A Stable and Easily Prepared Catalyst for the Enantioselective Reduction of Ketones. Applications to Multistep Syntheses

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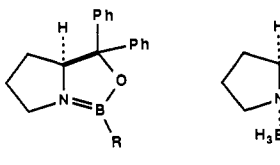
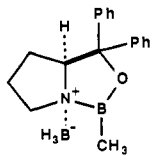
We have recently described a new method for the catalytic enantioselective reduction of ketones to chiral secondary alcohols.[1] The stoichiometric reagent in the reduction is borane (usually 0.6 mol/mol of ketone), and the catalyst is a chiral oxazaborolidine such as **1** (0.05–0.1 mol/mol of ketone). Excellent enantioselectivities, easy recoverability of the chiral catalyst predecessor, near quantitative yields, short reaction times (a few minutes at 23 °C), and predictability of the absolute configuration of the product contribute to the outstanding utility of this (CBS[1]) process. This paper reports several subsequent developments in this area with respect to improved practicality and important applications.

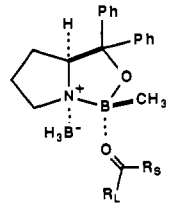
In contrast to **1** which is both air and moisture sensitive, the B-methylated oxazaborolidine **2** can be stored in closed containers at room temperature and weighed or transferred in air. Catalyst **2** is also much more easily prepared than **1**. Reaction of (*S*)-



1 R = H
2 R = CH_3



3a



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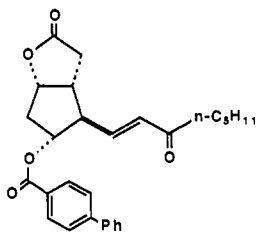

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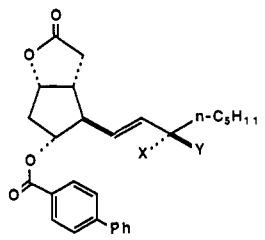
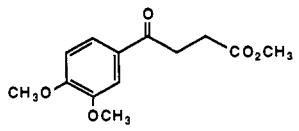


5 X = H, Y = OH
6 X = OH, Y = H



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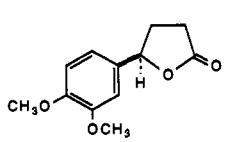

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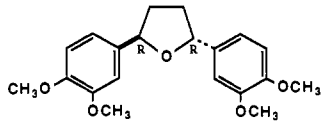

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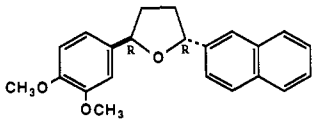

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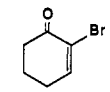
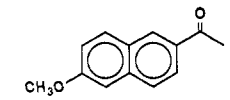
(−)-2-(diphenylhydroxymethyl)pyrrolidine and methylboronic acid[2]

Table I. Borane Reduction of Ketones Catalyzed by (*S*)-**2**

$$2R_1R_2CO + BH_3 \xrightarrow[2\text{ min}]{2,\ THF} (R_1R_2CH\text{-}O)_2BH \rightarrow R_1R_2CHOH$$

ketone	equiv BH_3	equiv **2**	reaction temp, °C	config of product[a] (% ee)[b]
$C_6H_5COCH_3$	0.6	0.1	2	*R* (96.5)
$C_6H_5COC_2H_5$	0.6	0.1	−10	*R* (96.7)
$C_6H_5COCH_2Cl$	0.6	0.1	32	*S* (95.3)
t-$BuCOCH_3$	0.6	0.1	−10	*R* (97.3)
α-tetralone	0.6	0.1	−10	*R* (83.3)
α-tetralone	0.6	0.25	−10	*R* (86.0)
c-$C_6H_{11}COCH_3$	0.6	0.1	−10	*R* (84)
	0.6	0.1	23	*R* (91)[c,d,e]
	0.6	0.1	23	*R* (97.6)[f]
$C_6H_5CO(CH_2)_2CO_2CH_3$	0.6	0.1	0	*R* (94)[f,g]
$C_6H_5CO(CH_2)_3CO_2CH_3$	0.6	0.1	0	*R* (96.7)[f,g]

[a] Absolute configuration is based upon measurement of rotation and comparison with the literature. [b] Enantiomeric excess (ee) was determined by gas chromatographic analysis of the menthyloxycarbonyl derivatives (Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978–3980). [c] Solutions of the ketone in THF and BH_3 in THF were added simultaneously to the catalyst in THF over 10 min. [d] Absolute configuration assignment based on mechanism. [e] Value of ee was determined by GC analysis of the MTPA ester (Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519). [f] Value of ee was determined by HPLC analysis of the MTPA ester (Du Pont Zorbax Sil Column). [g] In these entries the reaction time was 25 min.

