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Asymmetric Aldol Reactions of Trifluoromethyl Ketones with a Chiral Ni(II) Complex of Glycine: Stereocontrolling Effect of the Trifluoromethyl Group

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Abstract: Asymmetric aldol reactions between trifluoromethyl ketones and a Ni(II) complex of the *Schiff* base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB) have been studied. Sterically demanding aryl and *sec*-alkyl trifluoromethyl ketones, and highly enolizable benzyl trifluoromethyl ketone failed to react with the Ni(II) complex, while *n*-alkyl and acetylenyl trifluoromethyl ketones reacted readily and gave good yields (56-87%) of the aldol products with high diastereomeric excess (90-98%). Decomposition of the resultant complexes gave diastereo and enantiomerically pure (2*S*,3*S*)-3-trifluoromethyl-3-substituted serines of biomedicinal interest. A mechanistic working model that accounts for the observed sense of diastereoselectivity is discussed. Copyright © 1996 Elsevier Science Ltd

Introduction

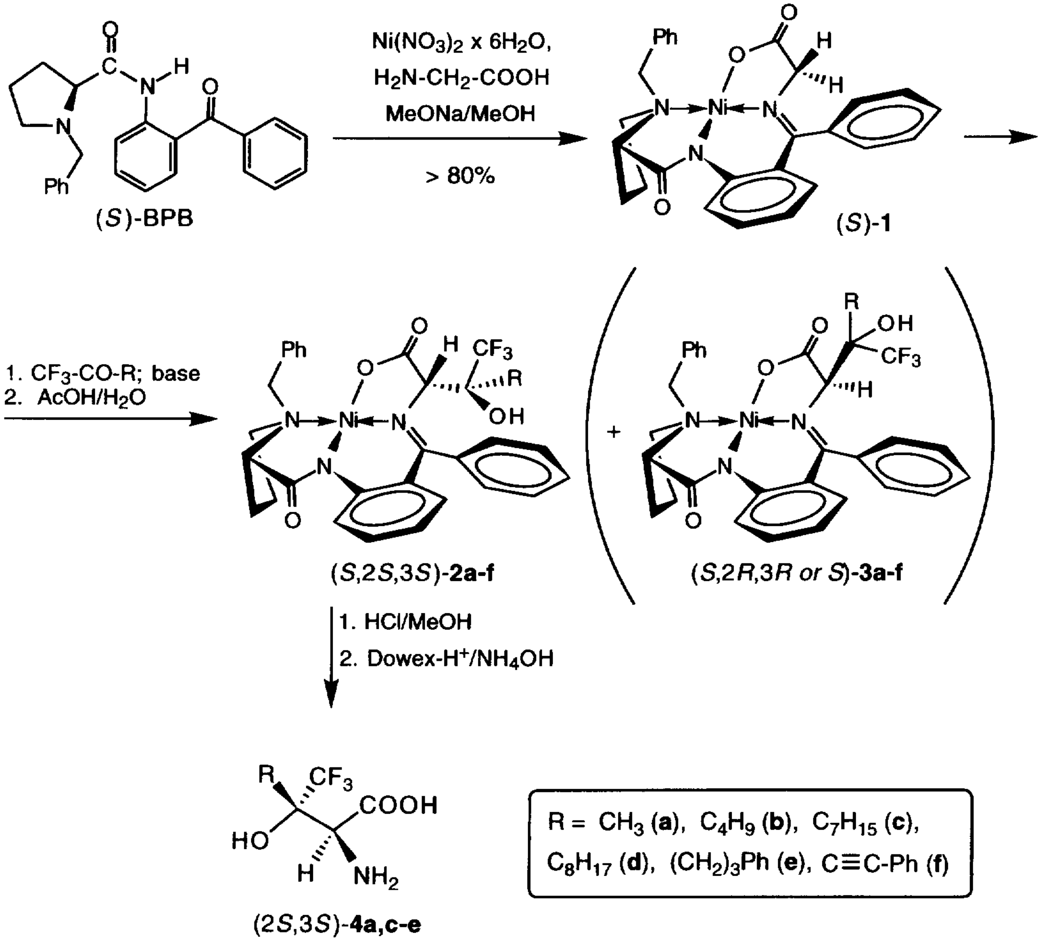
The asymmetric construction of quaternary carbon stereogenic centers represents one of the major challenges to synthetic organic chemistry. For the enantiocontrolled addition of carbon nucleophiles to prochiral ketones, only a limited number of reports are extant, among which the Ti-TADOLate-catalyzed reactions developed by *Seebach* stand as an exceptional achievement.[1] For the particular case of aldol condensations between chiral glycine α-anion equivalents and prochiral ketones, no examples of a synthetically valuable stereochemical outcome, over 90% ee (de), have been reported so far.[2] Apparently, poor electrophilicity, steric shielding of the carbonyl group, and limited stereochemical control might generally plague the involvement of prochiral ketones in the asymmetric methods developed for the synthesis of α-amino-β-hydroxy carboxylic acids. On the other hand, aldol reactions of trifluoromethyl ketones with chiral glycine equivalents would have a reasonable chance of success, since due to the strong electron-withdrawing effect of the trifluoromethyl group, the problem of reactivity could be eliminated. However, the issue of stereoselectivity in such condensations is rather ambiguous because the stereochemical behavior of the trifluoromethyl group is quite controversial and is not well understood yet.[3]

