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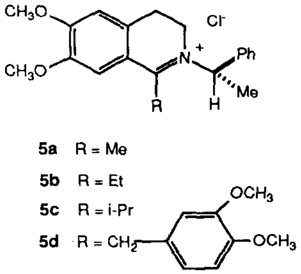
STEREOSELECTIVE REDUCTIONS OF CHIRAL IMINIUM IONS

Richard P. Polniaszek* and Julia A. McKee
Department of Chemistry, Duke University, Durham, NC 27706 USA

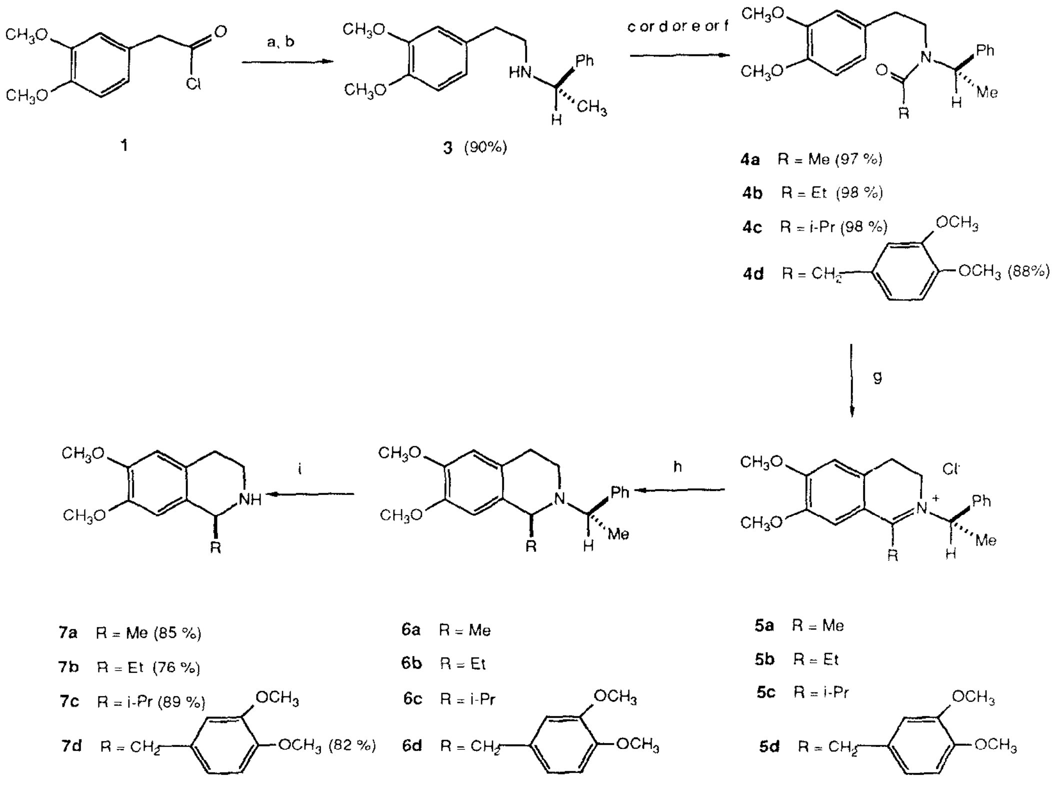
Abstract: Chiral iminium ions derived from α-phenethylamine have been reduced stereoselectively with $NaBH_4$. Diastereoselection of the reduction ranged from 88:12 to 94:6. The sense of asymmetric induction has been unambiguously assigned by correlation of reduction products with S-(-)-salsolidine and S-(-)-nor-laudanosine.

We are interested in understanding the stereochemistry of nucleophilic addition reactions to chiral iminium ions. Specifically, we wish to explore the conformational preferences of iminium ions whose asymmetry originates from a chiral center appended to the nitrogen atom of the iminium ion moiety, and the relation between conformation and reactivity.



This report describes surprisingly stereoselective reductions of cyclic chiral iminium ions **5a-5d**. These iminium ions were prepared by straightforward methods (Scheme 1). Acylation of commercially available (S)-(-)-α-phenethylamine with 3,4-dimethoxyphenylacetyl chloride[1] **1** afforded amide[2] **2** (96%, mp 107-109°) which was then reduced[3] with BH_3-THF (94%) to chiral amine **3**, $[\alpha]_D = -38.9^0$ ($c = 1.7$, CH_2Cl_2). Acylation of the amine with acetic anhydride, propionyl chloride, isobutyryl chloride or 3,4-dimethoxyphenylacetyl chloride produced amides **4a-4d** respectively. The amides were obtained as inseparable mixtures of E and Z configurational isomers. Conversion of these amides to chiral iminium ions **5a**[4]-**5d** was achieved by the Bischler-Napieralski reaction.[5] The iminium ions were reduced with $NaBH_4$ in methanol[6] at -78°C, and following aqueous workup afforded tetrahydroisoquinolines **6a-6d** with very high stereoselectivities (Table 1). The sense of asymmetric induction was determined by correlation of **6a** and **6d** with the natural products (S)-(-)-salsolidine[7] and (S)-(-)-nor-laudanosine.[8] Hydrogenolysis of

