



Enantioselective synthesis of (*R*)- and (*S*)-1-ferrocenylalkylamines. Reduction of enantiopure ferrocenylimines obtained from valinol and phenylglycinol

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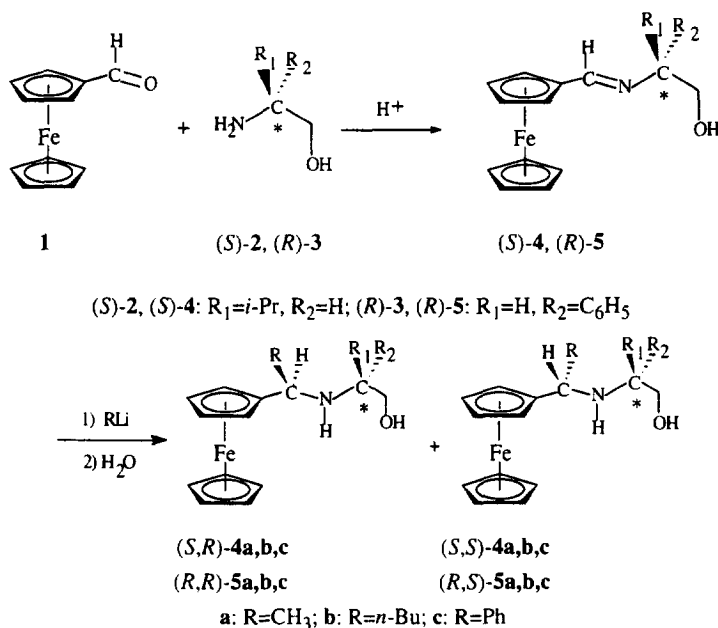
Abstract: Reduction of ferrocenylaldimines from ferrocene-carboxaldehyde and valinol or phenylglycinol with RLi, and reduction of ferrocenylketimine from ferrocenylketone and valinol or phenylglycinol with NaBH₄, give selectively the inverse configurations of the created stereogenic center. Cleavage of ferrocenylaminoalcohols gives the corresponding optically active (*R*)- or (*S*)-ferrocenylalkylamines. © 1997 Elsevier Science Ltd. All rights reserved.

Ferrocenyl derivatives presenting planar chirality are useful ligands for homogeneous asymmetric catalysis.¹ A general key intermediate in the synthesis of such ligands is the optically active *N,N*-dimethyl-1-ferrocenylethylamine.¹ Commonly, optically active *N,N*-dimethyl-1-ferrocenylalkylamines are obtained using resolution techniques² or via an enzymatic kinetic resolution.³ Unfortunately, to our knowledge, only two reports allow access to such chiral amines through asymmetric synthesis.⁴ More generally, only a few convenient synthetic methods are available for allowing access to optically active ferrocenes.⁵

The reduction of prochiral imines through nucleophilic addition to the imine followed by a cleavage leading to the free amine is a classical way to produce of α -aminoacids,⁶ or optically active amines.⁷ Accordingly, we sought to apply such a strategy to the synthesis of chiral ferrocenylamines. In this communication, we report the enantioselective synthesis of (*R*)- and (*S*)-1-ferrocenylalkylamines via highly diastereoselective reduction of ferrocenyliminoalcohol and their subsequent cleavage.

Ferrocene-carboxaldehyde **1** was reacted in benzene in the presence of molecular sieves with commercial enantiomerically pure⁸ (*S*)-valinol (*S*)-**2** and (*R*)-phenylglycinol (*R*)-**3** through modification of reported procedures⁹ giving imines **4** and **5** respectively. After isolation of the reaction products as a mixture through separation of the molecular sieves and evaporation of the solvent, both imines were used without further purification.¹⁰ Their reaction with an excess of RLi in THF under a nitrogen atmosphere, at room temperature or at reflux, led to the corresponding pairs of diastereomeric aminoalcohols (*S,R*)-**4a,b,c**/*S,S*-**4a,b,c**, (*R,R*)-**5a,b,c**/*R,S*-**5a,b,c** (Scheme 1, Table 1). The yields reported in Table 1 correspond to the two steps of the synthesis. The diastereomeric ratios were determined by ¹H NMR spectroscopy. The preceding reaction afforded chiral aminoalcohols with very high diastereoselectivities. Interestingly, when a more bulky organolithium derivative than methyl lithium was used, complete diastereoselectivity was obtained during the addition (entries 2, 3 and 5, Table 1). The complementary diastereomer was not detected by ¹H NMR spectroscopy. Unfortunately, only in one case were we able to separate the two diastereomers i.e. (*S,R*)-**4a**/*S,S*-**4a**, by silica gel chromatography. Thus, (*S,S*)-**4a** was obtained in 40% yield and fully characterized. Moreover, the (*S,S*)-configuration was determined by X-ray crystallography.¹¹

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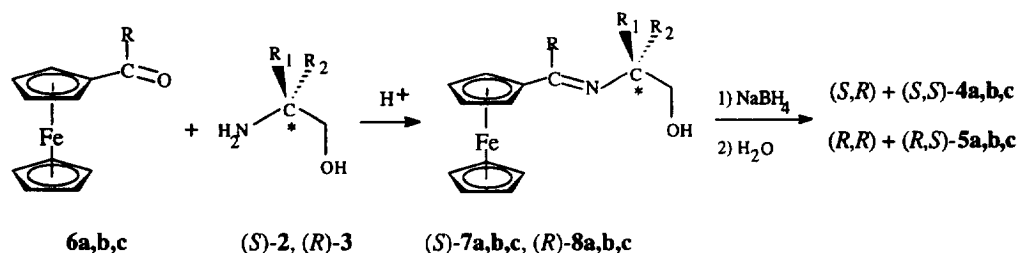
Scheme 1.