Apart from curiosity to further explore the stereocontrolling features of fluorine substituents, we studied aldol reactions between the readily available chiral Ni(II) complex of glycine (*S*)-**1** (Scheme 1) and fluorinated ketones to develop the asymmetric method for the synthesis of β-fluoroalkyl-β-substituted-β-hydroxy-α-amino carboxylic acids of potential biomedicinal interest.[4,5] A full account of our results is presented herein.[6]

Results and discussion

The chiral glycine α-anion equivalent, Ni(II) complex of glycine Schiff base (*S*)-**1**, employed in our studies is prepared from commercially available (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB)[7], glycine and $Ni(NO_3)_2 \cdot 6H_2O$, according to the well-established procedure (Scheme 1).[8] Complex (*S*)-**1**, first introduced by *Belokon'*,[9] was previously used by us for the asymmetric synthesis of fluorine and phosphorus

Scheme 1



containing amino acids *via* alkyl halide alkylation and *Michael* addition reactions.[10] Investigations into the aldol addition reactions of (*S*)-**1** with aldehydes have disclosed the particular reactivity of complex (*S*)-**1** and its exciting potential for preparing enantiopure β-hydroxy-α-amino acids.[8,9,11-13] In contrast to the other synthetically useful chiral glycine α-anion equivalents,[2] aldol condensations of complex (*S*)-**1** are reversible. Accordingly, the products stereochemistry could be subject to kinetic and/or thermodynamic control depending on the nature of aldehyde and the reaction conditions employed. On the other hand, reversibility of the reactions is a serious obstacle to complex (*S*)-**1** condensations with ketones, since the reaction equilibrium nearly entirely lies on the side of the starting materials. For instance, the condensation of (*S*)-**1** with acetone could be conducted in 1.3-1.7 *M* NaOMe/MeOH using 10-100 mole excess of the latter, to give (*R*)-β-hydroxyvaline in 70-72% ee and 54-56% chemical yield.[8] Acetophenone does not react with complex (*S*)-**1** at all, while ethyl methyl ketone condensation with (*S*)-**1**, under the conditions similar to that of acetone condensation, occurs with very low reaction rate giving rise to a mixture of all possible diastereomeric products unstable to purification and isolation.[14]

During the course of our investigations into the aldol condensations of (*S*)-**1** with perfluoroalkyl aldehydes we have found that these reactions proceeded with very high rates furnishing the corresponding complexes which were shown to be quite stable toward the retro reaction. Apart from the influence on the reactivity, the perfluoroalkyl group was demonstrated to play the stereodirecting role providing dominant formation of

(*S*,2*S*,3*S*)-configured[15] complexes that is just opposite to the (*S*,2*R*,3*S*)-stereochemistry observed in the reactions of hydrocarbon aldehydes.[11,12b,f,13] An attempt to involve fluorinated ketones in the condensation with (*S*)-**1** disclosed rather exciting result. The reaction of trifluoroacetone with (*S*)-**1** gave only one out of four possible diastereomeric products, complex **2a** (Scheme 1), the (*S*,2*S*,3*S*) absolute configuration of which was determined by single crystal X-ray analysis.[12f] However, the reaction conditions employed, causing substantial halogenoform-type decomposition of trifluoroacetone, necessitated a ten-fold excess of the ketone to achieve reasonable conversion of starting complex (*S*)-**1** and a 69% yield of **2a**.

To survey the generality of this surprisingly high stereoselectivity, we prepared a series of trifluoromethyl ketones bearing *n*-alkyl, *sec*-alkyl, ω-substituted alkyl, aryl and acetylenyl groups, and examined their aldol condensations with (*S*)-**1** under various reaction conditions. The results are collected in Table 1. As can be seen in the Table all of the *n*-alkyl trifluoromethyl ketones reacted readily with (*S*)-**1** in 2.5 *M* NaOMe/MeOH and gave aldol products **2b-d** with high diastereomeric excesses (over 95% de, ^{19}F NMR) regardless of the length of the alkyl chain (entries 3,4,8). Along with **2b-d** in some cases we succeeded in isolation of minor products **3c,e**. No other complexes containing β-(trifluoromethyl)-serines were found in the reaction mixtures. The same pattern of both reactivity and stereochemical outcome was obtained in the reaction of 3-phenylpropyl trifluoromethyl ketone with (*S*)-**1** (entry 9) which gave complex **2e** in 55% chemical yield and 95% de. Phenylacetylenyl, *c*-hexyl, phenyl and benzyl trifluoromethyl ketones failed to react with complex (*S*)-**1** (entries 10-13), albeit for different reasons. Thus, the acetylenic ketone, bearing both electron-withdrawing alkynyl and