[1.1 equiv either in toluene at 23 °C in the presence of 4A molecular sieves for 1.5 h or in toluene at reflux for 3 h using a Dean–Stark trap for water removal, evaporation of solvent, and evaporative distillation (0.1 mm, bath temperature 170 °C)] afforded **2** as a colorless solid, mp 74–87 °C, in 86% yield.[3,4] In general the reduction of ketones with **2** as catalyst proceeds with either appreciably higher or the same enantioselectivity as observed for corresponding reaction catalyzed by **1**. As is the case with **1**, catalyst **2** combines with borane in tetrahydrofuran (THF) solution to form a 1:1 adduct **3a**[5] which is considered to effect reduction via assembly **3b**.[1] Table I summarizes the excellent results obtained for ten different ketones of widely varying structure with use of 0.6 equiv of borane in THF in 2 min at the indicated temperature. All reactions proceeded to completion, and the secondary alcohol was the only detectable product by capillary gas chromatographic analysis. The absolute stereochemical course of the reductions was found to be in accord with the CBS mechanistic model (face-specific hydride transfer from boron to carbon within **3b**).[1]

The power of the CBS catalytic enantioselective reduction in synthesis can be illustrated by the examples which follow, one involving diastereoselectivity and the other combined enantio- and diastereoselectivity. The chiral ester keto lactone **4**, a standard intermediate in prostaglandin synthesis,[6] underwent selective

(1) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

(2) (a) Brown, H. C.; Cole, T. E. *Organometallics* **1985**, *4*, 816–821. (b) Wester, D. W.; Barton, L. *Org. Prep. Proc. Int.* **1971**, 191–195.

(3) Found for **2**: HRMS (EI), M^+ 277.16371 (calcd 277.16379); ^1H NMR (0.005 M in $CDCl_3$, 270 MHz, δ) 7.1–7.7 (m, 10 H, phenyl), 4.35 (dd, J = 6 Hz, J = 10 Hz, 1 H, N-C*H*-(C)-C), 3.25–3.45 (m, 1 H, N-CH_2-CH_2), 2.95–3.15 (m, 1 H, N-CH_2-CH_2), 1.70–1.90 (m, 2 H, N-CH_2-CH_2-C), 1.45–1.68 (m, 1 H, N-C(C)-CH_2-C), 0.71–0.90 (m, 1 H, N-C(C)-CH_2-C), 0.36 (s, 3 H, B-CH_3); ^{11}B NMR (0.075 M in THF) (BF_3·EtO_2 as external standard) +33.51 ppm (s, N-*B*(CH_3)-O, due to monomer), +7.94 ppm (s, N-*B*(CH_3)-O, due to dimer). Monomeric **2** predominates over dimeric **2** by ca. 3:1 in 0.075 M solution in THF, and the ^1H NMR spectrum is more complex than that described above for more dilute solutions.

(4) For comparison the preparation of **1** from borane and (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine requires heating at ca. 60 °C with excess borane (total pressure 1.7 bar) for 72 h.

(5) Found for solutions of **2** and borane in THF: ^{11}B NMR, +36.51 ppm (s, BH_3-N-*B*(CH_3)-O), +33.51 ppm (s, N-*B*(CH_3)-O), −1.34 ppm (q, J_{BH} = 104.9 Hz, *B*H_3·THF), −15.43 ppm (br q, *B*H_3-N-B(CH_3)-O).

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reduction of the keto group upon treatment with 0.6 equiv of borane in THF at 23 °C for 2 min in the presence of 10 mol % of **2** as catalyst to give the 15-*R* alcohol **5** and the 15-*S* diastereomer **6** in a ratio of 91:9. Under the same conditions but with use of the enantiomer of **2** as catalyst the opposite stereochemical preference was observed with the 15-*S* diastereomer **6** predominating over the 15-*R* form **5** in a ratio of 90:10.[7] In our view this catalytic reduction represents a very practical solution to the problem of controlling C-15 stereochemistry in prostaglandin synthesis.

