaster, J.E.; Harlow, R.L. *Tetrahedron:Asymmetry* **1991**, *2*, 569. (b) Burk, M.J; Harper, T.G.P.; Kalberg, C.S. *J. Am. Chem. Soc.* **1995**, *117*, 4423, and references therein.
3. (a) Mattson, A.; Öhrner, N.; Hult, K.; Norin, T. *Tetrahedron:Asymmetry* **1993**, *4*, 925. (b) Kim, M.-J.; Lee, I.S. *J. Org. Chem.* **1993**, *58*, 6483. (c) Nagai, H.; Morimoto, T.; Achiwa, K *Synlett* **1994**, 289. (d) Caron, G.; Kazlauskas, R.J. *Tetrahedron:Asymmetry* **1994**, *5*, 657. Also see ref. 1d.
4. Ross, S.D.; Finkelstein, M.; Rudd, E.J. *Anodic Oxidation*; Academic Press: New York, 1975. Also see ref. 2a.
5. For instance, (*S,S*)-hexane-2,5-diol has been prepared from parent hexane-2,5-dione by baker yeast reduction (Lieser, J.K. *Synth. Commun.* **1983**, 765) and by asymmetric hydrosilylation catalysed by a chiral rhodium complex (Kuwano, R.; Sawamura, M.; Shirai, J.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 5239).
6. Reduction of aromatic diketones with *B*-chlorodiisopinocampheylborane have recently been described: Ramachandran, P.V.; Chen, G.-M.; Lu, Z.-H.; Brown, H.C. *Tetrahedron Lett.* **1996**, *37*, 3795. Also see ref. 1c.
7. For recent reviews, see: (a) Wallbaum, S.; Martens, J. *Tetrahedron:Asymmetry* **1992**, *3*, 1475. (b) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.
8. (a) Quallich, G.J.; Keavey, K.N.; Woodall, T.M. *Tetrahedron Lett.* **1995**, *36*, 4729. (b) Chong et al. have also reported (ref. 1c) the oxazaborolidine-mediated reduction of 1,4-diphenylbutane-1,4-dione. For related reductions of other diketones, see: (c) 1,1'-ferrocenediones: Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 25; (d) aromatic 1,2-diketones: Prasad, K.R.K., Joshi, N.N. *J. Org. Chem.* **1996**, *61*, 3888; (e) nona-1,8-diyne-3,7-dione: Parker, K.A.; Ledeboer, M.W. *J. Org. Chem.* **1996**,*61*, 3214.
9. (a) Reduction of enones: Bach, J.; Berenguer, R.; Farràs, J.; Garcia, J.; Meseguer, J.; Vilarrasa, J., *Tetrahedron:Asymmetry* **1995**, *6*, 2683. (b) Reduction of ynones: Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, *J. Org. Chem.*, in press. For related reductions, see: (c) Corey, E.J., Helal, C.J. *Tetrahedron Lett.* **1995**, *36*, 9153. Also see ref. 8e.
10. Compounds **2a** and **2b** were easily obtained by oxidative opening of 2,5-dimethylfuran and 2,5-diethylfuran, respectively. For a review on the synthesis of 1,4-dicarbonyl compounds from furans, see: Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867.
11. Lower stereoselectivities of **7a** were recorded when 1 equiv. or 0.2 equiv. of **6** were used (77:23 *dl:meso* ratio, 95% e.e. and 69:31 *dl:meso* ratio, 81% e.e., respectively). This can be correlated with an increasing significance of the uncatalysed reduction by borane as the relative amount of **6** decreases. In fact, some experiments carried out in our laboratory suggested that the uncatalysed reduction of relatively more reactive diketones **2** could compete with the desired oxazaborolidine-catalysed process. For instance, BH_3:SMe_2 (2 mmol) in THF reduces very fast one of the carbonyl groups of the first mmol of **2b** (89% of ketol within 5 min) but much slower the second one (~22% of diol within 1 h). This fact agrees with the lower diastereoselectivity obtained in borane-mediated reductions of diketones **2** catalysed by **6** in relation to that expected from statistical arguments (assuming that both, the first and the second reduction, run independently and with similar facial selectivities to those noted for related unsaturated monoketones). Further details and additional experiments will be reported in the full paper.
12. Compounds **1a** and **1b** were readily obtained by hydrogenation (H_2, Pd/C, MeOH) of **2a** and **2b**, respectively.
13. A sample of diols **7a** (containing ~63% of the *S,S*-isomer, 69:31 *dl:meso* ratio, 81% e.e.) arising from reduction of **2a** under catalytic conditions (0.2 equiv. of (*R*)-**6**) was treated with 0.50 equiv. of (–)-diethyl tartrate, 0.40 equiv. of titanium(IV) isopropoxide and 0.5 equiv. of *tert*-butyl hydroperoxide in CH_2Cl_2 for 2 days at –20 °C (Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765). After work-up, recovered diol **7a** showed a 99:1 *dl:meso* ratio and 99% e.e. (52% overall yield from diketone **2a**).
14. In general, catalytic hydrogenation (Pt/C, MeOH or AcOEt) of chiral diols **7** and **9** gives the corresponding saturated diols in good yields and negligible loss of optical purity.
15. Compound **3b** was obtained by allylic oxidation (SeO_2/TBHP) of commercially available 4-octyne (Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* **1979**, *44*, 4202). From a practical point of view, better results were obtained (~50% overall yield) when the mixture of oxidation products was reduced ($NaBH_4$/EtOH), the propargylic diol **9b** chromatographycally isolated, and re-oxidised (Jones reagent) to diketone **3b**. Diketone **3b**, in turn, was easily and quantitatively transformed into its $Co_2(CO)_6$ complex **4b** by treatment with $Co_2(CO)_8$ in pentane.
16. Preparation of chiral 2-ene-1,4-diol based on organozinc chemistry has been reported: Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 5849.
17. Compound **3a** was prepared by Jones oxidation of commercially available diol **9a** (mixture of stereoisomers), whereas diketone **3c** was obtained by a one-pot double addition of bis(trimethylsilyl)acetylene to cyclohexanecarboxaldehyde (THF, –20 °C) catalysed by 0.05 equiv of anh. Bu_4NF (Cox, D.P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216) followed by oxidation (60% overall yield). As far as **3d** is concerned, we obtained better overall yields by means of a stepwise process:



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