Table 1. Asymmetric Aldol Reactions of Glycine Ni(II) Complex **1** with Trifluoromethyl Ketones

entry	ketone	reaction conditions					
		NaOMe/MeOH[a]			MeCN/DBU[b]		
		time, min	de, %[c]	yield, %[d]	time, min	de, %[c]	yield, %[d]
1	CF_3COCH_3	10	95	69	15	95	75
2	CF_3COCH_3				1	>98	73
3	$CF_3COC_4H_9$	15	95	55	10	98	71
4	$CF_3COC_7H_{15}$	15	96	56	15	97	71
5	$CF_3COC_7H_{15}$				1	>98	70
6	$CF_3COC_7H_{15}$				0.5	92[e]	
7	$CF_3COC_7H_{15}$				0.25	74[e]	
8	$CF_3COC_8H_{17}$	15	96	48	1	>98	75
9	$CF_3COC_3H_6Ph$	15	95	55	1	96	87
10	$CF_3COC{\equiv}CPh$	decomposition			30[f]	90	56
11	CF_3CO-*c*-C_6H_{11}	very slow reaction					
12	$CF_3COC_6H_5$	no reaction					
13	CF_3CO-CH_2-C_6H_5	very slow reaction					

[a] The reactions were carried out in 2.5 *M* NaOMe/MeOH solution at room temperature under argon atmosphere. Ratio (mol) complex **1**/ketone =1/2-10; 0.2 mmol scale. [b] The reactions were carried out in acetonitrile solution at room temperature under argon atmosphere. Ratio (mol) complex **1**/ketone/DBU = 1/2/3, 0.2 mmol scale. [c] Diastereomeric excess of (*S*,2*S*,3*S*)-diastereomers was determined by ^{1}H and ^{19}F NMR (300 MHz) analysis of crude reaction mixtures. Absolute (*S*,2*S*,3*S*)-configuration of **2a** was determined by X-ray analysis; see ref. 12f. All other products **2b-f** are assumed to have the same (*S*,2*S*,3*S*)-configuration by similarity in their chiroptical properties and patterns of NMR spectra; see text. [d] Isolated (column chromatography) yield of diastereomerically pure (*S*,2*S*,3*S*)-complexes **2a-f**. [e] α-(*R*)-Configured complex **3c** was isolated as the minor product. [f] Reaction in MeCN solution in the presence of NEt_3; see text.

trifluoromethyl groups, underwent rapid decomposition under the strongly nucleophilic reaction conditions employed. Sterically hindered *c*-hexyl and phenyl trifluoromethyl ketones did not react with complex (*S*)-**1** probably due to steric reasons whereas failure of benzyl trifluoromethyl ketone to react with (*S*)-**1** could be accounted for by its highly enolizable nature. Furthermore, we noticed that apart from the starting ketones, final products **2,3a-e** are also unstable under the strongly nucleophilic conditions employed. Successive screening of MeONa, K_2CO_3, DBU, Dabco and triethylamine as bases, and MeOH, DMF, MeCN, $CHCl_3$ and benzene as solvents, to optimize the reaction conditions, have revealed that the base/solvent system of choice is DBU/MeCN. It is worth noting that application of strong base (MeONa, K_2CO_3, DBU) and polar solvent (MeOH, DMF, MeCN) was found to be essential for the reactions to occur. The only exception was the condensation of highly electrophilic phenylacetylenyl trifluoromethyl ketone (entry 10). In this case the use of triethylamine as a base in MeCN allowed us to prepare diastereomerically pure complex **2f** in 56% yield. The results in Table 1 (entries 1-9) show that aldol condensations of *n*-alkyl trifluoromethyl ketones with (*S*)-**1** conducted in MeCN/DBU afforded aldol products **2a-e** with virtually the same or even higher diastereomeric excesses and with significantly better chemical yields as compared with those of the reactions run in NaOMe/MeOH. Moreover, under the new set of reaction conditions, MeCN/DBU, 2 mol excess of the initial ketone was found to be sufficient to achieve complete conversion of complex (*S*)-**1** into the aldol products.

On the example of *n*-heptyl trifluoromethyl ketone condensation with complex (*S*)-**1** (entries 4-7) we found that the stereoselectivity depends on the reaction time, increasing from 74% de to over 98% de (entries 5-7), and then ceasing to change (entry 4). Further standing (over 15 min) of the reaction mixture caused the formation of by-products that hindered an accurate evaluation of diastereoselectivity, however no significant amount of other complexes of definite structure, except for **2c**, were detected. These results suggest that the observed (2*S*,3*S*) diastereoselectivity is likely to be thermodynamically controlled.

