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Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones

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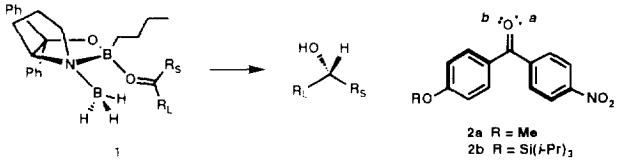
Summary: *A new class of highly enantioselective oxazaborolidine-catalyzed reductions of achiral ketones is reported which depends on stereoelectronic effects involving p-substituted non-planar aromatic ketones, or π-coordinated transition-metal containing ketones, or strained ring ketones, as exemplified in Table 1. The discovery of these reactions was guided by the transition-state model* ***1****, for which they provide experimental support. Because high enantioselectivities (> 30 : 1) are achievable, these reductions define an excellent method for the synthesis of, for example, chiral benzhydrols, chiral propargylic, or chiral allylic alcohols. Lower enantioselectivities observed with CH_2Cl_2 as solvent, relative to toluene as solvent, are consistent with the transition-state model* ***1*** *and indicate that CH_2Cl_2 hydrogen bonds to the donor groups in the π-electron-rich carbonyl substituent (R_L in* ***1****) thereby diminishing electron supply.*

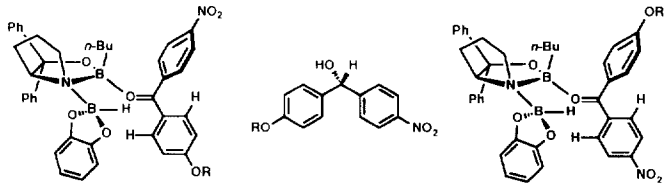
The catalytic enantioselective reduction of ketones mediated by chiral oxazaborolidines[1] (CBS reduction[1a]) is an intriguing synthetic reaction not only because of the very broad range of practical applications,[2] but also because of the clear insights into fine mechanistic detail which have emerged from its investigation.[1,3] The enantioface-selective reduction of a large number of achiral ketones with an *S*-proline derived oxazaborolidine can be understood in terms of the transition state representation **1**, in which R_L and R_S refer to the effective steric size of these groups with respect to their effect on the equilibrium (and rate) of coordination of the syn carbonyl lone pair with the catalytic oxazaborolidine–borane complex. The hydride transfer occurs as an irreversible, rate-limiting step after a generally fast and reversible formation of the ketone-borane-oxazaborolidine complex. However, in the case of unusually electrophilic ketones, such as $RCOCF_3$, the transition state for hydride transfer (within the three-component complex) is very early and the hydride transfer may occur at a rate which is comparable to the association/dissociation of ketone with the oxazaborolidine–borane complex.[1e,3] In this paper we present a number of remarkable new findings regarding electronic effects on the effective size of the groups R_L and R_S and on the enantioselectivity of CBS reductions.

The general idea which forms the basis of this study may be illustrated by the specific case of *p*-methoxy-*p'*-nitrobenzophenone **2a**. This substrate may combine with the catalytic boron center (BX_3) at either lone pair *a* or *b*. It can be argued that coordination of BX_3, a rather bulky Lewis acid, will occur more strongly (and more rapidly) at lone pair *a*, since the resulting complex, for example **3** with the (*S*)-catalyst and catechol borane (CB), allows maximum π-electron donation from *p*-methoxyphenyl to the electron deficient carbonyl carbon with simultaneous orthogonality between the planes of the *p*-methoxyphenyl and *p'*-nitrophenyl groups to minimize steric repulsion with the bulky BX_3 moiety, as is depicted in ternary complex **3**. This mode of reduction, which leads to the *R*-carbinol **4**, ought to be considerably more favorable than reduction of **2** via **5** (coordination to lone pair *b*), assuming correctness of the mechanistic model, because **5** does not allow conjugation of the *p*-methoxyphenyl group with the electron deficient carbonyl carbon. The same arguments apply to the reduction of *p*-triisopropylsilyloxy-*p'*-nitrobenzophenone **2b**, which because of its ready solubility in organic solvents allows reduction at lower temperatures than does the *p*-methoxy analog **2a**. The predictions based on these



1

2a R = Me
2b R = Si(*i*-Pr)$_3$



3 4a R = Me 4b R = Si(*i*-Pr)$_3$ 5

considerations were strikingly confirmed by experiments performed with unsymmetrical benzophenones and a variety of other ketonic substrates with the results summarized in Table I.