Table 1. Reaction of aldimines (S)-4 and (R)-5 with RLi

entry	R_1, R_2	R	products	ratio	yield %	de %
1	<i>i</i> Pr, H	CH ₃	(<i>S,R</i>)-4a/(<i>S,S</i>)-4a	10/90	50	80
2		<i>n</i> -Bu	(<i>S,S</i>)-4b		45	>98
3		C ₆ H ₅	(<i>S,R</i>)-4c/(<i>S,S</i>)-4c		72	>98
4	H, C ₆ H ₅	CH ₃	(<i>R,R</i>)-5a/(<i>R,S</i>)-5a	92/8	28	84
5		<i>n</i> -Bu	(<i>R,R</i>)-5b		46	>98
6		C ₆ H ₅	(<i>R,R</i>)-5c/(<i>R,S</i>)-5c	98/2	66	96

Another synthetic approach to obtain such diastereomeric ferrocenylaminoalcohols was investigated. Ferrocenyliminoalcohols (*S*)-7a,b,c and (*R*)-8a,b,c were obtained respectively through reaction of ferrocenyl-carbonyl derivatives 6a,b,c with (*S*)-2 and (*R*)-3 (Scheme 2, Table 2) following an analogous procedure to that previously reported for imines 4 and 5. Reduction in the presence of NaBH₄ in ethanol afforded the chiral aminoalcohols 4a,b,c and 5a,b,c previously obtained. This approach was also capable of producing adducts with high diastereomeric excess (entry 5, Table 2). However, comparison with the configuration reported in Table 1 revealed the opposite configurations for the carbon atoms involved in the reduction process, consistent with the normal attack of the nucleophile on the side *anti* to the bulky isopropyl or phenyl groups. The spectroscopic data of products obtained by the two different ways were in agreement with identical structures.⁵

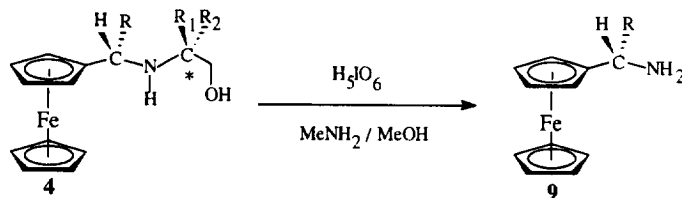
We next turned our attention to the preparation of optically active ferrocenylalkylamines. As reported,¹² compounds (*S,S*)-4b and (*S,S*)-4c underwent oxidative cleavage without loss of enantiomeric purity in the presence of periodic acid, giving (*S*)-9b (88% yield, >98% ee) and (*S*)-9c (72% yield, >98% ee) respectively (Scheme 3). The same periodic acid treatment of (*R,R*)-5b and (*R,R*)-5c produced respectively (*R*)-9b (61% yield, 90% ee) and (*R*)-9c (50% yield, 86% ee) respectively.



Scheme 2.

Table 2. Reduction of ketimines with NaBH₄

entry	R ₁ , R ₂	R	imines	products	ratio	yield %	de %
1	<i>i</i> Pr, H	CH ₃	(<i>S</i>)-7a	(<i>S,R</i>)-4a/(<i>S,S</i>)-4a	78/22	30	56
2		<i>n</i> -Bu	(<i>S</i>)-7b	(<i>S,R</i>)-4b/(<i>S,S</i>)-4b	74/26	7	48
3		C ₆ H ₅	(<i>S</i>)-7c	/	/	trace	/
4	H, C ₆ H ₅	CH ₃	(<i>R</i>)-8a	(<i>R,R</i>)-5a/(<i>R,S</i>)-5a	13/87	41	74
5		<i>n</i> -Bu	(<i>R</i>)-8b	(<i>R,R</i>)-5b	/	26	>98
6		C ₆ H ₅	(<i>R</i>)-8c	(<i>R,R</i>)-5c/(<i>R,S</i>)-5c	9/91	12	82



Scheme 3.

Thus, in the case of the preparation of ferrocenylaminoalcohols starting from (*R*)-phenylglycinol (*R*)-3 and ferrocene-carboxaldehyde 1 and subsequent addition to the obtained ferrocenyliminoalcohol by *n*-BuLi or PhLi, partial racemisation could occur over the course of the reaction at the amino alcohol auxiliary's stereogenic center due to its being a benzylic position.

In conclusion, two synthetic procedures to chiral ferrocenylaminoalcohols have been developed giving access to complementary diastereomers of the same compound. The first route (ferrocenylaldimine+RLi) allowed the synthesis of diastereomeric (*R,R*) and (*S,S*) ferrocenylaminoalcohols with good yields and high to complete diastereoselectivities starting from commercial enantiomerically pure aminoalcohols (*S*)-valinol and (*R*)-phenylglycinol. The second procedure (ferrocenylketimines+NaBH₄) led to the diastereomeric ferrocenylaminoalcohols (*S,R*) and (*R,S*) with generally lower overall yields and selectivities. Thus, the first route using (*S*)- and (*R*)-valinol as chiral auxiliaries corresponds to an efficient and general strategy to the synthesis of the respective enantiopure (*S*)- and (*R*)-ferrocenylalkylamines.

Acknowledgements

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