In all cases of successful aldol condensations, the main products, complexes **2a-d**, were isolated in diastereomerically pure state and fully characterized. Despite the presence of the perfluoroalkyl group, products **2a-d** were found to be less stable than corresponding complexes derived from (*S*)-**1** and fluoroalkyl aldehydes, slowly decomposing to starting materials while standing at room temperature in chloroform solution. Diastereomerically pure complexes **2a,c-e** were treated by HCl in MeOH to give enantiomerically pure (2*S*,3*S*)-

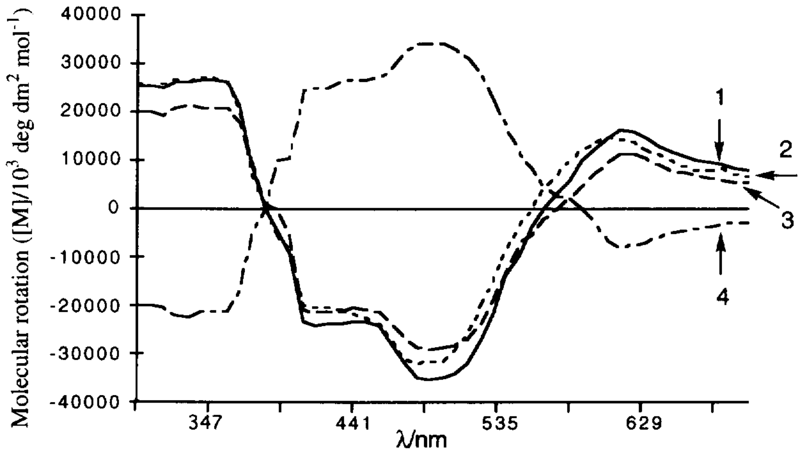


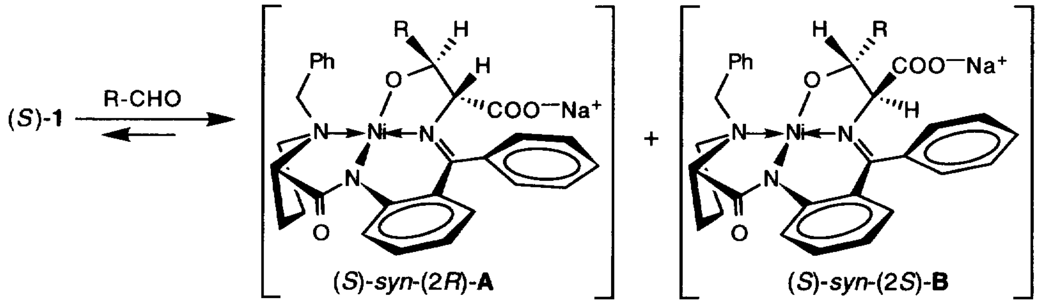
Fig. 1 ORD curves of the diastereomerically pure complexes **2c,e,f** and **3e** (*c* 1.9-2.0 mg in 5 mL $CDCl_3$) at 23 °C. Curve 1 — **2c**, Ni-(*S*)-BPB-(2*S*,3*S*)-3-*n*-hexyl-3-trifluoromethylserine. Curve 2 — **2f**, Ni-(*S*)-BPB-(2*S*,3*S*)-3-(2-phenylacetylenyl)-3-trifluoromethylserine. Curve 3 — **2e**, Ni-(*S*)-BPB-(2*S*,3*S*)-3-(3-phenyl-*n*-propyl)-3-trifluoromethylserine. Curve 4 — **3e**, Ni-(*S*)-BPB-(2*R*,3*R* or *S*)-3-(3-phenyl-*n*-propyl)-3-trifluoromethylserine.

3-substituted-3-trifluoromethylserines **4a,c-e** along with the initial chiral auxiliary (*S*)-BPB (97% recovery).

As noted above, the absolute (*S*,2*S*,3*S*) configuration of **2a** was determined by X-ray analysis.[12f] All other products **2b-d** are assumed to have the same (*S*,2*S*,3*S*) configuration by similarity in their chiroptical properties and patterns of NMR spectra. Furthermore, α-(*S*)-configuration of the amino acid residues in **2b-d** is confirmed by ORD spectra of complexes **2a-d**. Thus, as established previously,[8-13] CD and ORD spectra of Ni(II) complexes of this type in neutral solutions ($CHCl_3$) exhibit two characteristic maxima (*Cotton* effects) in the region of metal d-d transition. In the ORD spectra, the sign of *Cotton* effects at 600 nm region strictly depends on the conformation of the polycyclic system of chelate rings; that is the result of the bulkier α-substituent orientation in the amino-acid moiety. In the case of complexes containing an α-monosubstituted α-amino acid, with a pseudoaxial orientation of amino acid side chain that corresponds to α-(*L*)-configuration of the amino acid, a positive sign of *Cotton* effect at 600 nm region and a negative sign at 500 nm are observed. Consequently, pseudoequatorial orientation of amino acid side chain brings about opposite signs of *Cotton* effects at 500 (positive) and at 600 nm (negative) region. This general trend is not influenced by the structure and the nature of the α-amino acid side chain, or by the configuration of more remote stereogenic centers within it. Fig. 1 represents ORD spectra of complexes **2c,e,f** which show positive sign of *Cotton* effects at 600 nm region followed by the negative sign at 500 nm. Accordingly, the absolute configuration of α-stereogenic center of the amino acids in complexes **2c,e,f** is (*S*). By contrast, ORD spectra of **3e** shows the opposite order of *Cotton* effects thus indicating that α-stereogenic center contained in the amino acids in complexes **3c,e** is (*R*)-configured. Due to the low chemical yield of **3c,e**, relative stereochemistry of the amino acids in **3c,e** was not determined.