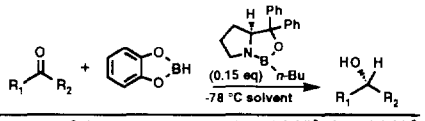
The reduction of *p*-triisopropylsilyloxy-*p'*-nitrobenzophenone (**2b**) in toluene at -78 °C was remarkably selective and afforded the predicted major enantiomer **4b** with 97.5 : 2.5 (39/1) selectivity. Reduction of **2b** under the same conditions except for CH_2Cl_2 as solvent also afforded mainly **4b**, but was considerably less selective (9/1). The reduction of *p*-methoxy-*p'*-nitrobenzophenone (**2a**) could not be carried out at -78 °C due to poor solubility of the substrate. Nonetheless, even at 0 °C the reduction proceeded enantioselectively (10 : 1 in toluene, 7 : 1 in CH_2Cl_2) to give the predicted major enantiomer **4a**.[4] In contrast to the major substituent effects observed in the reductions of **2a** and **2b**, the (*S*)-oxazaborolidine catalyzed reductions of 6-methoxy- and 6-nitro-1-tetralone proceeded to give the (*R*)-alcohol with excellent enantioselectivity in each case (Table 1, entries 3 and 4) with no appreciable substituent effects. These data support the proposition that the enantioselectivity of the reduction of **2a** or **2b** is due to preferential coordination to lone pair *a* as shown in **3** so as to allow maximum π-electron donation to the complexed carbonyl group, and that substituent effects do not operate in coplanar aryl ketones such as the 1-tetralones.

Another way of enhancing the π-electron donor properties of an aromatic ring is by complexation with the chromium tricarbonyl moiety.[5] As shown in Table I, entry 5, such complexation with one ring of a benzophenone allows the realization of highly enantioselective reduction (32 : 1 in toluene) leading to the *R*-enantiomer, as expected for reduction via coordination of BX_3 to the lone pair anti to the $Cr(CO)_3$-complexed aromatic ring. In the BX_3-complexed ketone, the *d*-electrons of chromium can flow into the electron deficient carbonyl group if the interconnecting aromatic ring is coplanar. The synthesis of π-chromium-tricarbonyl-*p'*-chlorobenzophenone was effected as shown in Scheme 1. The absolute configuration of the reduction product was established by X-ray diffraction analysis.[6]

A different case of this type of stereoelectronic effect of remote aromatic substituents is revealed by entries 6, 7 and 8 of Table 1. The superior π-conjugating/electron-donating properties of the *E*-styryl and *E*-*p*-methoxystyryl groups account for the excellent enantiomeric ratios for the reductions summarized in entries 6 and 7 (*ca.* 50 : 1) as contrasted with the diminished selectivity for the reduction *E*-*p*-nitrostyryl methyl ketone, entry 8 (*ca.* 6 : 1).[7] In each of these cases the effective size of the *E*-styryl group is greater than methyl for the stereoelectronic reasons detailed above, which also account for the adverse effect of a *p*-nitro substituent on enantioselectivity. The previously observed enantioselective reduction of a number of *E*-β-substituted vinyl *n*-alkyl ketones to *R*-vinyl carbinols using the (*S*)-proline-derived oxazaborolidine as catalyst[1b,1e] is now readily understandable in the context of the present study.

