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Highly Diastereoselective Asymmetric Aldol Reactions of Chiral Ni(II)-Complex of Glycine with Alkyl Trifluoromethyl Ketones[1]

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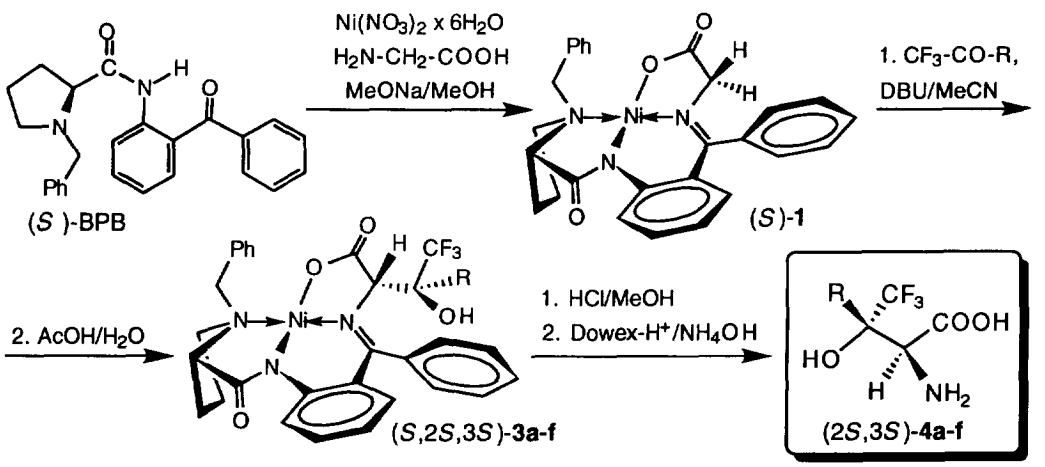
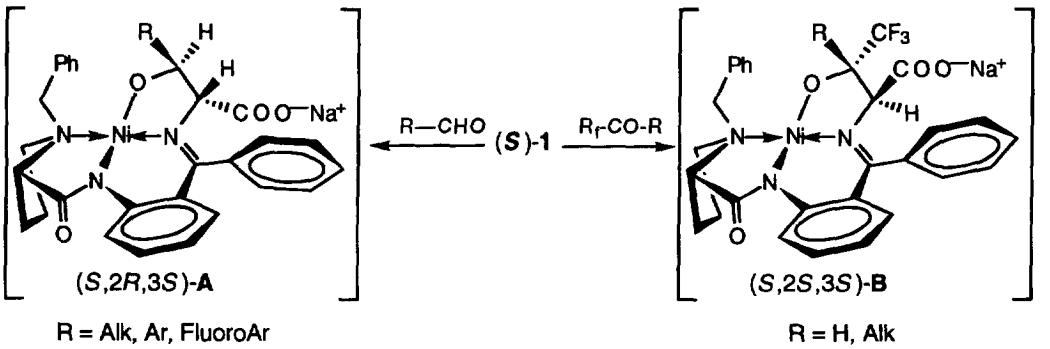
Abstract: Asymmetric aldol reactions between prochiral trifluoromethyl ketones and Ni(II)-complex of monochiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BBP) are described. General stereodirecting features of the trifluoromethyl group controlling (2*S*,3*S*)-absolute configuration (90-98 %de) of the resultant amino acids is demonstrated. New set of reaction conditions allowing preparative synthesis of diastereo and enantiomerically pure (2*S*,3*S*)- 3-trifluoromethyl-3-substituted serines of biomedicinal interest is presented.

Despite the impressive recent achievements in the asymmetric aldol methodology, involvement of prochiral ketones into the stereocontrolled aldol addition reactions still remains one of the most challenging synthetic targets.[3] In particular, aldol condensations between chiral glycine α-anion equivalents and prochiral ketones, performed with a synthetically valuable stereochemical outcome, over 90% ee (de), have not been reported so far.[4] In this communication we would like to report our results on the aldol reactions of trifluoromethyl ketones with monochiral Schiff base-Ni(II) complex **1**, derived from (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BBP) and glycine, which, due to a surprising stereocontrolling effect of trifluoromethyl group, occur with excellent diastereoselectivity and thus give grounds for a generalized and preparatively useful entry to the family of enantiomerically pure (2*S*,3*S*)-3-(trifluoromethyl)-3-substituted serines of biological interest (Scheme 1).[5-7]



Scheme 1 R = CH_3 (**a**), C_4H_9 (**b**), C_7H_{15} (**c**), C_8H_{17} (**d**), $(CH_2)_3Ph$ (**e**), C≡C-Ph (**f**)



Scheme 2

Recently we have found that in 2.5 *M* MeONa/MeOH solution at room temperature, trifluoroacetone reacts with glycine Ni(II)-complex **1**, giving rise to only one, (*S*,2*S*,3*S*)-configurated product, out of four possible diastereomers. However, the reaction conditions employed, causing substantial decomposition of trifluoroacetone, necessitated ten-fold excess of the ketone to achieve even though 90% conversion of starting complex **1**.[8] An excellent diastereoselectivity observed in this aldol condensation, encouraged us to search for more practical reaction conditions, as well as to explore its generality and the origin of high stereocontrol.

