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Asymmetric Synthesis of (*S*)-Carbinoxamine. New Aspects of Oxazaborolidine-Catalyzed Enantioselective Carbonyl Reduction.

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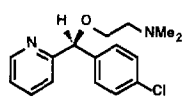
Summary: *A new process has been developed for the highly enantioselective catalytic reduction of 2-aroylpyridines and successfully applied to the synthesis of (S)-carbinoxamine (**1**), a therapeutically important histamine H_1 antagonist. Related enantioselective reductions of 4-aroylpyridines and ortho-substituted benzophenones are also described.*

(*S*)-Carbinoxamine (**1**), a medically useful histamine H_1 antagonist,[1,2] has previously been produced by resolution of the racemate with *d*-tartaric acid.[3] We report herein the first enantioselective synthesis of **1** by a short and efficient process which utilizes as a key step a novel version of the oxazaborolidine-catalyzed reduction of ketones.[4,5] We have previously demonstrated that electronic effects of the remote substituents in 4,4'-substituted benzophenones can lead to a kind of second-order steric effect which allows the highly enantioselective reduction of such substrates.[6] In addition, η^6-π-complexation of one of the benzophenone aromatic rings with $Cr(CO)_3$ also can result in efficient enantioselective reduction.[6] The latter process has been used for the enantioselective synthesis of the therapeutic agent cetirizine hydrochloride (**2**).[7] The present approach to the synthesis of **1** required the enantioselective reduction of 2-(4-chlorobenzoyl)-pyridine to the corresponding secondary alcohol, which necessitated a new modification of the oxazaborolidine catalytic methodology.

Initial experiments on the oxazaborolidine-catalyzed reduction with 2-benzoylpyridine as a model were carried out with and without added Lewis acid to coordinate to the Lewis basic pyridine nitrogen. The results were unsatisfactory, as indicated by the data summarized in Table 1. Low enantioselectivity in these cases may be due to the intervention of a completely non-enantioselective reduction pathway involving coordination of catecholborane at the pyridine nitrogen and internal (6-membered pericyclic) delivery of hydrogen to the carbonyl carbon without participation of the chiral catalyst. Such a pathway would still be possible with the BX_3-coordinated substrates if some BX_3 dissociation occurs. These considerations led to the study of the reduction of the *N*-methyl and *N*-allylpyridinium derivatives of 2-benzoylpyridine (which are not subject to dissociation) with the results summarized in Table 2. High asymmetric induction was noted with the *N*-Me derivative, but difficulty in the demethylation step led us to investigate the *N*-allylpyridinium substrate. The achievement of high enantioselectivity (99%) in the reduction of the *N*-allylpyridinium ketone derivative provided the critical information required for the synthesis of (*S*)-carbinoxamine which is outlined in Scheme 1.

4-Chlorophenylmagnesium bromide (2 equiv in THF) was heated with 1 equiv of 2-cyanopyridine in THF at 40 °C for 12 h, and quenched with sat. NH_4Cl solution to give after hydrolysis (H_2SO_4-THF-H_2O), extractive isolation and recrystallization from hexanes at -20 °C ketone **3** (66%, m.p. 61 °C). A solution of 1.2 equiv of diisopropylethylamine and 1.2 equiv of allyl alcohol in CH_2Cl_2 was added dropwise to 1.2 equiv of



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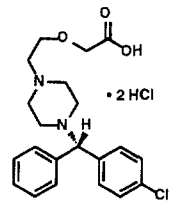

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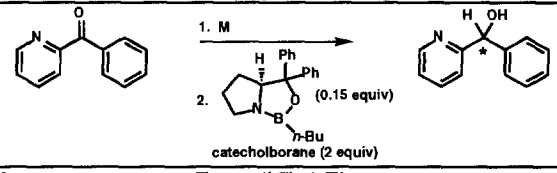
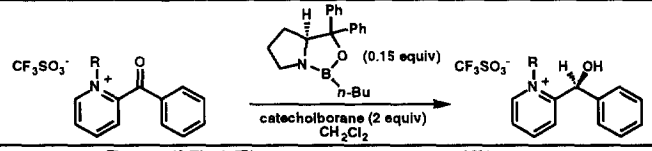
Table 1. Enantioselective Reduction of 2-Benzoylpyridine Using Lewis Acid Protecting Groups



