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Addition of *tert*-butylcuprate to (2*S*)-*N*-acyl-Δ^5-dehydroprolinates as a diastereoselective synthetic procedure for obtaining (2*S*,5*S*)-5-*tert*-butylproline

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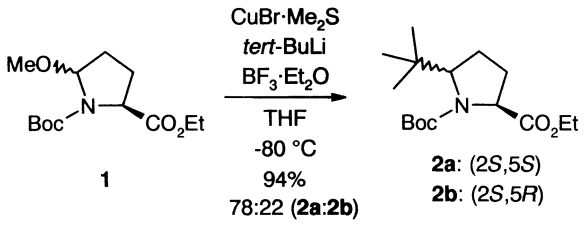
Abstract—The synthesis of (2*S*,5*S*)-Boc-5-*tert*-butylproline ethyl ester via the addition of *tert*-butylcuprate to (2*S*)-*N*-Boc-Δ^5-dehydroproline ethyl ester, formed from (2*S*)-*N*-Boc-5-methoxyproline ethyl ester, gives an excellent yield of 94% and a high diastereoselectivity (2*S*,5*S*):(2*S*,5*R*) 78:22. This synthesis opens up a new synthetic route to (2*S*,5*S*)-5-*tert*-butylproline, which is a useful, conformationally rigid, analogue of L-proline.

The amino acid proline is interesting because amides N-terminal to proline have energetically similar *cis* and *trans* isomers. This isomer geometry plays an important role in the recognition, reactivity and stability of bioactive peptides and proteins that possess a prolyl residue. It can be studied by the use of conformationally rigid surrogates of the *cis* and *trans* isomers. One useful surrogate is 5-*tert*-butylproline, which has a bulky 5-substituent that increases the *cis* isomer population.[1–5]

Recently both (2*S*,5*R*)- and (2*S*,5*S*)-5-*tert*-butylprolines have been synthesized via reductive amination of (2*S*)-6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoic acid or its ester or amide (PhF is 9-(9-phenylfluorenyl)), where the diastereoselectivity was directed by the choice of method of reduction.[2] The (2*S*,5*R*)-diastereomer was obtained in high yield with excellent diastereomeric and enantiomeric purity via catalytic hydrogenation with palladium-on-carbon. Although the (2*S*,5*S*)-diastereomer was obtained in a good (2*S*,5*S*):(2*S*,5*R*) 86:14 diastereomeric ratio via formation of (2*S*)-5-*tert*-butyl-Δ^5-dehydroproline trifluoroacetate with trifluoroacetic acid followed by reduction with $Me_4NHB(OAc)_3$, the product was a mixture of two enantiomers due to partial racemization. An improved, but somewhat longer synthetic route via the intermediate (2*S*,5*S*)-*N*-Boc-5-*tert*-butylprolinol, overcame the problem of racemization.[5] In the same article, the authors reported to have made attempts to synthesize the product via addition of *tert*-butylcuprate to (2*S*)-*N*-Boc-Δ^5-dehydroproline benzyl ester, formed from (2*S*)-*N*-Boc-5-methoxyproline benzyl ester. After succeeding once to obtain the desired product in a low yield of 32% with a diastereoselectivity of (2*S*,5*S*):(2*S*,5*R*) 4:1, they were not able to reproduce this result.



Scheme 1.

Independently, our group also studied the addition of organocuprate reagents to *N*-acyl-Δ^5-dehydroprolinates. Although the addition of organocuprate reagents to (2*S*)-*N*-acyl-Δ^5-dehydroprolinates had previously been described for synthesizing a variety of (2*S*,5*S*)-5-alkylprolines in good yields and with high diastereoselectivities,[6–11] the *tert*-butyl derivative had not been made. In our first attempt to synthesize the *tert*-butyl

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derivative a general procedure from the literature was applied using (2*S*)-*N*-Boc-5-methoxyproline ethyl ester **1** as the starting material and generating the organocuprate from the Grignard reagent (*tert*-butylmagnesium chloride).[10] The desired product was obtained in a very low yield. The instability of the *tert*-butylcuprate reagent was thought to be the main problem.

