Enantioselective Synthesis of (*R*)- and (*S*)-Cizolirtine; Application of Oxazaborolidine-Catalyzed Asymmetric Borane Reduction to Azolyl Phenyl Ketones

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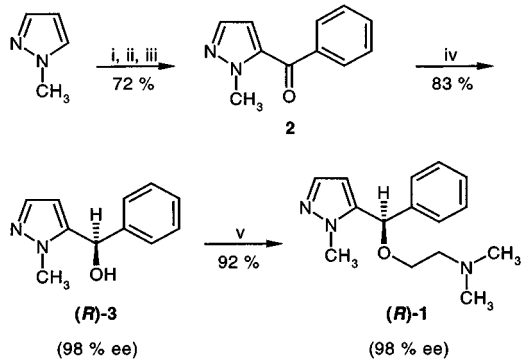
Abstract: An efficient enantioselective synthesis of (*R*)- and (*S*)-cizolirtine **1** is described. The key step of the procedure is the CBS-oxazaborolidine asymmetric reduction of phenyl pyrazolyl ketone **2**. Related enantioselective reductions of several azolyl phenyl ketones are also reported.

Key words: asymmetric synthesis, cizolirtine, oxazaborolidine, azolyl phenyl ketones, enantioselective reduction

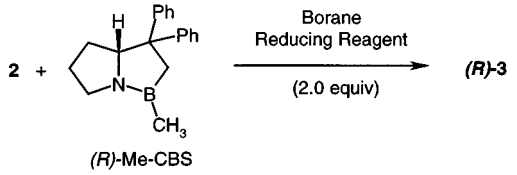
Cizolirtine **1** is an analgesic developed in our company that is currently undergoing Phase II clinical trials.[1] The two enantiomers (+)-**1** and (-)-**1** have been previously obtained in our laboratory by optical resolution of the racemate with (-)- and (+)-di-*p*-toluoyltartaric acid.[2] In addition, an EPC synthesis starting from ethyl (*R*)-mandelate permitted the assignation of the *R* absolute configuration to the isomer (+)-**1**.[3] We report herein the enantioselective synthesis of (*R*)- and (*S*)-cizolirtine by a short and efficient procedure which utilizes as a key step the oxazaborolidine-catalyzed reduction of prochiral ketone **2** to the corresponding secondary alcohol **3** (Scheme 1).



Scheme 1 Reagents and conditions: (i), n-BuLi, THF –40°C; (ii), benzonitrile –40°C to rt 20 h; (iii), HCl 2N, reflux, 10 h; (iv), (*R*)-Me-CBS, catecholborane, toluene –15°C to rt , 20 h; (v), NaOH 40%, 2-chloro-1-dimethylaminoethane hydrochloride, triethylbenzylammonium chloride, toluene, reflux, 10 h

Oxazaborolidines are well known catalysts for the efficient asymmetric borane reduction of ketones. After the pioneering work of Itsuno and co-workers,[4] Corey et al. were the first to report the enantioselective reduction of ketones to chiral secondary alcohols (CBS reduction).[5] Since then, numerous publications[6] have described optimization, variations, mechanistic proposals and applications in total synthesis of this methodology which has been extensively applied to aryl alkyl ketones. It has been reported that the CBS catalyst works well when the two groups attached to the carbonyl group to be reduced have significantly different steric bulk,[7] but conformational[8] and electronic effects[9] are also important. When strong coordinating groups such as pyridine or nitrogen heterocycles are close to the carbonyl, the site selectivity of the chiral reducing reagent must generally decrease due to the coordination effect of the heteroatom.[10] Therefore, very few examples dealing with diaryl ketones,[9,11] and even less with phenyl heteroaryl ketones have been described. Only several benzoylpyridines have been reduced by Corey *et al.* with a remarkable modified procedure.[11] The lone pair of the pyridyl nitrogen atom was masked through the formation of an N-allylpyridinium salt, or by addition of a Lewis acid before asymmetric reduction.

Table 1. Enantioselective Reduction of Ketone **2**



Entry[a]	Reducing reagent	Temp (°C)	% mol cat.	Solvent	Yield (%)[b]	ee (%)[c]
1	BH3-Me_2S	0°→rt	20	THF	94	54
2	Catecholborane	-40°→rt	20	THF	79	91
3	Catecholborane	-20°→rt	15	Et_2O	81	46
4	BH3-Me_2S	40°	20	THF	93	52
5	Catecholborane	-78°→rt	15	toluene	84	97
6	Catecholborane	-15°→rt	15	toluene	83	98
7	Catecholborane	-15°→rt	10	toluene	82	92
8	Catecholborane	rt	15	toluene	81	92
9	BH3-Me_2S	0°→rt	15	toluene	95	84
10	Catecholborane	-15°→rt	20	CH_2Cl_2	82	50
11	Catecholborane	-15°→rt	2.5	toluene	85	91
12	BH3-THF	0°→rt	15	toluene	94	57
13	$BH_3$1,4-oxathiane	0°→rt	15	toluene	90	69
14	BH3-Me_2S	0°→rt	5	toluene	92	74
15[d]	Catecholborane	-15°→rt	15	toluene	84	97[d]