Recently a series of the racemic *trans*-2,5-diarylfurans has been found to be potent antagonists of platelet activating factor (PAF).[8,9] We report here the first enantioselective route to chiral *trans*-2,5-diarylfurans. Reduction of methyl 3-(3,4-dimethoxybenzoyl)propionate (**7**) with 0.6 equiv of borane and 2 mol % of **2** as catalyst at 0 °C for 30 min was highly selective for the keto function and produced the corresponding *R* secondary alcohol (98%, 95% ee), which upon treatment with 0.2 weight % of sodium hydride in THF at 23 °C for 1 h furnished the *R* lactone **8** (90%), mp 118-119 °C, $[\alpha]^{23}_D$ +17.15° (*c* 2, $CHCl_3$). Reduction of γ-lactone **8** with diisobutylaluminum hydride in toluene at −78 °C afforded the corresponding γ-lactol (88% as a 1:1 mixture of cis and trans isomers), which was converted to the corresponding α-bromo ether by reaction with trimethylsilyl bromide in methylene chloride at −78 °C. Coupling of this bromo ether with 3,4-dimethoxyphenylmagnesium bromide in THF at −100 °C afforded the trans 2*R*,5*R* product **9** selectively (ratio of **9** to the cis isomer, ca. 10:1), mp 115-116 °C, $[\alpha^{23}_D$ +54.2° (*c* 2, $CHCl_3$), in 70% yield. The 2*S*,5*S* enantiomer of **9** was synthesized similarly by using the enantiomer of **2** as catalyst for the CBS reduction of keto ester **7**. To demonstrate generality the same synthetic approach starting from **7** and employing β-napthylmagnesium bromide in the coupling step (86% yield, trans/cis selectivity 18:1) was used for the synthesis of (2*R*,5*R*)-diarylfuran **10**,[8c] mp 106-107 °, $[\alpha]^{23}_D$ +127° (*c* 2, $CHCl_3$). The *S*,*S* enantiomer of **10** was synthesized by a parallel process starting from the *S* enantiomer of **8**. These results demonstrate the outstanding effectiveness of the catalytic and enantioselective CBS reduction in the synthesis of medically interesting compounds such as **9**, **10**, and their enantiomers.[10]

The ligand (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine (DPP) and the *R* enantiomer are readily available from (*S*)- and (*R*)-proline, respectively. However, because (*R*)-proline is expensive, we have developed an alternative and economical route to both ligands. Racemic 2-(diphenylhydroxymethyl)pyrrolidine, mp 82-83 °C, was synthesized from the inexpensive pyroglutamic acid by the sequence (1) esterification with methanol containing 5 mol % hydrogen chloride (from acetyl chloride) at 23 °C for 24 h (95%), (2) reaction with phenylmagnesium chloride in THF at 23 °C for 24 h (70%), and (3) reduction with borane in THF (77%). A solution of the racemic DPP in ethanol was treated with (*S*)-(+)-*O*-acetylmandelic acid to give a solid which by a single recrystallization from methanol–ethanol afforded a salt, mp 226-228 °C, $[\alpha]^{23}_D$ +81.68° (*c* 2, in methanol), from which (*S*)-DPP, $[\alpha]^{23}_D$ −59° (*c* 2 in methanol) (99.3% ee),[11] was obtained (60% of the theoretical yield). The filtrates from the above operations were processed to give free DPP (enriched in the R isomer) which was treated with (*R*)-(−)-*O*-acetylmandelic acid to afford, after one recrystallization as described above, a salt, mp 226-228 °C, $[\alpha]^{23}_D$ −80.8° (*c* 2 in methanol) from which (*R*)-DPP, $[\alpha]^{23}_D$ +59° (*c* 2 in methanol) (99.5% ee),[11] was obtained in 65% yield. Both the resolving agent and unresolved DPP could be recovered efficiently for reuse.

We believe that the CBS methodology for enzyme-like, catalytic enantioselective reduction as elaborated by this research will prove to have many applications. Related research on the catalytic enantioselective addition of carbon to carbonyl groups also shows promise.[12,13]

(6) (a) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491-1493. (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616-8618.

(7) The analysis of mixtures of **5** and **6** was performed by HPLC with use of a DuPont Zorbax Sil column (4.6 mm × 25 cm) with 7:3 hexane–THF for elution (at a flow rate of 2 mL/min the 15*S* diastereomer **6** and the 15*R* diastereomer **5** eluted at 9.24 and 12.5 min, respectively.

