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An Efficient Asymmetric Synthesis of (2*S*,3*S*)-3-Trifluoromethylpyroglutamic Acid

Vadim A. Soloshonok*
National Industrial Research Institute of Nagoya, Hirate-cho 1-1, Kita-ku, Nagoya City, Aichi Pref. 462, Japan

Dimitry V. Avilov, Valery P. Kukhar'
Institute of Bioorganic Chemistry and Petrochemistry, Ukrainian Academy of Sciences, Kiev 253160, Ukraine

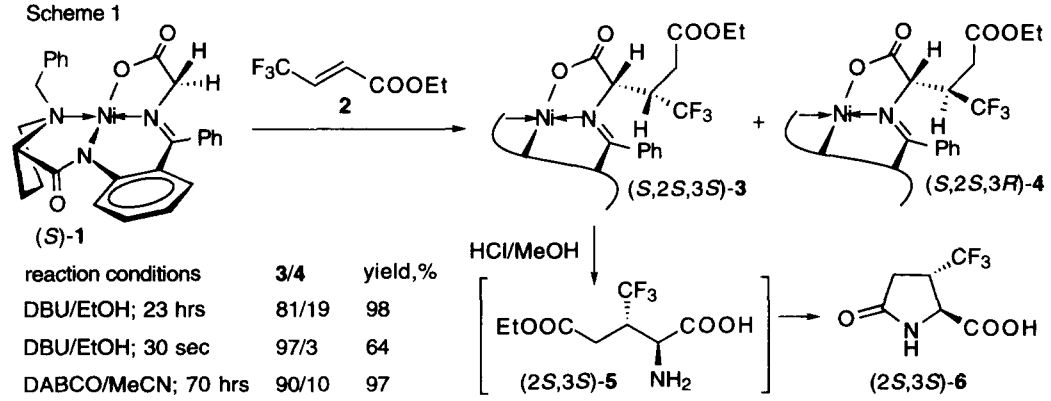
Luc Van Meervelt, Nikolai Mischenko
K. U. Leuven - Department of Chemistry, Celestijnenlaan 200F, B-3001 Heverlee-Leuven, Belgium

Abstract: The stereochemical outcome of the *Michael* reaction between ethyl 4,4,4-trifluorocrotonate and a Ni(II) complex of the *Schiff* base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone was found to be subjected to kinetic and thermodynamic control. Thus, under kinetically controlled conditions high values of diastereoselectivity, up to 94% de, allowing for an efficient asymmetric synthesis of (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid, could be obtained, while the thermodynamically controlled stereoselectivity is rather modest (54-60% de).

The extraordinary potential of fluoro-amino acids in bio-medicinal field has been generally recognized and well-documented.[1] Among the targets of current importance trifluoromethyl-containing pyroglutamic acids are of particular interest.[2] Herein, we report the results of our study on the asymmetric *Michael* reactions between Ni(II) complex of the *Schiff* base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone **1** and fluorinated acrylic acid derivatives, allowing for an efficient access to enantiomerically pure (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid (Scheme 1) and thus to the glutamic acid and glutamine as well.

For the reactions of acrylic acid derivatives with complex **1** only a few examples are extant. It was shown that the additions of **1** with the methyl methacrylate and the methyl *trans*-cinnamate occur in the presence of MeONa to afford, regardless of the nature of the electrophile, a mixture of two α-(*S*) configured diastereomeric products in a ratio of about 2:1.[3] We have found that Ni(II) complex **1** readily reacts with ethyl 4,4,4-trifluorocrotonate in ethanol solution in the presence of DBU to afford a mixture of two diastereomers **3**,**4** in a ratio of 81:19, respectively, isolated with an excellent chemical yield. The absolute configuration of the α-stereogenic center of the amino acid residues in complexes **3**,**4** was assigned to be (*S*) by investigation of the chiroptical properties of products **3**,**4**. To determine the relative configuration, the diastereomerically pure complex **3** was decomposed to give the targeted 3-trifluoromethylpyroglutamic acid **6**, without isolation of the intermediate glutamic acid derivative **5**. Comparison of the spectral data and $[\alpha]_D$ value of compound **6** with those reported in the literature[2b] for (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid, revealed that product **6** might be of the same absolute configuration.[4] A final determination of the stereochemistry by X-ray analysis of

Scheme 1



reaction conditions	3/4	yield,%
DBU/EtOH; 23 hrs	81/19	98
DBU/EtOH; 30 sec	97/3	64
DABCO/MeCN; 70 hrs	90/10	97