[a]All experiments were performed on a 5 mmole scale. The reaction time was 20 h when catecholborane was used and 5 h with the other reducing reagents. Entries 6 and 9 have been scaled up to 0.05 mol[13] and 0.8 mol, respectively. [b]Isolated yields. [c]Determined by HPLC[14]. [d](*R*)-n-Bu catalyst was used

The present approach to the synthesis of **1** required the enantioselective reduction of 5-benzoyl-1-methyl-1*H*-pyrazole **2**, previously obtained from 1-methylpyrazole by lithiation with n-BuLi, followed by reaction with benzonitrile and hydrolysis with hydrochloric acid[1a] (Scheme 1). We thought that the similar steric bulk of the aromatic rings attached to the carbonyl group and the presence of two nitrogen atoms in the pyrazole ring of **2** might be an additional difficulty to obtain high enantioselectivity, so we tested a large battery of conditions to carry out the reduction. The results are summarized in Table 1.

Contrary to our expectations, carbinol **3**[3] was obtained with moderate to high ee in almost all conditions tested. It is noteworthy that the temperature did not affect dramatically the enantioselectivity while the solvent and reducing reagent used were very important. Borane-methyl sulfide complex in toluene and particularly catecholborane gave the best results. Commercially available (*R*)-3,3-diphenyl-1-methyl-l-pyrrolidino[1,2-*c*]-1,3,2-oxazaborole [(*R*)-Me-CBS] catalyst proved to be excellent to afford high ee, and n-Bu-CBS[12] did not enhance significantly the enantioselectivity. On the other hand, the percentage of catalyst could be reduced to 2.5 mol % without drastic decrease of the ee. Optimum conditions for the reduction of **2** (entry 6) were 15 mol % (*R)*-Me-CBS catalyst, catecholborane as reducing reagent and toluene as solvent. Carbinol (*R*)-**3** was obtained in 98% ee[13] determined by chiral HPLC.[14] Similarly, when (*S*)-Me-CBS was used the corresponding enantiomer (*S*)-**3** was obtained in 98% ee. The observed high enantioselectivity may suggest that because of the steric interaction between the methyl group at position 1 and the carbonyl oxygen in ketone **2**, the pyrazole ring twists out of the plane,[11] increasing the distance between the second nitrogen atom and the carbonyl group thus avoiding interaction with the catalyst[15] (Figure 1). The observed absolute configuration of the products[3] indicates that the pyrazole ring behaves as the small group. The stereochemical pathway of the reaction is in agreement with the mechanism described in the literature.[9, 11]

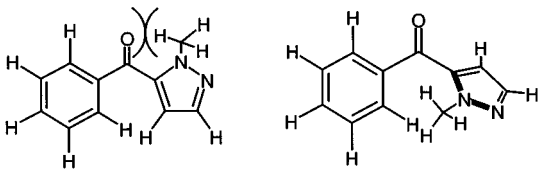
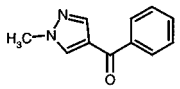
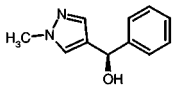
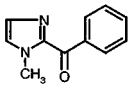
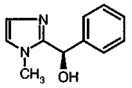
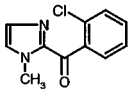
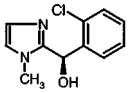
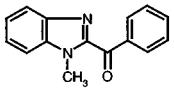
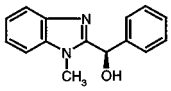


Figure 1 Representation of planar and molecular mechanics optimized structures of ketone 2

To the best of our knowledge, the synthesis of carbinols (*R*)- and (*S*)-**3** represents the first application of CBS reduction to an azolyl phenyl ketone.[16] Alkylation of (*R*)-**3** with 2-chloro-1-dimethyl-aminoethane and NaOH under phase transfer conditions led to (*R*)-(+)-cizolirtine (*R*)-**1** in 92% yield and with 98% ee[17] (Scheme 1).