(8) See: (a) Braquet, P.; Godfroid, J. J. *Trends Pharmacol. Sci.* **1986**, *7*, 397-403. (b) Hwang, S.-B.; Lam, M.-H.; Biftu, T.; Beattie, T. R.; Shen, T.-Y. *J. Biol. Chem.* **1985**, *260*, 15639-15645. (c) Biftu, T.; Hwang, S.-B.; Doebber, T. W.; Beattie, T. R.; Shen, T.-Y. Eur. Pat. Appl. EP 199 324; *Chem. Abstr.* **1987**, *106*, 50026r.

(9) In contrast the cis isomers are inactive as anti-PAF agents.

(10) The biological properties of the chiral 2,5-diarylfurans will be reported separately.

(11) Enantiomeric excess was determined by conversion to the amide using α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and analysis by HPLC (Zorbax Sil column using 5% THF in hexane for elution).

(12) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, in press.

(13) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Models for the Molybdenum–Phosphate Interactions in "Oxo-Type" Molybdoenzymes and Their Cofactors

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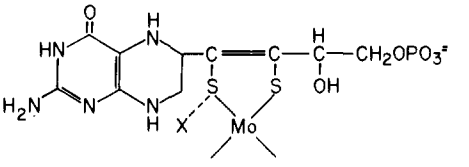
Molybdoenzymes such as xanthine oxidase, sulfite oxidase, and nitrate reductase have been intensively studied in recent years.[1] To date, however, the structures of these metalloproteins and their cofactors remain unsolved. A common cofactor I is proposed to



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be present in all these molybdoenzymes,[2] and there is mounting chemical evidence that one or more covalently bound phosphate groups exist within ~10 Å of the catalytically active molybdenum atom of these enzymes.[3] Recent ^{31}P NMR studies show that xanthine oxidase contains three moles of acid-dissociable phosphorus per mole of catalytic center.[4] While several laboratories are engaged in research on molybdenum–thiolate[5] and molybdenum–pterin complexes,[6] to date no model compounds are available for molybdenum–phosphate interactions. We report here the syntheses (Scheme I) and properties of three oxo–molybdenum(V) complexes possessing pendant phosphate esters (**5a**, **5b**, **6**) with molybdenum–phosphorus interactions of less than 10 Å.[7]

The precursor Mo(V) complexes (**2a**,**b** and **4**) are obtained in good yields (50–95%) from the reaction between $LMoOCl_2$ (L = hydrotris(3,5-dimethyl-1-pyrazolyl)borate) and the appropriate hydroxy-substituted catechols in the presence of an equimolar

(1) (a) Johnson, J. L. In *Molybdenum and Molybdenum-Containing Enzymes*; Coughlan, M. P., Ed.; Pergamon Press: New York, 1980; p 374. (b) Burgmayer, S. J. N.; Stiefel, E. I. *J. Chem. Educ.* **1985**, *62*, 943.

(2) Johnson, J. L.; Rajagopalan, K. V. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 6856.

(3) Johnson, J. L.; Hainline, B. E.; Rajagopalan, K. V.; Arison, B. H. *J. Biol. Chem.* **1984**, *259*, 5414.

(4) Davis, M. D.; Edmondson, D. E.; Müller, F. *Eur. J. Biochem.* **1984**, *145*, 237.

(5) (a) Garner, D. C.; Bristow, S. In *Molybdenum Enzymes*; Spiro, T. G., Ed.; J. Wiley: New York, 1985; p 343. (b) Kaul, B. B.; Enemark, J. H.; Merbs, D. L.; Spence, J. T. *J. Am. Chem. Soc.* **1985**, *107*, 2885.

(6) Burgmayer, S. J. N.; Stiefel, E. I. *J. Am. Chem. Soc.* **1986**, *108*, 8310.

(7) For **5a** and **5b** the Mo···P distance is a function of the rotation of the phosphate ester group about the C(cat)–O bond. The range is 4.1–6.0 Å for **5a** and 5.8–6.6 Å for **5b** as determined by molecular modeling calculations. For **6** the Mo···P distance depends on rotation about the C(cat)–CHMe bond and the CHMe–O bond. The maximum possible Mo···P distance is 6.8 Å, the minimum distance will be determined by repulsions between the phenyl groups of the pendant phosphate ester and the bulky 3,5-dimethylpyrazole rings of L and is 6.0 Å.

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