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Highly Diastereoselective aza-Aldol Reactions of a Chiral Ni(II) Complex of Glycine with Imines. An Efficient Asymmetric Approach to 3-Perfluoroalkyl-2,3-Diamino Acids

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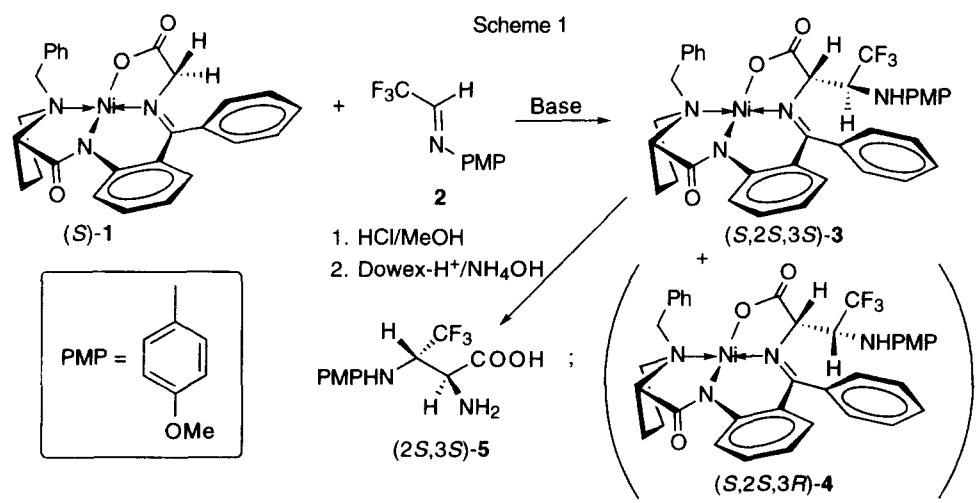
Abstract: The LiCl/base-assisted asymmetric aldol-type addition reaction between the *N*-(*p*-methoxyphenyl)imine of trifluoroacetaldehyde and the chiral non-racemic Ni(II) complex of the *Schiff* base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone was found to proceed with excellent chemical and stereochemical outcomes allowing for an efficient access to hitherto unknown stereochemically defined β-perfluoroalkyl-α,β-diamino carboxylic acids. A mechanistic rationale for the observed stereochemical preferences is proposed. © 1997 Elsevier Science Ltd.

The asymmetric addition reactions to C,N double bonds remain a least studied class of stereoselective reactions. The configurational instability and poor electrophilicity are the main problems which traditionally plague the involvement of imines in the asymmetric transformations established for carbonyl compounds. In particular, highly diastereoselective aldol-type condensations between chiral glycine α-anion equivalents and imines, which would provide the most direct and efficient approach to α,β-diamino acids, have not been developed so far.[1,2] We report herein that, in the presence of LiCl, base-assisted addition between the chiral non-racemic Ni(II) complex of the *Schiff* base of glycine **1** and *N*-(*p*-methoxyphenyl)imine of trifluoroacetaldehyde (**2**) occurs with an excellent diastereoselectivity allowing for an efficient access to hitherto unknown stereochemically defined β-perfluoroalkyl-α,β-diamino carboxylic acids (Scheme 1).

Scheme 1



α,β-Diamino acids are biologically important naturally occurring compounds.[3] Our experience in the fluorine-containing α- and β-amino acids[4] has lead us to a conclusion that fluorinated analogs of α,β-diamino acids would be a highly promising new class of biomedicinally relevant compounds. This, along with the challenge associated with the stereocontrolled synthesis of α,β-diamino acids, has set us studying the asymmetric aldol-type addition reactions of fluorinated imines. Considering our design, apart from a lack of asymmetric aza-aldol methodology in general, there might be additional limitations imposed by the specific electronic and steric characteristics of the trifluoromethyl, or a fluoroalkyl group in general, on the starting imine. 4,4,4-Trifluoro-2,3-diaminobutanoic acid, a fluorinated analog of the corresponding hydrocarbon diaminobutanoic acid critically involved in the biological activity of the peptide antibiotics aspartocin,[5a] glumamycin,[5b] amphomycin,[5c] antrimycin,[5d] cirratiomycin[5e] and lavendomycin,[5f] was our first target to be synthesized.