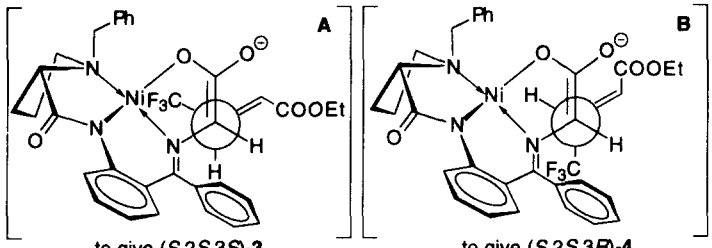


Figure 1

complex **3**, revealed its (*S*,2*S*,3*S*) configuration.[5] Accordingly, the absolute configuration of the 3-trifluoromethyl glutamic acid in complex **4** should be (2*S*,3*R*).

Having determined the absolute configuration of products (*S*,2*S*,3*S*)-**3** and (*S*,2*S*,3*R*)-**4**, we set about the improvement of the diastereoselectivity. Monitoring the reaction by TLC and NMR (^{19}F) has revealed that the ratio of diastereomers **3**,**4** remarkably depends on the reaction time. Thus at the earlier stage (30 sec) of the reaction the ratio of **3**,**4** was found to be 97:3, respectively, while after complete conversion of starting complex **1** it was 81:19 (*vide supra*). These data suggest that the addition reaction occurs reversibly with the stereochemical result subjected to kinetic and thermodynamic control. Further attempts to influence the diastereoselectivity by varying the reaction medium revealed rather promising results. Thus, while triethylamine did not assist the reaction, DABCO was found to be effective in catalyzing the addition between complex **1** and trifluorocrotonate **2**, when conducted in polar organic solvents. In particular, in an acetonitrile solution glycine complex **1** reacted with trifluorocrotonate **2** to afford a mixture of complexes **3**,**4** in excellent chemical yield (97%) and with 80% de of diastereomer **3**. Decomposition of the diastereomerically pure complex **3** could be readily accomplished under standard conditions[3] to give directly targeted enantiopure (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid **6**.

Considering the stereochemical outcome of the reaction under study, we could propose two transition states (TS) **A** and **B** (Figure 1), leading to diastereomers **3**,**4**, respectively. In TS **A**, the trifluoromethyl group occupies a position of the larger substituent, thus avoiding unfavorable non-bonding interactions with the phenyl ring at the ketimine bond of the Ni(II) complex. Moreover, this position of the trifluoromethyl in **A**, just under the metal, also would allow for attractive electrostatic interactions between the electron-rich trifluoromethyl group and the partially positively charged Ni(II) atom.[6] On the other hand, the trifluoromethyl group in TS **B** might interact unfavorably with the phenyl, which, apparently, would render **B** much less favorable than **A**.

In conclusion, we have found that in sharp contrast to the reactions of hydrocarbon acrylic acid derivatives with Ni(II) complex (*S*)-**1**, the addition between ethyl 4,4,4-trifluorocrotonate and (*S*)-**1** occurs with high kinetically controlled diastereoselectivity allowing for an efficient asymmetric synthesis of (2*S*,3*S*)-3-trifluoromethyl-pyroglutamic acid **6**. Appreciable chemical and stereochemical outcomes of the reaction would render this approach an immediately useful alternative to existing methods.[2]

References and Notes

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4 **6**: $[\alpha]_D^{25}$ = +24.9 (*c*, 0.5, MeOH); lit:[2a] $[\alpha]_D$ = +25.3 (*c*, 1.2, MeOH); ^{1}H-NMR (CD_3OD, TMS): 3.09 (d, *J* =16.5 Hz, 1H), 3.42 (m, 1H), 4.17 (m, 1H), 5.04 (d, *J* =16.5 Hz, 1H); ^{19}F-NMR [$(CD_3)_2CO$, CCl_3F]: -72.87 (d, *J* = 8.1 Hz).

5 Crystals of compound **3** were grown from chloroform. Crystal data for **3**: $C_{33}H_{32}F_3N_3NiO_5$, orthorhombic, space group $P2_12_12_1$. Radiation: Mo Kα λ = 0.71073 Å. Crystal size: 0.4 x 0.3 x 0.3 mm^3. Unit cell dimensions: *a* = 10.324(5), *b* = 13.570(2) *c* = 22.233(3) Å, *V* = 3115(2) Å^3, *Z* = 4, D_x = 1.421 Mg/cm^{-3}. Diffraction data were measured on an SiemensP4-PC diffractometer. 2503 Reflections were collected and 2342 independent reflections used in the analysis. System used: Siemens SHELXTL PLUS (PC Version); solution: direct methods; refinement method: Full-Matrix Least-Squares on F^2. 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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