The reduction of α,β-acetylenic ketones in the oxazaborolidine system proceeds with only mediocre enantioselectivity. For example, under the conditions outlined in Table 1, the reduction of 4-phenoxy-but-1-yne-3-one affords the corresponding propargylic alcohol in only 74% ee.[8] However, the π-adducts of α,β-ynones with the dicobalt hexacarbonyl moiety undergo the CBS reduction with superb enantioselectivity. As shown in Table 1, entry 9, the $Co_2(CO)_6$ adduct of non-3-yn-2-one is reduced to the corresponding *R* alcohol in toluene with 97% ee, 65 : 1 enantiomeric ratio. Coordination of the $Co_2(CO)_6$ unit with the C–C triple bond greatly enhances the electron-donating power relative to uncomplexed C≡C,[9] while also increasing effective steric size. Both effects contribute to enantioselection by favoring coordination of BX_3 to the lone pair anti to the $Co_2(CO)_6$-complexed triple bond. This CBS reduction of $Co_2(CO)_6$-complexed α,β-acetylenic ketones provides a very

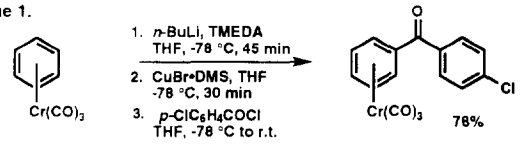
Table I. (*S*)-Oxazaborolidine-Catalyzed Reduction of Ketones



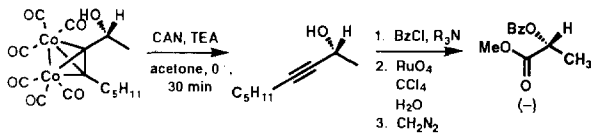
	Substrate R_1	R_2	% ee (yield)[a] Toluene	% ee (yield)[a] CH_2Cl_2
1.	TIPSO	(2b) NO_2	95 (88)	80 (81)
2.	MeO	(2a) NO_2	81 (88)[b]	75 (72)[b]
3.	MeO		--	99 (98)
4.	O_2N		--	98 (86)
5.	$Cr(CO)_3$	Cl	94 (90)	92 (87)
6.		CH_3	97 (90)	87 (76)
7.	MeO	CH_3	95 (88)	86 (86)
8.	O_2N	CH_3	72 (88)	48 (86)
9.	$(CO)_3Co$, $Co(CO)_3$, n-C_5H_{11}	CH_3	97 (89)[c]	95 (89)[c]

[a] Ee's determined by HPLC analysis with Chiralcel columns except for entries 1 and 2 which involved ^1H NMR analysis of the Mosher ester.
[b] Reaction temperature was 0 °C due to limited substrate solubility.
[c] The catalyst used had the Me_3SiCH_2 substituent on boron instead of *n*-butyl (which afforded product of *ca.* 87%ee).

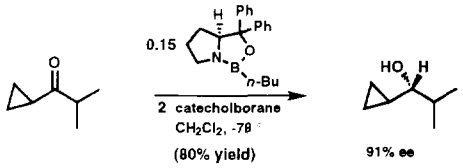
Scheme 1.



Scheme 2.



Scheme 3.



effective and useful new synthetic route to a broad range of propargylic alcohols, since the removal of cobalt is readily accomplished as shown in Scheme 2 which also depicts the method used for determination of the absolute configuration of the reduction product, correlation with levorotatory (*R*) methyl benzoyllactate.[10,11]

Cyclopropyl isopropyl ketone[12] represents an interesting test of the stereoelectronic proposal discussed above. Since the cyclopropyl group is much more electron-donating[13] than the isopropyl group, it was predicted that the CBS reduction with the (*S*)-proline-derived oxazaborolidine should produce predominantly the *R* carbinol. Indeed, this is the case, as is indicated in Scheme 3. Thus, despite the somewhat smaller steric size of cyclopropyl relative to isopropyl, the cyclopropyl group effectively functions as the bulkier group for stereoelectronic reasons[13,14] and directs BX_3 coordination to the anti lone pair in the CBS reduction. The absolute configuration of the carbinol was established by esterification with *N*-(*t*-butoxycarbonyl)-(*S*)-alanine (DCC, DMAP (cat), CH_2Cl_2, 23 °C), recrystallization of the product and X-ray analysis.[6b,15]