The exciting reactivity of the Ni(II) complex of the *Schiff* base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]-benzophenone **1**, revealed in the aldol reactions with fluorinated carbonyl compounds,[6] prompted us to explore this readily available chiral glycine α-anion equivalent in the reactions with imines. On the other hand, the choice of the *N*-protective group on the starting imine was of paramount importance. Having tried some routinely used *N*-protective groups,[7] we have found that the *p*-methoxyphenyl (PMP) substituent is the most suitable since the electronic and steric effects of the PMP on the imine function provide the most desirable mode of reactivity of the C,N double bond and its *trans* configurational stability as well.[8] Moreover, in most cases, *N*-*p*-methoxyphenyl derivatives could be readily prepared by the direct condensation between the corresponding amine and a carbonyl compound, and this group could be subsequently removed to afford the free amino function.[7] *N*-(*p*-methoxyphenyl)imine **2** was found to react smoothly with complex (*S*)-**1** at room temperature (20-22 °C) in a DMF solution in the presence of NEt_3 to afford a mixture of two diastereomeric complexes **3** and **4** in ratio 66/34, respectively (Scheme 1, Table 1, entry 1). Investigation of chiroptical properties of complexes **3**, **4** revealed that both contained α-(*S*)-configured diamino acids.[9] The (*S*,2*S*,3*R*) absolute configuration of the minor product **4** was unambiguously established by X-ray analysis.[10,11]

Table 1. The Asymmetric aza-Aldol Reactions of Complex (*S*)-**1** with Trifluoromethyl Imine **2**

entry	reaction conditions[a]			ratio of diastereomers[b]		yield, %[c]
	base	solvent	time, h	*syn*-(2*S*)-**3**	*anti*-(2*S*)-**4**	
1	NEt_3	DMF	32	66	34	94
2	DABCO	MeCN	116	80	20	—
3	DBU	$CHCl_3$	14	65	35	—
4	DBU	MeCN	22	71	29	89
5	DBU	MeOH	17	66	34	—
6	MeONa	MeOH	5	63	37	95
7	NEt_3/LiCl	DMF	1	99	1	91
8	NEt_3/LiCl	DMF	4 days	97	3	86
9	NEt_3/LiCl	DMF	32 days	91	9	70

[a] The reactions were carried out at room temperature under argon atmosphere. Ratio complex (*S*)-**1**/imine **2** = 1/1.3-3; 0.4 mmol scale. [b] Ratio of diastereomers **3**/**4** determined by ^1H and ^{19}F NMR (300 MHz) analysis of crude reaction mixtures. [c] Combined isolated (column chromatography) yield of both diastereomerically pure complexes **3** and **4**.

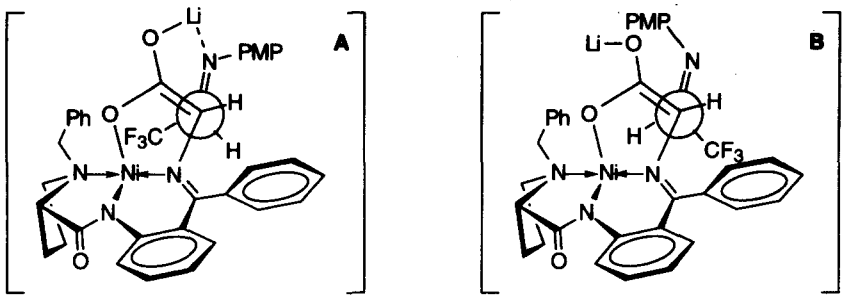


Figure 1

Accordingly, the configuration of the major product **3** is (*S*,2*S*,3*S*). Since the condensation was shown to proceed reversibly, the observed diastereoselectivity might reflect thermodynamic effects influencing the stereochemical outcome of the reaction. As shown for the condensations of (*S*)-**1** with aldehydes, under similar reaction conditions, the thermodynamic diastereoselectivity strongly favors the α-(*S*) configuration for the amino acid moiety while the control over the relative configuration, the ratio *syn*-(2*S*)/*anti*-(2*S*), is normally low.[4c]

In order to improve the diastereoselectivity we carried out series of the experiments varying the solvent and base used. The representative results collected in entries 2-6 (Table 1) show that the reaction rate greatly depends on the conditions applied (entry 2 *vs* 6), while the thermodynamically controlled stereochemical outcome could be only slightly influenced by the nature of both solvent and base used (entries 3-6 *vs* 2). Drawing inspiration from the recent review by *Seebach et al.*,[12] we have tried to modify the basicity of NEt_3 by addition of LiCl to the reaction mixture. The result was totally unexpected (entry 7). Thus, the addition of LiCl dramatically influenced both the rate and stereochemical outcome of the reaction (entry 7 *vs* 1) affording a complete conversion of the starting materials to product **3** in less than 2 hrs and with an excellent diastereoselectivity (98% de). In order to get insight in the origin of the diastereoselectivity observed we have kept the reaction mixture for 4 and 32 days to allow thermodynamic equilibration of diastereomers **3** and **4**, if it could take place at all. Determination of the ratio of **3/4** in these experiments revealed that the diastereoselectivity is a function of time, gradually decreasing from the initial 98% ee to 88% ee in 32 days (entry 7 *vs* 8,9). These data suggest that the initial high diastereoselectivity (98% de, entry 7) is rather kinetically controlled.