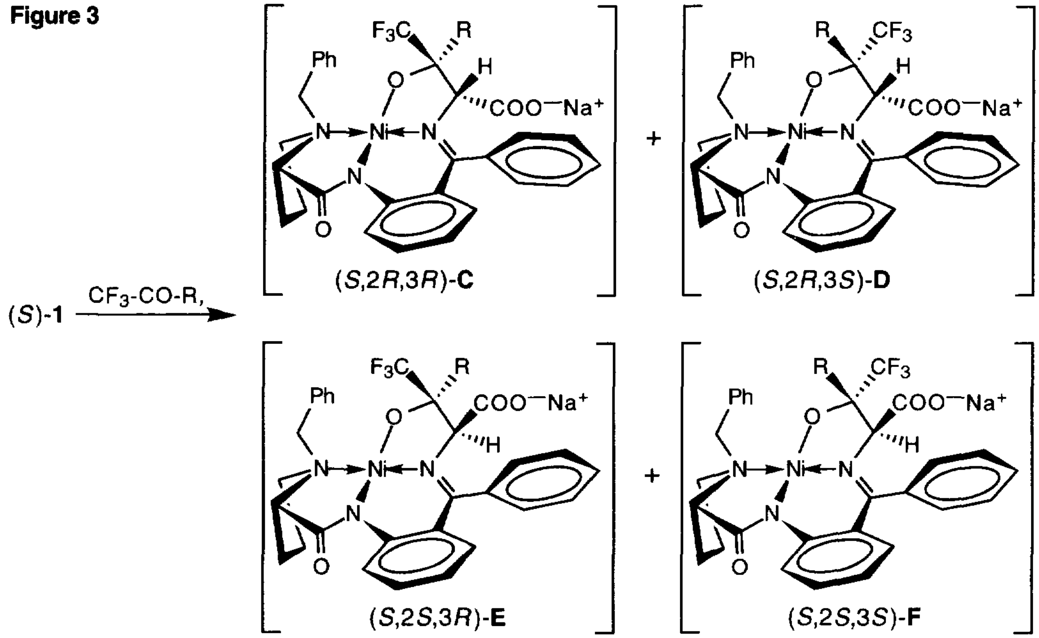
The stereochemistry of aldol reactions of complex (*S*)-**1** with aldehydes at high pH (NaOMe/MeOH) of the reaction medium can be rationalized with the following arguments: a) in a solution of high basicity, the hydroxyl group on the amino acid side chain of the aldol product is ionized, followed by the substitution of an ionized carboxyl group for an ionized hydroxyl group in the main co-ordination sphere of Ni(II) to give a more thermodynamically stable hydroxyl-co-ordinated complex (for instance, complexes **A**,**B**, Fig. 2). Upon neutralization of the reaction mixture the hydroxy-co-ordinated complex becomes protonated and rearranges itself to the regular carboxyl-co-ordinated complex; b) due to the non-bonding interactions of the pseudoequatorially orientated ionized carboxyl group with the phenyl substituent at the carbon atom of the C=N bond (complex **B**, R = CH_3), the ionized carboxyl group adopts a pseudoaxial position (complex **A**, R = CH_3), thus favoring an α-(*R*) absolute configuration of the amino acid side chain in the hydroxyl-co-ordinated complex; c) relative stereochemistry within the amino acid moiety in the complexes is effectively controlled by the energetic advantage of *trans*-relationships between substituents at the five-membered chelate ring (complexes **A**, **B**).[8,9,11-13] While the formation of the hydroxyl-co-ordinated complexes, as a stabilized form for the aldol

Figure 2



R	CH_3	$C(CH_3)_3$	CF_3
Ratio **A/B**	95 / 5	57.5 / 42.5	5 / 95

Figure 3



products at high pH, has been unambiguously confirmed,[8,12f] the sense of stereochemical preferences in the above mechanistic rationale was seriously challenged upon our recent investigation into the condensations of complex (*S*)-**1** with aliphatic aldehydes.[12b,f,13] We have shown that the reactions of aliphatic aldehydes, conducted in 2.5 *N* NaOMe/MeOH, have two definite time-dependent stages of stereoselectivity allowing for the stereodivergent preparation of enantiomerically pure (2*S*,3*R*)-β-alkylserines at the initial stage (pseudothermodynamic control), and (2*R*,3*S*)-β-alkylserines after complete thermodynamic equilibration.[13] Accordingly, two hydroxyl-co-ordinated structures **A** and **B** (Figure 2) were suggested to account for the stereoselectivity observed. Another salient feature of these reactions is that the increase in the steric bulk of substituent R interferes with the formation of structure **A**. Thus, aldol condensation of (*S*)-**1** with pivalaldehyde after complete equilibration gave a mixture of *syn*-(2*R*)- and *syn*-(2*S*)-configured products in the ratio of 57.5/42.5; that is dramatically lower compared with the stereochemical outcome of an acetaldehyde reaction (R = CH_3 *vs* R = $C(CH_3)_3$, Figure 2).[13] Furthermore, as mentioned above, aldol reactions of per(poly)fluoroalkyl aldehydes with complex (*S*)-**1** afforded the thermodynamically controlled products of (*S*,2*S*,3*S*)-configuration, with normally over 90% de. (*S*)-*syn*-(2*S*)-Configured complex **B** was shown to be involved in the stereoselective step of these reactions.[12b,f] Considering the order of the stereochemical preferences given in Figure 2 (ratio **A**/**B**),[12f,13] and taking into account that the steric bulk of the *tert*-butyl group was shown to be responsible for the thermodynamic disfavoring of structure **A**,[13] one could arrive in the conclusion that a trifluoromethyl is bulkier than a *tert*-butyl group.[16] However, we believe that a more reasonable explanation of this puzzling stereochemistry might consider combined effects of the electrostatic and steric features of the trifluoromethyl group influencing the stereochemical outcome in aldol reaction of complex (*S*)-**1** with fluorinated carbonyl compounds. Our working mechanistic rationale, accounting for thermodynamic preference of complex **B** (R = CF_3) over **A** (R = CF_3), apart from the steric effects, postulates: a) electrostatic attractive interaction between partially positively charged Ni-atom and the trifluoromethyl group, and b) electrostatic repulsive interaction between negatively charged ionized carboxy group and CF_3.[12f]

