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A SIMPLE AND EFFECTIVE ENANTIOMERIC SYNTHESIS OF A CHIRAL PRIMARY AMINE

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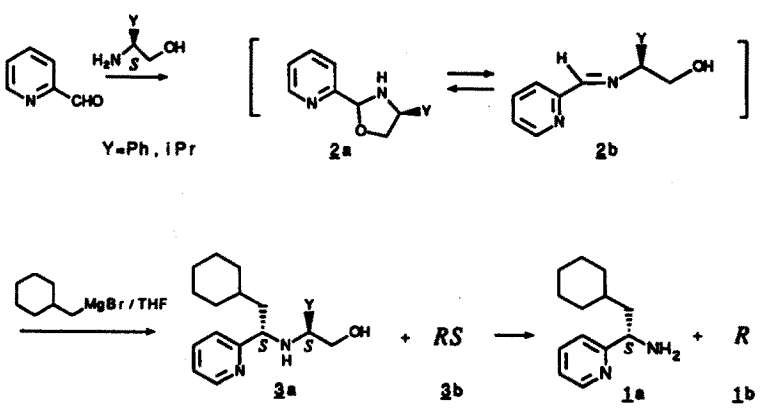
Summary: Catalytic reduction of chiral 2-(2-pyridyl)-1,3-oxazolidines and 2-pyridyl imines derived from (*R*)-phenylglycinol and (*R*)-valinol afforded high diastereomeric selectivity. Upon oxidative cleavage, the *S*- primary amine with high ee was obtained.

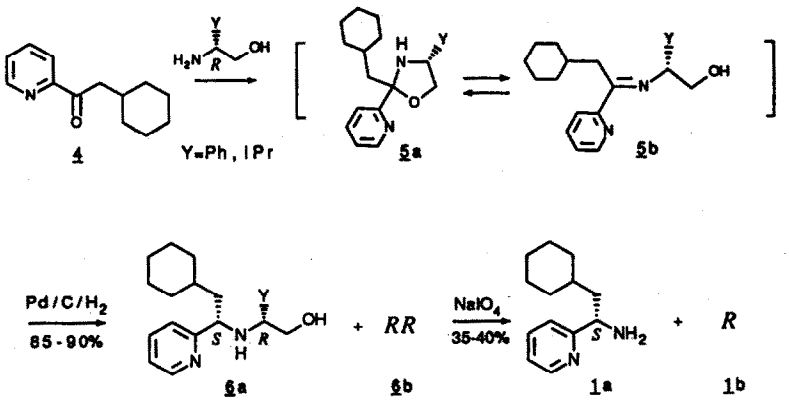
Interest in an effective chiral amine synthesis of the target compound **1a**, the (*S*)-enantiomer, as an intermediate, prompted us to search for a simple and practical synthetic methodology. The use of chiral amino alcohols as auxilliaries attracted our attention because they are easily obtained from amino acids. We explored the use of an equilibrium mixture of 2-pyridyl-4-substituted-1,3-oxazolidine **2a** and the corresponding imine **2b** in the preparation of **3a** based on work by Pridgen[1] and Takahashi.[2] We found the solution equilibrium ratio of **2a** and **2b** to be solvent dependent. Since the reaction was done in THF, we feel that the true reaction intermediates are represented by the ratio in THF. In THF, **2b** is the predominant form (Y=Ph, **2a**:**2b** is 5:95; Y=iPr,**2a**:**2b** is



Scheme 1

1:3) while in $CHCl_3$, **2a** predominates (Y=Ph, **2a**:**2b** is 54:46; Y=iPr, **2a**:**2b** is 80:20).[3,4] Grignard addition to **2** yields **3**,[5] which upon oxidative cleavage afforded **1**, **Scheme 1**. We found an 87:13 diastereomeric ratio of **3a** : **3b** in the crude reaction mixture when Y=iP,[6] which is comparable to that recently obtained by Higashiyama.[7] This was oxidatively cleaved with $NaIO_4$[8] to a 75% ee based on chiral HPLC results.[9] The absolute configuration of **1a** was determined by comparison with an authentic sample of **1a**, which we had resolved from our earlier work.[10]

We also investigated an alternative route to **1a** which proved superior by starting with the ketone **4**,[11] **Scheme 2**. In this case, the (*R*)-amino alcohol is needed in order to obtained the (*S*)-enantiomer, **1a**. Upon coupling with the appropriate amino alcohol, an equilibrium mixture of the oxazolidine and the imine **5** was obtained. Due to the complexity of the equilibrium mixture, we were not able to determine the ratio between **5a** and **5b**. Without further purification, the reaction mixture was catalytically reduced giving a high diastereomeric selectivity for **6**. The major diasteromer obtained is the *SR* when starting with the (*R*)-amino alcohol (when Y=Ph, *SR*:*RR* is 98:2; Y=iPr, *SR*:*RR* is 90:10).[12] Noteworthy is the diastereomeric distribution of **6** in **Scheme 2** in which the major diastereomer is the *SR* **6a** instead of the *RR* **6b** as compared to **Scheme 1** where *SS* **3a** is the predominant



4 5a 5b 6a 6b 1a 1b

Scheme 2

diastereomer. Oxidative cleavage of the diastereomers **6** with $NaIO_4$[8] provided the desired amine **1a** with 96% ee when Y=Ph and 80% ee when Y=iPr based on chiral HPLC results.[9] Again the absolute configuration of **1a** was compared with an authentic sample of **1a**, which we had resolved from our earlier work.[10] No purification is necessary in this reaction sequence until the final step. We believe this constitutes an effective synthesis of a chiral amine.[13]