M	Solvent	Temp (°C) / Time	ee (%)[a]	Yield (%)
-	toluene	-40° / 15 h	0	89
BF_3	CH_2Cl_2	-78° / 72 h	2	30
BBr_3	CH_2Cl_2	-78° / 72 h	11	19

[a] ee% determined by HPLC analysis (Chiralpak AD)

Table 2. Enantioselective Reduction of 2-Benzoyl-*N*-alkylpyridinium Triflates[a]



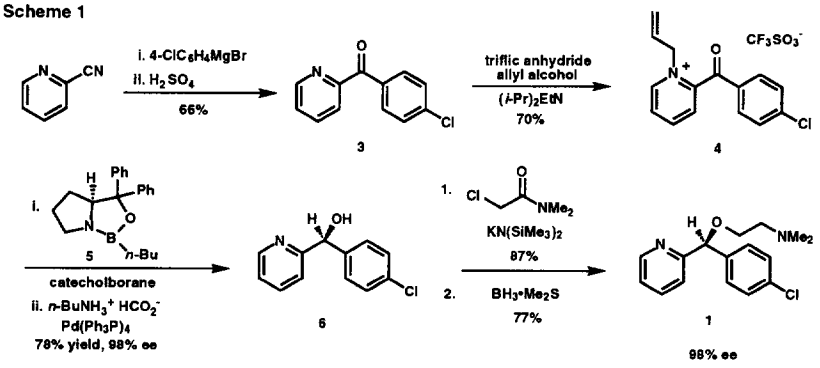
R	Temp (°C) / Time	ee (%)	Yield (%)
CH_3-	-78° / 51 h	>90[b]	95
H_2C=CH-CH_2-	-40° / 20 h	99[c]	65

[a] The substrates were prepared by reaction of 2-benzoylpyridine with the corresponding triflate. [b] Determined by conversion of the salt to the Mosher ester and ^1H NMR analysis. [c] Determined by HPLC analysis (Chiralpak AD) of the deallylated product.

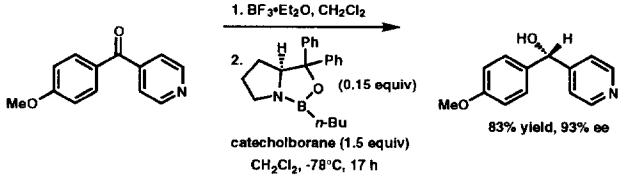
trifluoromethanesulfonic anhydride (2 M in CH_2Cl_2) at -30 °C, stirred for 5 min, warmed to 0 °C for 5 min, cooled to -30 °C and treated with Et_2O to precipitate the ammonium salts. After filtration into a solution of **3** in CH_2Cl_2 at -50 °C, the reaction mixture was allowed to warm to 23 °C over a period of 4 h. Purification by silica gel chromatography provided **4** as a white solid (70%, m.p. 92-94 °C). Addition of a CH_2Cl_2 solution of **4** to 0.15 equiv of the chiral oxazaborolidine **5** and 2 equiv of catecholborane in CH_2Cl_2 at -78 °C over 5 min gave a heterogeneous mixture which was warmed to -40 °C, vigorously stirred for 36 h (during which time a homogeneous solution resulted), and quenched by the addition of 20 equiv of MeOH. The solution was warmed to 23 °C, treated with 0.05 equiv of $Pd(Ph_3P)_4$ and 5 equiv of *n*-butyl ammonium formate,[8] stirred for 3 h, diluted with Et_2O, washed with pH 13 buffer, and purified by silica gel chromatography to provide **6** in 78% yield and 98% ee[9] $[\alpha]_D^{23}$ +120 (*c* 0.50, $CHCl_3$), (lit. for the (*R*)-isomer at 16 °C, -132.5).[10] A solution of **6** in THF at -78 °C was treated with 1.2 equiv of potassium hexamethyldisilazide followed by 4 equiv of 2-chloro-*N,N*-dimethylacetamide and the solution was stirred at -78 °C for 8 h to give after isolation the coupled amide as a colorless oil in 87% yield, $[\alpha]_D^{23}$ +18 (*c* 0.50, $CHCl_3$). Reduction of the amide in THF with 6 equiv of BH_3-Me_2S at 40 °C for 4 h gave (*S*)-carbinoxamine (**1**) in 77% yield with an enantiomeric purity of 98%.[11]