For the reactions of trifluoromethyl ketones with (*S*)-**1**, by analogy with the condensations between (*S*)-**1** and aldehydes or acetone at high pH of the reaction medium,[8,9,11-13] four hydroxyl-co-ordinated complexes **C**-**F** (Figure 3) are possible.[17] Complex **F**, which upon neutralization of the reaction medium gives carboxyl-co-ordinated (*S*,2*S*,3*S*)-**2** (Scheme 1), is thus the most favored among structures **C**-**F**. Thermodynamic preference of hydroxyl-co-ordinated complex **F** relative to **C-E** is the result of a favorable *trans*-disposition of CF_3 relative to COONa[18] and the position of the trifluoromethyl group, which is pointing down and away from the benzyl on the nitrogen of the proline ring. This orientation of the CF_3 group is the most sterically favorable[13] and allows for the electrostatic attractive interaction between the Ni atom and trifluoromethyl group.[12f] However, high diastereoselectivity observed in the reactions studied is rather surprising since, in contrast to aldehyde intermediate **B** (R = CF_3, Figure 2), substituent R in **F** might interact unfavorably with ionized carboxyl group. It is likely that the large steric and electrostatic demands of the trifluoromethyl group[20] are more pronounced in the controlling of stereochemistry in these reactions than the effects brought about by the *n*-alkyl or acetylenic substituents.[18]

In conclusion, we have demonstrated that aldol addition reactions between the chiral Ni(II) complex of glycine (*S*)-**1** and trifluoromethyl ketones occur with high diastereoselectivity to give enantiomerically pure β-trifluoromethyl-β-substituted-β-hydroxy-α-amino carboxylic acids of potential biomedicinal interest. In these reactions the trifluoromethyl group was shown to play the role of stereodirecting factor providing, regardless of the nature of the substituent R on the starting ketone, (2*S*,3*S*) stereochemistry of the resulting products. We emphasize that the rationale for stereochemistry presented herein is to serve exclusively as a model. The ability of the trifluoromethyl group to interact with positively charged species, such as metal cations, and its stereochemical consequences for asymmetric transformations must certainly await further investigations.

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Experimental.

General. ^{1}H-NMR was performed on a Varian VXR-300 (299.94 MHz), Gemini-200 (199.98 MHz) and Brucker WP-200 spectrometers. TMS and CCl_3F were used as internal standards. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. ORD curves were recorded on Jasco ORD/UV-5 instrument. TLC were run on silica gel 60 PF_{254} and 50 PF_{245} Merck plates, column chromatography was performed with silica gel $L_{5/40}$ and $L_{40/60}$ obtained from Chemapol and Aldrich respectively. Melting points (mp) are uncorrected and were obtained in open capillaries. Aldol condensations were carried out under Ar atmosphere; acetonitrile of HPLC grade (99.9+%) was used as a solvent. Synthesis of the Ni(II) complex of the Schiff base of (*S*)-BPB and glycine **1** was accomplished by the procedure given in refs. 8 and 13, starting from commercially available chiral auxiliary (*S*)-BPB.

Aldol Reactions of Complex (*S*)-1 with Alkyl Trifluoromethyl Ketones.