Experimental: The cyclohexyl methyl-2-pyridyl ketone (1 equiv.) was condensed with valinol (1 equiv.) in the

presence of anhydrous $MgSO_4$ (2 equiv.) in $CHCl_3$. The resulting suspension was refluxed for two days, the $MgSO_4$ was filtered off with the aid of Celite and the filtrate was concentrated to give a colorless oil **5** (>95% yield). Without further purification, this oil was taken up in THF and hydrogenated in the presence of dry 10% Pd/C (10% cat. by weight) for 4h. The ^{1}HNMR of the crude reaction mixture indicated the diastereomeric ratio of *SR*:*RR* is 90:10.[12] Oxidative cleavage of **6** with $NaIO_4$ (2 equiv.) in THF/H_2O/2NHCl (10:3:1 by volume) at r.t. overnight under Argon afforded 35-40% yield of **1** after flash column chromatography.

Acknowledgement: We thank Arvind Shah for providing the chiral HPLC data.

References:

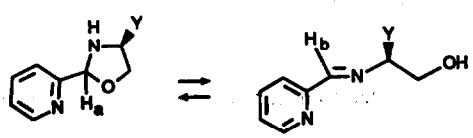
1) L.N. Pridgen, M.K. Mokhallalati and M-J Wu, *J. Org. Chem.*, **1992**, *57*, 1237.

2) H. Takahashi, Y. Chida, T. Yoshi, T. Suzuki and S. Yanaura, *Chem. Pharm. Bull.* **1986**, *34*(5), 2071; H. Takahashi, B.C. Hsieh and K. Higashiyama, *Chem. Pharm. Bull.*, **1990**, *38*(9), 2429.

3) The oxazolidines (**2a**) and imines (**2b**) referred to in the text were identified based on their characteristic ^{1}HNMR spectra, which are consistent with that published for analogous model compounds.[2,3a] Spectral assignment ambiguities were eliminated by selective decoupling experiments. Oxazolidine:imine ratios were determined by comparison of peak areas for the well-resolved Ha of the oxazolidine and Hb of the imine resonances (See Ref.4), and were corroborated by peak area comparisons for other well-resolved resonances where necessary.

3a) E. Pretsch, T. Clerc, J. Seibl, W. Simon; "Tabellen zur Strukturaufklarung Organischer Verbindungen mit Spektroskopischen Methoden", Springer-Verlag, 1976.

4)



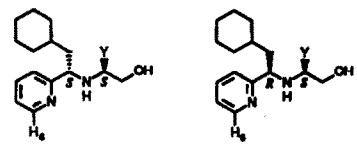
	$CDCl_3$			THF-d_8		
Y	Ha	Hb	Ha:Hb	Ha	Hb	Ha:Hb
Ph	5.65,d	8.50,s	54:46	5.50,*	8.07,s	5*:95
iPr	5.42,d	8.28,s	80:20	5.33,s	8.25,d	1:3

*The assignment of Ha is less certain due to the very small amount present.

5) The diastereomeric pairs **3a,3b**, and **6a,6b** were identified based on their ^{1}HNMR spectra in the same manner as **2a**, and **2b** (See Ref.3). The Grignard reactions were generally done in THF. When ether was used as the solvent, the Grignard addition reaction did not work. In our hands, using organocerium reagent did not improved the diastereoselectivity, in some cases, the chemical yield were much lower.

6) The reported ratios between the sets of the diastereomers were also determined in a manner analogous to that described in Ref.3 using the well resolved H_6 of the pyridine ring resonances.

^{1}HNMR ($CDCl_3$)	Y	*SS*	*RS*
	Ph	8.45,d	8.6,d
	iPr	8.57,d	8.5,d



In addition to **3a** and **3b**, we also isolated a side product, the N-alkylated compound, in 10-20% yield. This product has been charaterized based on its ^{1}HNMR spectrum, which is consistent with the proposed structure.

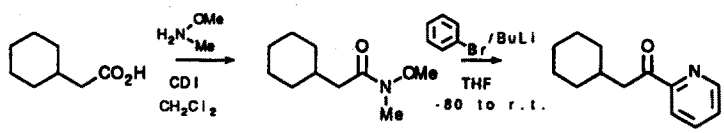
7) K. Higashiyama, H. Inoue, and H. Takahashi, *Tetrahedron Lett.*, **1992**, *33*(2), 235.

8) R.M. Williams and J.A. Hendrix, *J. Org. Chem.*, **1990**, *55*, 3723; Although $Pb(OAc)_4$ gave slightly higher yield (45%), $NaIO_4$ was used instead in the oxidative cleavage should this reaction needed to be scaled up.

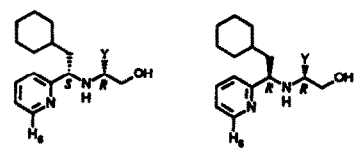
9) Chromatographic separation was carried out on Amylose-tris[3,5-dimethyl phenyl carbamate] coated on silica gel stationary phase and using hexane/isopropanol/diethylamine (980/20/5) as the mobile phase.

10) C.K. Miao, R. Sorcek and J. Nagel, *Org. Prep. Proc. Int.*, **1992**, *24*(1),87.

11) This ketone can be prepared as following:



12) ^{1}HNMR ($CDCl_3$)	Y	*SR*	*RR*
	Ph	8.6,d	8.45,d
	iPr	8.5,d	8.57,d



As expected, the major diastereomer obtained is the *RS* when starting with the (*S*)-amino alcohol.

13) The mechanism of the diastereomeric selectivity in the catalytic hydrogenation is not clear in terms of the role of the Pd catalyst in a highly rigid system. Further work is in progress.

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