The solvent and the reaction temperature have been reported to be crucial for the stability of *tert*-butylcuprates.[12] The solvent was changed from diethyl ether to tetrahydrofuran, the reaction temperature for generating the organocuprate was lowered from −40 to −80°C, and the more reactive *tert*-butyllithium was used instead of the Grignard reagent. The new procedure afforded Boc-5-*tert*-butylproline ethyl ester **2a** (2*S*,5*S*) and **2b** (2*S*,5*R*) in an average 94% yield with a ratio of **2a**:**2b** 78:22 (Scheme 1).

Experimental

$CuBr{\cdot}Me_2S$ (4.11 g, 20 mmol) in anhydrous tetrahydrofuran (40 ml) was cooled to −80°C and 1.5 M *tert*-butyllithium (13.3 ml, 20 mmol) was added. After 30 min $BF_3{\cdot}Et_2O$ (2.5 ml, 20 mmol) was added and after a further 20 min a solution of **1** (1.28 g, 4.7 mmol) in anhydrous tetrahydrofuran (10 ml) was added. The reaction mixture was stirred for 15 min at −80°C, whereafter it was allowed to warm to room temperature over 3 h. A mixture of aqueous 25% NH_3 (12 ml) and saturated aqueous NH_4Cl (12 ml) was added and the reaction was stirred for 1 h at room temperature. The tetrahydrofuran layer was separated and evaporated. The residue was dissolved in diethyl ether. The remaining aqueous layer was extracted with diethyl ether. Both diethyl ether layers were combined and washed with saturated aqueous $NaHCO_3$, dried with anhydrous $MgSO_4$ and evaporated. The product was purified by flash chromatography (9% ethyl acetate in petroleum ether). Yield 1.27 g (4.2 mmol, 91%). The reaction was repeated on a 9.4 mmol scale and the product was obtained in 97% yield. ^{1}H NMR ($CDCl_3$), 500 MHz δ 0.89 and 0.96 (two s, 9H), 1.23–1.29 (m, 3H), 1.39, 1.43 and 1.46 (three s, 9H), 1.77–2.13 (m, 3H), 2.19–2.32 (m, 1H), 3.76–4.33 (m, 4H). ^{13}C NMR ($CDCl_3$), 125 MHz δ 14.20, 25.13, 27.56, 28.18, 30.19, 36.90, 60.75, 61.46, 66.17, 79.65, 155.46, 173.90 (the peaks corresponding to the major isomer of **2a**). ESI-MS $m/z = 300$ ($[M+H]^+$). Anal. ($C_{16}H_{29}NO_4$) C, H, N: calcd 64.18, 9.76, 4.68 and found 63.93, 9.99, 4.64.

The diastereomeric ratio was determined by ^{1}H NMR in $CDCl_3$ with the help of (2*S*,5*R*)-Boc-5-*tert*-butylproline methyl ester, synthesized according to a reported procedure.[2] For compound **2b** the 5-*tert*-butyl protons gave a singlet at δ 0.96 and the Boc protons gave a singlet at δ 1.43. The integrals of both singlets were 22% of the whole integrals. For **2a** the 5-*tert*-butyl protons gave a singlet at δ 0.89 and the Boc protons gave two singlets at δ 1.39 (major) and 1.46 (minor). The two Boc singlets from **2a** are due to the *cis–trans* isomerism of the 'amide' bond of the carbamate group, and the integral for the major and minor isomers were 52 and 26%, respectively, of the whole integral. In the ^{1}H NMR spectra measured in $(CD_3)_2CO$ and CD_3OD, both the 5-*tert*-butyl and the Boc protons appeared as three singlets with an unchanged ratio for the peaks corresponding to **2a** and **2b**. The diastereomeric ratio was also later verified by HPLC.

The enantiomeric purity of the (2*S*,5*S*)-diastereomer has not been verified in our study, but the reaction via addition of an organocuprate reagent to (2*S*)-*N*-Boc-Δ^5-dehydroproline ethyl ester, formed from (2*S*)-*N*-Boc-5-methoxyproline ethyl ester, has earlier been reported to yield enantiomerically pure products.[10]

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