Encouraged by these results, we extended the reaction to other azolyl phenyl ketones. The results are summarized in Table 2. Initially, we investigated the reduction of the isomeric 4-benzoyl-1-methyl-1*H*-pyrazole[18] and 2-benzoyl-1-methyl-1*H*-imidazole.[19] As expected, better results were obtained in the preparation of the pyrazolyl carbinol[1a] than in the synthesis of the corresponding 2-imidazolyl derivative.[20] In this case, a low ee (8%) was observed, probably due to the proximity of the second nitrogen atom to the carbonyl group.

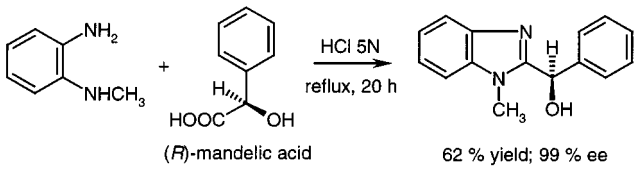
Table 2. Asymmetric Reduction of Prochiral Azolyl Phenyl Ketones

Starting material[a]	Product	Reducing reagent	Config.	Ee (%)
		BH_3-Me_2S	(*R*)[b]	81[d]
		catechol-borane	(*R*)[b]	8[d]
		catechol-borane	(*R*)[b]	59[d]
		BH_3-Me_2S	(*R*)[c]	12[e]
		catechol-borane	(*R*)[c]	23[e]

[a]All experiments were performed on a 5 mmole scale with 15 mol % of (*R*)-Me(CBS) catalyst in toluene. [b]Estimated on the basis of the mechanism described. [9,11] [c]Assigned by comparison with a sample obtained by EPC synthesis. [d]Determined by ^{1}H-NMR using β-cyclodextrin as chiral solvating agent. [e]Determined by HPLC[14]

A very interesting effect was observed when a Cl atom was introduced in the *ortho* position of the phenyl group.[21] An important increase of enantioselectivity was achieved (59% ee)[22] suggesting that a non-planar arrangement of the imidazole ring relative to the benzoyl group is favoured.

Next, we examined the effect of a bulky heterocyclic ring in the case of 2-benzoyl-1-methyl-1*H*-benzimidazole.[23] The corresponding carbinol was obtained with moderate ee (Table 2). In order to assign the absolute configuration of α-(1-methyl-1*H*-benzimidazol-2-yl)-α-phenyl-methanol[20] we carried out an EPC synthesis, starting from (*R*)-mandelic acid. Phillips condensation[24] with *N*-methyl-*o*-phenylenediamine gave the (*R*)-carbinol with 62% yield and 99% ee[14,25] (Scheme 2).



Scheme 2

It is noteworthy that the difference in steric bulk of benzimidazole ring *versus* pyrazole of ketone **2** did not affect the enantioselective site of the reaction. In both cases the (*R*)-carbinol was obtained confirming that in these two examples the heterocyclic ring behaves as the small group.

In conclusion, we have achieved the asymmetric synthesis of the enantiomers of cizolirtine with high enantiomeric excess. The application of CBS reduction to other heteroaryl phenyl ketones will be further investigated.

Acknowledgement

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References and Notes

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(13) A typical experimental procedure is as follows: To a stirred solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine 1M in toluene (7.5 mL, 7.5 mol) under argon cooled to -10° C, a solution of catecholborane 1M in THF (100 mL, 100 mmol) was slowly added. To the mixture was then added a solution of 5-benzoyl-1-methyl-1*H*-pyrazole **2** (9.30 g, 50 mmol) in dry toluene (100 mL) and the reaction was stirred 1 h a -15° C and 20 h at room temperature. MeOH (10 mL) was added carefully with stirring for 2 h. The mixture was concentrated at reduced pressure to 100 mL, washed successively with water, HCl 1N and brine, dried and evaporated to give an oil which was purified by silicagel column chromatography, using ethyl acetate: petroleum ether (7:3) as eluent to afford (*R*)-(+)-1-methyl-α-phenyl-1*H*-pyrazole-5-methanol (*R*)-**3** in 98% ee (7.82 g, 83%).; mp: 81-83° C; $[\alpha]_D$= +16.6 (c= 1.02, $CHCl_3$).
(14) Enantiomeric excess determined on a Chiralcel OD-H column at λ= 230 nm; flow rate: 1 mL/min; eluent: hexane: i-PrOH (93:7) with 0.1% diethylamine.
(15) The structure of **2** was optimized by molecular mechanics using the modelling software Chem-X (Chemical Design Ltd., UK). The calaculated distance between carbonyl oxygen and pyrazole N-2 increased from 4.21 Å in the planar structure to 4.46 Å in the optimized structure.
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(25) Physical data of (*R*)- α−(1-methyl-1*H*-benzimidazol-2-yl)- α−phenylmethanol: mp: 185-188° C; $[\alpha]_D$= +119.1 (c= 1.0, MeOH).

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