In connection with the successful development of the enantioselective process for the synthesis of (*S*)-carbinoxamine which is described above, we have had occasion to examine a number of related oxazaborolidine reductions. First of all, the reduction of the 4-(*p*-methoxybenzoyl)pyridine-BF_3 adduct could be accomplished with ca. 30:1 enantioselectivity as shown below. In this case BF_3 coordination is probably more robust and, in addition, there is no competing 6-membered, pericyclic, internal reduction pathway. Also, the electronic

Scheme 1



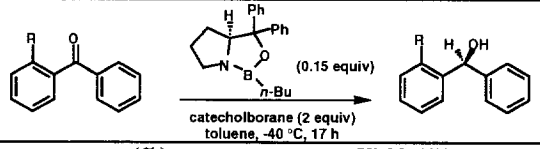
dissymmetry of the BF_3 adduct clearly favors coordination of the oxazaborolidine catalyst to the lone pair of the ketone which is *anti* to the *p*-methoxyphenyl group.[6]

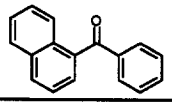


The effect of a single *ortho* substituent in the benzophenone series appears to be sufficient to guarantee excellent enantioselectivity in the oxazaborolidine catalyzed reduction as shown by the examples in Table 3. It is worthy of note that the enantiomeric ratios are higher at -40 °C (66:1) as compared to -78 °C (32:1), and that the reaction time is decreased at the higher temperature by a factor of 5 (17 h, -40 °C; 84 h, -78 °C).

The presence of the *ortho* substituent on the aryl ring has an interesting effect in the oxazaborolidine-catalyzed reduction.[5q,12] Although it might appear that this group should increase the effective bulk of the aryl ring, this is not the case. Because of the steric interaction between the *ortho* substituent and the carbonyl oxygen (Figure 1),[13] the *ortho*-substituted aryl ring twists out of the plane of the carbonyl and behaves as effectively smaller than the unsubstituted aromatic ring. This is clear from the observed absolute configuration of the

Table 3. Enantioselective Reduction of *Ortho*-Substituted Benzophenones



Substrate	ee (%)	Yield (%)	Configuration[13]
R = CH_3	97[a]	99	*S*
R = Br	97[b]	90	*S*
	97[b]	99	*S*

[a] ee% determined by conversion to Mosher ester and ^1H NMR analysis; [b] ee% determined by HPLC (Chiralcel OD)

products which indicates that the catalyst binds to the electron pair *syn* to the *ortho*-substituted aryl group as the major reaction pathway, as shown in Figure 1.

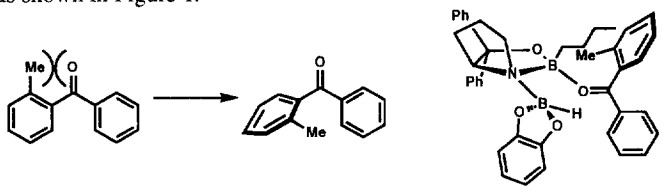


Figure 1

The above described asymmetric synthesis of (*S*)-carbinoxamine (**1**) in 6 steps, 24% overall yield, and 98% ee, utilizes a readily removable allyl group both to protect the nitrogen and to provide spatial bias for the enantioselective reduction of ketone **4**. The same type of bias in the asymmetric reduction of *ortho*-substituted benzophenones to chiral benzhydrols has been demonstrated.[14,15]

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