Aldol condensations of (*S*)-**1** with fluorinated ketones in 2.5 *M* MeONa/MeOH solution were performed as described for trifluoroacetone reaction in ref. 12f. Yields of the isolated products and stereochemical outcomes of the reactions are given in Table 1. ***Condensations of trifluoromethyl ketones with (S)-1 in acetonitrile catalyzed by DBU. General Procedure.*** The procedure is illustrated by the synthesis of **Ni(II) Complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-β-trifluoromethyl-β-*n*-heptylserine 2c.** To a solution of 500 mg (1 mmol) of complex **1** in 5 mL of MeCN was added 450 mg (3 mmol) of DBU. The mixture was stirred for 1-2 min to a homogeneous solution, and then 392 mg (2 mmol) of neat 1,1,1-trifluorononan-2-one was added with stirring at ambient temperature. The reaction mixture was vigorously stirred for 15 min and then quenched with 5% aqueous acetic acid. The oily product formed was extracted with $CHCl_3$, dried over $MgSO_4$, and the $CHCl_3$ was evaporated. The crude product obtained was purified on silica gel (column 15 × 4 cm, eluent $CHCl_3$/acetone as 7/1). Two main fractions isolated in the order of their emergence from the column yielded compound **3c** (minor) and **2c** (major). Complex **2c**: mp 99-100 °C, $[\alpha]_D^{25}$ +2000.0 (*c* 0.04, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 0.89 (t, *J*=6.9 Hz, 3H, CH_3), 1.05-1.35 [m, 12H, $(CH_2)_6$], 1.55-3.50 (m, 7H, Pro-H), 3.39, 4.26 (2H, AB, *J*=12.5 Hz, CH_2Ph), 4.24 (s, 1H, OH), 4.28 (s, 1H, α-CH), 6.55-7.60 (m, 11H, ArH), 8.06 (m, 2H, ArH), 8.45 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -72.94 (s, CF_3). Anal. Calcd for $C_{36}H_{40}F_3N_3NiO_4$: C, 62.27; H, 5.81; N, 6.05. Found: C, 62.01; H, 5.32; N, 5.98.

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*R*,3*R* or 3*S*)-β-trifluoromethyl-β-*n*-heptylserine 3c: (2%), mp 92-95 °C, $[\alpha]_D^{25}$ —981 (*c* 0.35, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): 0.90 (t, *J*=7 Hz, 3H, CH_3),1.05-1.30 [m, 12H, $(CH_2)_6$], 1.40-4.00 (m, 7H, Pro-H), 4.20, 5.07 (2H, AB, *J*=13.5 Hz, CH_2Ph), 4.38 (s, 1H, α-CH), 6.60-7.63 (m, 13H, ArH), 8.51 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -74.2 (s, CF_3), Anal. Calcd for $C_{36}H_{40}F_3N_3NiO_4$: C, 62.27; H, 5.81; N, 6.05. Found: C, 62.93; H, 6.22; N, 6.14.

The rest of the complexes **2a-b,d-f** and **3e** were prepared from complex (*S*)-**1** and the appropriate ketone as described for **2c** and **3c**. Yields of isolated products and stereochemical outcomes of the reactions are given in Table 1.

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-β-(trifluoromethyl)threonine 2a:[12f] mp 167-170 °C, $[\alpha]_{578}^{20}$ +1214 (*c* 0.026, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.45 (s, 3H, CH_3), 1.60-3.48 (m, 7H, Pro-H), 4.21 (s, 1H, α-CH), 3.38, 4.26 (2H, AB, *J*=12.6 Hz, CH_2Ph), 4.75 (s, 1H, OH), 6.60-7.57 (m, 11H, ArH), 8.08 (m, 2H, ArH), 8.42 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -77.8 (s, CF_3).

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-β-trifluoromethyl-β-*n*-butylserine 2b: mp 95-98 °C, $[\alpha]_{578}^{20}$ +786 (*c* 0.04, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 0.90 (t, *J*=6.5 Hz, 3H, CH_3), 1.10-1.35 [m, 6H, $(CH_2)_3$], 1.55-3.50 (m, 7H, Pro-H), 3.39, 4.26 (2H, AB, *J*=12.6 Hz, CH_2Ph), 4.28 (s, 1H, α-CH), 4.48 (s, 1H, OH), 6.55-7.60 (m, 11H, ArH), 8.06 (m, 2H, ArH), 8.45 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -73.20 (s, CF_3). Anal. Calcd for $C_{33}H_{34}F_3N_3NiO_4$: C, 60.76; H, 5.25; N, 6.44. Found: C, 60.13; H, 5.48; N, 6.41.

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-β-trifluoromethyl-β-*n*-octylserine 2d: mp 89-92 °C, $[\alpha]_{578}^{20}$ +794 (*c* 0.03, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.87 (t, *J*=6.5 Hz, 3H, CH_3), 1.10-1.30 [m, 14H, $(CH_2)_7$], 1.55-3.50 (m, 7H, Pro-H), 3.40, 4.27 (2H, AB, *J*=12.8 Hz, CH_2Ph), 4.20 (s, 1H, OH), 4.29 (s, 1H, α-CH), 6.55-7.64 (m, 11H, ArH), 8.07 (m, 2H, ArH), 8.45 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -73.03 (s, CF_3). Anal. Calcd. for $C_{37}H_{42}F_3N_3NiO_4$: C, 62.73; H, 5.97; N, 5.93. Found: C, 63.26; H, 5.98; N, 6.41.

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-β-trifluoromethyl-β-*n*-(3-phenyl)propylserine 2e: mp 70-72 °C, $[\alpha]_D^{25}$ +1684.2 (*c* 0.038, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 1.30-3.50 [m, 13H, $(CH_2)_3$, Pro-H], 3.38, 4.25 (2H, AB, *J*=12.5 Hz, CH_2Ph), 4.28 (s, 1H, α-CH), 4.48 (s, 1H, OH), 6.55-7.60 (m, 16H, ArH), 8.06 (m, 2H, ArH), 8.45 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -72.85 (s, CF_3). Anal. Calcd. for $C_{38}H_{36}F_3N_3NiO_4$: C, 63.88; H, 5.08; N, 5.88. Found: C, 64.18; H, 5.72; N, 5.68.