Scheme 1

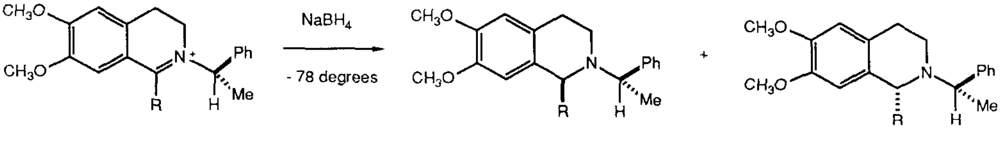


Reagents: a: (S)-(-)-α-phenethylamine, 1.1 NEt$_3$, 0.1 DMAP, CH$_2$Cl$_2$, 25°; b: Excess BH$_3$-THF, reflux, 3 days; c: 1.1 Ac$_2$O, 0.2 DMAP, 1.2 NEt$_3$, CH$_2$Cl$_2$, 25°; d: 1.5 Propionyl chloride, 0.2 DMAP, 1.7 NEt$_3$, CH$_2$Cl$_2$, 0°; e: 2 Isobutyryl chloride, 0.2 DMAP, 2.4 NEt$_3$, CH$_2$Cl$_2$, 0°; f: 1.5 3,4-Dimethyoxyphenylacetyl chloride, 0.2 DMAP, 1.6 NEt$_3$, CH$_2$Cl$_2$, 0°; g: 2:1 Benzene:POCl$_3$, reflux 5-24 hr.; h: 2-4 NaBH$_4$, MeOH, -78°; i: 10% Pd/C, EtOH, 10% HCl.

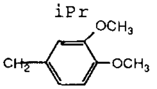
6a with hydrogen and palladium on carbon in acidic ethanol afforded (S)-(-)-salsolidine, **7a**. Similarly, amine **6d** was hydrogenolyzed to afford (S)-(-)-nor-laudanosine, **7d**. The configurations of **6b** and **6c** are assigned by analogy.

The stereoselectivities presented in Table 1 represent differences in free energies between competing diastereomeric transition states ($\Delta\Delta G^{\ddagger}$) of 0.77 to 1.1 kcal/mol. A simple empirical model which accounts for the observed results is the selection of a ground state iminium ion conformation **8** which minimizes allylic A(1,3) interactions.[9] Nucleophilic attack may then

Table 1

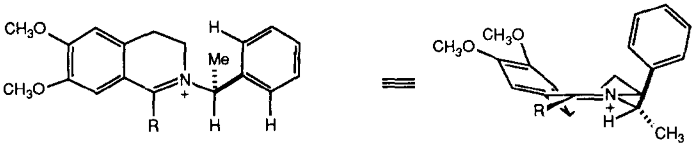


D$_1$ D$_2$

Iminium Ion	R	D$_1$:D$_2$^{a}	D$_1$:D$_2$	Yield^d	ΔΔG‡ (kcal/mol)
5a	Me	90.5:9.5	93:7^b	77%	0.87
5b	Et	92:8	---	75%	0.94
5c	iPr	88:12	---	61%^{e} 6%^{f}	0.77
5d		94:6	c	72%	1.1

a: Diastereomeric ratio determined by HPLC on an ISCO 5 mm x 25 cm silica column (254 nm); b: Based on optical rotation[6] of S-(-)-salsolidine, **7a**; c: See reference 8; d: Isolated yield after purification by chromatography. This represents overall yield from amides **4a-4d**; e: Isolated yield of major diastereomer D$_1$ purified by MPLC (Merck Lobar A column); f: Isolated yield of minor diastereomer D$_2$.

proceed by approach to the less sterically hindered iminium ion diastereoface.



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These reactions represent efficient examples of 1,3 asymmetric induction. They are remarkable to the extent that they possess only one point contact of the chiral auxiliary with the iminium ion and/or attacking reagent. This is in stark contrast to the iminium ion chiral auxiliaries of Husson,[10] Mazaleyrat,[11] and Overman.[12] The utility of the α-phenethyl chiral auxiliary is further demonstrated by the selective hydrogenolysis of the doubly benzylic amine **6a-6d** to tetrahydroisoquinolines **7a-7d**. We are continuing to explore nucleophilic additions to iminium ions prepared from α-phenethylamine and its derivatives.[13]

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