The reactions reported herein represent a new class of highly enantioselective carbonyl reduction, dependent on stereoelectronic effects involving special groups or remote substituents. The discovery of these reactions was guided by the transition-state model **1**, for which they provide strong support. The greater magnitude of the stereoelectronic effects in toluene vs CH_2Cl_2 as solvent (see Table 1) is of great interest and may be due to a hydrogen bonding effect of CH_2Cl_2 which effectively reduces the electron-donating power of the π-rich carbonyl substituent (R_L in **1**). Finally, these results are valuable because they open the way for numerous extensions and practical synthetic applications.[16]

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4. The absolute configuration of **4a** was established by the sequence: (1) acetylation, (2) oxidation of the *p*-methoxyphenyl group to carboxyl (cat. $RuCl_3$–$NaIO_4$), (3) reduction of COOH to CH_2OH with BH_3–THF, and (4) deacetylation to form *levorotatory* (2*R*)-2-hydroxy-2-*p*-nitrophenylethanol; see Westkaemper, R. B.; Hanzlik, R. P. *Arch. Biochem. Biophys.* **1981**, *208*, 195. Alcohol **4b** was correlated with **4a** by sequential desilylation and phenol methylation.
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6. (a) The yellow crystals of the chromium tricarbonyl complexed benzhydrol, from $CHCl_3$–pentane bilayer at 4 °C, mp 90-91 °C, $[\alpha]_D^{22}$ +29.4° (c=0.034, $CHCl_3$), were found to contain 4 molecules per unit cell: empirical formula $C_{16}H_{11}ClCrO_4$ (354.70); crystal size 1.00 x 0.90 x 0.50 mm^3; space group $P2_1$; a = 10.040(2) Å, b = 12.758(2) Å, c = 11.6750(10) Å, β = 96.450(10)°; V = 1486.0(4) $Å^3$; d = 1.585 g/cm^3; (Mo-K_α radiation, -100°C); all reflections (8772) were used in the refinement; $R_w(F^2)$ = 0.0971 with R_w (F;conventional) = 0.0378; GOF = 1.124. The crystal was shown to correspond to the major enantiomer via HPLC analysis (Chiralcel OD). (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
7. For absolute configuration of the product, see ref. 1e.
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14. The most stable conformer of the cyclopropyl ketone (or the corresponding complex with BX_3) is that in which the cyclopropyl α–CH bond is coplanar with the carbonyl σ-plane, a geometry which maximizes the effective bulk of the cyclopropyl moiety. See (a) Volltrauer, H. N.; Schwendman, R. H. *J. Chem. Phys.* **1971**, *54*, 260. (b) Pelissier, M.; Serafini, A.; Devanneaux, J.; Labarre, J-F.; Tocanne, J-F. *Tetrahedron* **1971**, *27*, 3271.
15. The colorless crystals of the ester of the major cyclopropylisopropyl carbinol with *N*-(*t*-butoxycarbonyl)-L-alanine, grown from hexane at r.t., mp 86-90 °C, $[\alpha]_D^{22}$ -4.96° (c=2.40, $CHCl_3$), were found to contain 4 molecules per unit cell: empirical formula $C_{15}H_{27}NO_4$ (285.38); crystal size 1.00 x 0.35 x 0.20 mm^3; space group $P2_12_12$; a = 18.959(2) Å, b = 8.941(2) Å, c = 10.1400(10) Å; V = 1718.9(5) $Å^3$; d = 1.103 g/cm^3; (Mo-K_α radiation, 20 °C); all reflections (4132) were used in the refinement; $R_w(F^2)$ = 0.1091 with R_w (F;conventional) = 0.0431; GOF = 0.852.
16. This research was supported by the National Science Foundation and the National Institutes of Health. We are indebted to Dr. Axel Fischer for the X-ray crystal structures.

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