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*R*,3*R* or 3*S*)-β-trifluoromethyl-β-*n*-(3-phenyl)-propylserine 3e: (2%), mp 80-85 °C, $[\alpha]_D^{25}$ —947.4 (*c* 0.38, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): 1.30-3.98 [m, 13H, $(CH_2)_3$, Pro-H], 4.16, 5.01 (2H, AB, *J*=13.5 Hz, CH_2Ph), 4.38 (s, 1H, α-CH), 6.60-7.50 (m, 18H, ArH), 8.52 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -74.2 (s, CF_3). Anal. Calcd. for $C_{38}H_{36}F_3N_3NiO_4$: C, 63.88; H, 5.08; N, 5.88. Found: C, 63.96; H, 5.17; N, 5.73.

Ni(II) Complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-β-trifluoromethyl-β-(2-phenyl)acetylenylserine 2f: mp 129-132 °C, $[\alpha]_D^{25}$ +2075.0 (*c* 0.04, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): 1.50-3.60 (m, 7H, Pro-H), 3.31, 4.27 (2H, AB, *J*=12.5 Hz, CH_2Ph), 4.41 (s, 1H, α-CH), 5.09 (s, 1H, OH), 6.56-7.60 (m, 16H, ArH), 8.10 (m, 2H, ArH), 8.33 (m, 1H, ArH); ^{19}F-NMR ($CDCl_3$): -77.6 (s, CF_3). Anal. Calcd. for $C_{37}H_{30}F_3N_3NiO_4$: C, 63.82; H, 4.34; N, 6.04. Found: C, 63.28; H, 4.26; N, 6.08.

***Isolation of Amino Acids from the Ni(II) Complexes and Recovery of Chiral Auxiliary (S)*-BPB**. The isolation of amino acids **4a,c-e** and recovery of chiral auxiliary (*S*)-BPB were carried out according to the standard procedure described in refs. 9,13. Yields and spectral data for amino acids **4a,c-e** are as follows:

(2*S*,3*S*)-β-(trifluoromethyl)threonine 4a:[12f] mp 226-231 °C (dec.), $[\alpha]_D^{25}$ —12.7 (*c* 1.5, H_2O), +7.13 (*c* 2.0, 6 *N* HCl); ^{1}H-NMR $[(CD_3)_2CO]$: 1.24 (s, 3H, CH_3), 4.25 (s, 1H, α-CH); ^{19}F-NMR $[(CD_3)_2SO]$: -77.06 (s, CF_3).

(2*S*,3*S*)-β-trifluoromethyl-β-*n*-heptylserine (hydrochloride) 4c: mp 174-178 °C, $[\alpha]_{578}^{20}$ -35.0 (*c* 0.79, Me_2CO); ^{1}H-NMR $[(CD_3)_2CO]$: 0.87 (t, *J*=7.2 Hz, 3H, CH_3), 1.17-1,73 [m, 12H, $(CH_2)_6$], 4.30 (s, 1H, α-CH); ^{19}F-NMR $[(CD_3)_2SO]$: -75.10 (s, CF_3). Anal. Calcd. for $C_{11}H_{20}F_3NO_3$: C, 48.70; H, 7.43; N, 5.16. Found: C, 48.38; H, 7.35; N, 5.37.

(2*S*,3*S*)-β-trifluoromethyl-β-*n*-octylserine (hydrochloride) 4d: mp 168-171 °C, $[\alpha]_{578}^{20}$ -36.3 (*c* 0.81, Me_2CO); ^{1}H-NMR $[(CD_3)_2CO]$: 0.87 (t, *J*=7.2 Hz, 3H, CH_3), 1.18-1.76 [m, 14H, $(CH_2)_7$], 4.30 (s, 1H, α-CH); ^{19}F-NMR $[(CD_3)_2SO]$: -75.08 (s, CF_3). Anal. Calcd. for $C_{12}H_{22}F_3NO_3$: C, 50.52; H, 7.77; N, 4.91. Found: C, 50.78; H, 7.80; N, 5.19.

(2*S*,3*S*)-β-trifluoromethyl-β-*n*-(3-phenyl)propylserine (hydrochloride) 4e: mp 165-166 °C, $[\alpha]_{578}^{20}$ -39.9 (*c* 0.45, Me_2CO); ^{1}H-NMR $[(CD_3)_2CO]$: 1.51-1.98 [m, 4H, $(CH_2)_2$], 2.52-2.67 (m, 2H, $PhCH_2$), 4.29 (s,1H, α-CH), 7.12-7.38 (m, 5H, ArH); ^{19}F-NMR $[(CD_3)_2SO]$: -75.58 (s, CF_3). Anal. Calcd. for $C_{13}H_{16}F_3NO_3$: C, 53.60; H, 5.54; N, 4.81. Found: C, 53.62; H, 5.50; N, 4.96.

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