Our rationale for the observed stereochemical preferences and the role of LiCl in the diastereoselection process in the addition between Ni(II) complex **1** and imine **2**, is given in Figure 1, where **A** and **B** represent two possible transition states for the reaction under study. Obviously, the co-ordination of the imine *via* the lone pair of electrons on the nitrogen, is of paramount importance in the thermodynamic preference of **A** over **B**. Furthermore, the trifluoromethyl group in **A** occupies the position of sterically larger substituent and being in a close proximity to the nickel atom, could additionally stabilize transition state **A** *via* attractive electrostatic interactions with the metal.[13] By contrast, in **B**, the geometry of imine **2** would not allow for efficient co-ordination of the nitrogen, and unfavorable steric interactions between the trifluoromethyl group and the phenyl at the ketimine bond of the complex are apparent.

In conclusion, we have demonstrated that the LiCl/NEt_3-assisted aldol-type condensation between the Ni(II) complex of the *Schiff* base of glycine (*S*)-**1** and *N*-(PMP)imine **2** occurs with an excellent diastereoselectivity. The expansion of this methodological finding to other fluorinated and fluorine-free imines will constitute the subject of our future efforts.

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8 For instance, *N*-acyl imines were found to be exceptionally electrophilic, while *N*-P(O)Ph_2 derivatives were rather inert toward the addition reactions.

9 As has been shown previously (see refs. 5), CD and ORD spectra of Ni(II)-complexes of this type in neutral solutions exhibit two maxima in the region of the metal d-d transition (*Cotton* effects at 450 and 550 nm). In the ORD spectra, the sign of the *Cotton* effects in this region strictly depends upon the conformation of the polycyclic system of chelate rings. Thus, in the case of complexes containing an α-monosubstituted α-amino acid, a pseudoaxial orientation of the amino acid side chain, corresponding to an α-(*L*) configuration of the α-amino acid, causes a *Cotton* effect with a positive sign at the 500-700 nm region and a negative sign at 400-450 nm. Consequently, a pseudoequatorial orientation of the amino acid side chain brings about opposite signs of the *Cotton* effects at the 400-450 (positive) and 500-700 nm (negative) region. As was established in numerous studies, this general trend is not influenced by the structure and nature of the α-amino acid side chain, and the configuration of stereogenic centers within it. **3**: mp 214-217 °C, $[\alpha]_{578}^{25}$ = +3030 (*c* 0.018, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): 1.30-3.70 (8H, m, Pro-H, β-CH), 3.74 (3H, s, OMe), 3.61, 4.36 (2H, AB, *J* = 12.7 Hz, CH_2Ph), 4.21 (1H, d, *J* = 5.0 Hz, α-CH), 5.10 (1H, d, *J* = 10.0 Hz, NH), 6.10-7.50 (15H, m, ArH), 8.05 (2H, m, ArH), 8.21 (1H, m, ArH); ^{19}F-NMR ($CDCl_3$): -68.6 (d, *J* = 7.4 Hz, CF_3). **4**: mp 234-237 °C, $[\alpha]_{578}^{25}$ = +5870 (*c* 0.011, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): 1.60-3.47 (7H, m, Pro-H), 3.49, 4.39 (2H, AB, *J* = 12.8 Hz, CH_2Ph), 3.74 (3H, s, OMe), 3.77-3.85 (1H, m, β-CH), 4.11 (1H, d, *J* = 12.2 Hz, NH), 4.48 (1H, s, α-CH), 6.66-7.61 (15H, m, ArH), 8.08 (2H, m, ArH), 8.19 (1H, m, ArH); ^{19}F-NMR ($CDCl_3$): -72.36 (d, *J* = 7.6 Hz, CF_3). (2*S*,3*S*)-**5**: mp 191-194 °C, $[\alpha]_{578}^{25}$ = +47, (*c* 0.11, MeOH), ^{1}H-NMR (CD_3OD): 3.84 (3H, s, CH_3), 5.51 (1H, d, α-CH), 5.92 (1H, m, β-CH), 7.07, 7.50 (4H, AB, *J* = 9.0 Hz, ArH).

10 Crystals of compound **4** were grown from chloroform. Crystal data for **4**: $C_{36}H_{33}F_3N_4NiO_4$, tetragonal, space group $P4_12_12$. Crystal size: 0.40 x 0.35 x 0.30 mm^3. Unit cell: *a* = 16.723(2), *c* = 23.974(4) Å, *V* = 6704.5(16) $Å^3$, *Z* = 8, D_x = 1.39 Mg/cm^{-3}. Diffraction data were measured on an Siemens P4-PC diffractometer; radiation MoKα (λ = 0.71073 Å); temperature 289 K. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Center and are available on request from L.V.M.

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