Previous investigations into the aldol condensations of complex **1** with aldehydes have revealed a great dependence of their thermodynamically controlled chemical and stereochemical outcome on the pH of the reaction medium.[8,9] Thus, at low pH sluggish reactions give rise normally to a mixture of diastereomers containing *syn*-(2*S*) and *anti*-(2*S*)-configurated amino acids, while at high pH these aldol condensations occur with high reaction rates furnishing mainly complexes with amino acids of *syn*-(2*R*)-configuration. The working model for stereochemistry of complex **1** aldol reactions, being performed at high pH of reaction medium, postulates thermodynamic stabilization of (*S*,2*R*,3*S*)-configurated diastereoisomers through the formation of hydroxy-co-ordinated complex **A** (Scheme 2). Structure **A** is organized *via* substitution of a carboxy group in the main co-ordination plane of the complex by an ionized hydroxyl on an amino acid's side chain and upon neutralization of the reaction medium rearranges to the regular carboxy-co-ordinated complex. Due to the chelation of an amino acid residue into the rigid five-membered ring (Scheme 2, structure **A**), its stereochemistry is effectively controlled at both stereogenic centers by the thermodynamic preference of the relative trans configuration and pseudoaxial orientation of ionized carboxy group.[9a] On this mechanistic background it is difficult to rationalize (*S*,2*S*,3*S*)-stereochemistry of product **3a** (Scheme 1) obtained in the condensation of complex **1** with trifluoroacetone, however, intermediate formation of the hydroxy-co-ordinated structure **B** (Scheme 2) could be reasonably assumed to account for high diastereoselectivity observed as well as for failure to conduct this reaction at low pH of reaction medium. On the other hand, we have shown that application of polar solvent and strong base is essential for the reaction to be observed. As a result of the series of experiments, varying for solvent and base used, we have found that aldol condensation of complex **1** with trifluoroacetone in acetonitrile solution in the presence of 3 mol of DBU proceeds with the rate and stereochemical outcome similar to that of MeONa-catalyzed reaction (Table 1, entry 1), but in contrast to the latter, only 2 mol of ketone is necessary to accomplish complete conversion of initial glycine complex **1** to the desired product (*S*,2*S*,3*S*)-**3a**. Diastereomerically pure complex **3a** was decomposed to give biologically interesting enantiomerically pure (2*S*,3*S*)-3-trifluoromethyl-threonine **4a**,[10] which was isolated in 94% of chemical yield along with chiral auxiliary (*S*)-BPB (97% of recovery), (Scheme 1).

With this success in hands, we next explored aldol condensations of glycine complex **1** with the series of trifluoromethyl ketones bearing long-chain *n*-alkyl groups, 3-phenylpropyl and phenylacetylenyl moieties. As it follows from the results reported in the Table 1, highly diastereoselective formation of (*S*,2*S*,3*S*)-configured

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

entry	ketone	reaction conditions					
		MeOH/MeONa[a]			MeCN/DBU[b]		
		time, min	de, %[c]	yield, %[d]	time, min	de, %[c]	yield, %[d]
1	CF_3COCH_3	10	>95	69[e]	15	95	75
2	CF_3COCH_3				1	>98	73
3	$CF_3COC_4H_9$				10	98	71
4	$CF_3COC_7H_{15}$	15	96	56	15	97	71
5	$CF_3COC_7H_{15}$				1	>98	70
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

[a] The reactions were carried out in 2.5 *M* MeONa/MeOH solution at room temperature under argon atmosphere. Ratio 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 complex **1**/ketone/DBU = 1/2/3, 0.2 mmol scale. [c] Diastereomeric excess of (*S*,2*S*,3*S*)-diastereomers determined by ^1H and ^{19}F NMR (300 MHz) analysis of crude reaction mixtures. Absolute (*S*,2*S*,3*S*)-configuration[11] of **3a** was determined by X-ray analysis. All other products **3b-f** are assumed to have the same (*S*,2*S*,3*S*) configuration by similarity in their chiroptical properties and patterns of NMR spectra.[12] [d] Isolated (column chromatography) yield of diastereomerically pure (*S*,2*S*,3*S*)-complexes **3a-f**. [e] Previously reported data; see ref. 8. [f] Reaction in MeCN solution in presence of NEt_3.

products **3a-f** was observed in all reactions studied, regardless the nature of substituent R in the starting trifluoromethyl ketone. Comparison of the chemical and stereochemical outcome of these aldol condensations run under the standard MeONa-catalyzed reaction conditions and the conditions disclosed here, shows apparent synthetic advantage of the latter with respect to initial ketone consumption and chemical yield of the desired products. Thus, for instance, highly electrophilic ketone, containing phenylacetylenic and trifluoromethyl groups, was completely decomposed in the presence on MeONa in MeOH solution, while triethylamine-catalyzed condensation in MeCN gave targeted product, albeit in moderate chemical yield (entry 10). All other complexes **3b-e** were prepared under the new reaction conditions in diastereomerically pure form with the chemical yields over 70 % and decomposed to give previously unknown amino acids (2*S*,3*S*)-**4d-e** (87-94% chemical yields) in enantiopure state. On the other hand, a similar stereochemical outcome of the reactions run under the different reaction conditions (MeONa/MeOH *vs* DBU/MeCN), strongly suggest that the same intermediate might be responsible for high (*S*,2*S*,3*S*)-diastereoselectivity observed. A plausible rationale for the stereochemical outcome of these aldol reactions could involve a formation of hydroxy-co-ordinated complex **B** (Scheme 2) as a stabilized state for (*S*,2*S*,3*S*)-diastereomer under the reaction conditions reported here.

In conclusion, we have demonstrated that aldol reactions of monochiral glycine complex (*S*)-**1** with trifluoromethyl ketones, using new set of reaction conditions reported here, occur with high-to-excellent diastereoselectivity providing generalized access to (2*S*,3*S*)-configured 3-substituted 4,4,4-trifluorothreonines in preparatively valuable chemical yields. The origin of electronic and/or steric influence of a trifluoromethyl group in the diastereoselection process in the asymmetric aldol reactions under study is not yet clear and provides a subject for further exploration.

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