[10] Spectral data for **5**: red-brown solid; m.p. 92–93 °C; ^{1}H NMR (300 MHz, [D$_6$]benzene, TMS): $\delta = 0.15$ (s, 6H), 1.17 (s, 36H), 2.06 (s, 12H), 2.81 (s, 6H), 6.73 (s, 4H); ^{13}C{^{1}H} NMR (75.5 MHz, [D$_6$]benzene, TMS): $\delta = -3.2$, 22.5, 25.8, 30.3, 30.6, 128.8, 139.1, 139.2, 143.6; ^{29}Si{^{1}H} NMR (59.6 MHz, [D$_6$]benzene, TMS): $\delta = 31.4$, 146.9 (*Si*=Ge); HRMS *m*/*z*: calcd for $C_{36}H_{64}GeSi_3$: 654.3536, found: 654.3531; UV/Vis (hexane) $\lambda_{max}(\varepsilon)$: 237 (31700), 289 (8700), 430 nm (5300).

[11] We recently reported stable germasilenes: a) 2-disilagermirene: V. Ya. Lee, M. Ichinohe, A. Sekiguchi, N. Takagi, S. Nagase, *J. Am. Chem. Soc.* **2000**, *122*, 9034; b) 1,2-disila-3-germacyclopenta-2,4-diene: V. Ya. Lee, M. Ichinohe, A. Sekiguchi, *J. Am. Chem. Soc.* **2000**, *122*, 12604; c) (tBu$_2$MeSi)$_2$Si=GeMes$_2$: M. Ichinohe, Y. Arai, A. Sekiguchi, N. Takagi, S, Nagase, *Organometallics* **2001**, *20*, 4141.

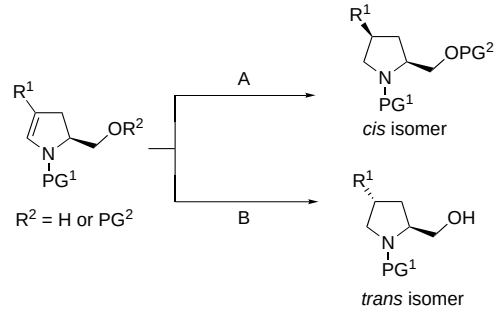
Stereoselective Synthesis of Boc-Protected *cis* and *trans*-4-Trifluoromethylprolines by Asymmetric Hydrogenation Reactions**

Juan R. Del Valle and Murray Goodman*

The effect of the proline residue on peptide conformation[1–3] has been the impetus for the design of various unnatural substituted prolines. These amino acid surrogates have featured in a number of biologically active[4–7] and highly ordered peptides.[8, 9] Prolines substituted at the 4-position have been shown to enhance the thermal stability of collagen-mimetic triple helices, with *trans*-4-fluoroproline yielding the most striking results.[10–12] The nature of the functional group and the steric constraints imposed by the C4 substituent can greatly influence the conformation of the pyrrolidine ring, as well as the rate of *cis*–*trans* isomerization about the amide bond.[13–15] For these reasons, the preparation of 4-substituted prolines is an attractive goal in peptidomimetic chemistry.

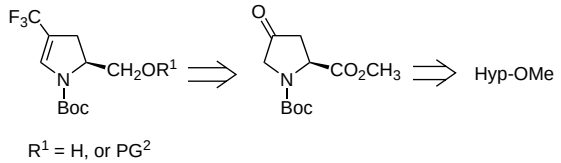
The synthesis of *cis*-4-phenylproline by a hydrogenolysis reaction, which starts from hydroxyproline was recently described by Hruby and co-workers.[16] In addition, Nevalainen et al. reported a preparation of Fmoc-*trans*-4-methylproline (Fmoc = 9-fluorenylmethoxycarbonyl) by asymmetric hydrogenation, which yields the desired isomer in a 6:1 diastereomeric ratio before purification.[17] Although these and other syntheses of 4-substituted prolines are in the literature,[18–21] a number of desirable targets continue to pose a synthetic challenge. In particular, several *trans*-substituted prolines have been difficult to synthesize with high stereoselectivity. In connection with our studies on bioactive and highly ordered peptides, we undertook the synthesis of both stereoisomers of 4-trifluoromethyl-L-proline. These building blocks are expected to have profound conformational effects on their host structures, which arise from the electronegative nature of the trifluoromethyl group.

Our strategy for the preparation of the title compounds employs asymmetric hydrogenation of the pyrrolines shown in Scheme 1. For the synthesis of the *cis* isomer, the facial



Scheme 1. Strategies for the asymmetric hydrogenation of pyrroline intermediates. A = Sterically directed hydrogenation, B = hydroxy-directed hydrogenation.

selectivity of the hydrogenation was expected to depend on steric factors, which result from protection of the hydroxy functionality as an ether or ester moiety. We were unable to find previous syntheses of *trans*-substituted prolines that exploit the potential for hydroxy-directed hydrogenation of pyrroline intermediates. We envisioned this as a viable route towards the *trans*-proline isomer as well as related analogues. The retrosynthesis in Scheme 2 shows Boc-4-prolinone (Boc = *tert*-butoxycarbonyl) as a precursor to the desired pyrrolines.



Scheme 2. Retrosynthesis of Boc-4-trifluormethyl-L-proline; Hyp = hydroxyproline.

The synthesis of Boc-4-trifluoromethyl-L-proline (Scheme 3) begins with the methyl ester of commercially available and inexpensive *trans*-4-hydroxyproline (**1**). Boc-protection was carried out under normal conditions, followed by oxidation using trichloroisocyanuric acid and catalytic 2,2,6,6-tetramethyl-1-piperidinoxyl (free radical; TEMPO)[22] to give ketone **3**.

With the protected prolinone in hand, the trifluoromethyl group was introduced by treatment of **3** with trimethyl(trifluoromethyl)silane, in the presence of a fluoride initiator[23, 24] to afford the tertiary alcohol **4** in 56% yield. Compound **4** was a single diastereomer which we presumed to be the 2*S*,4*S* isomer from the steric implications of the reaction.

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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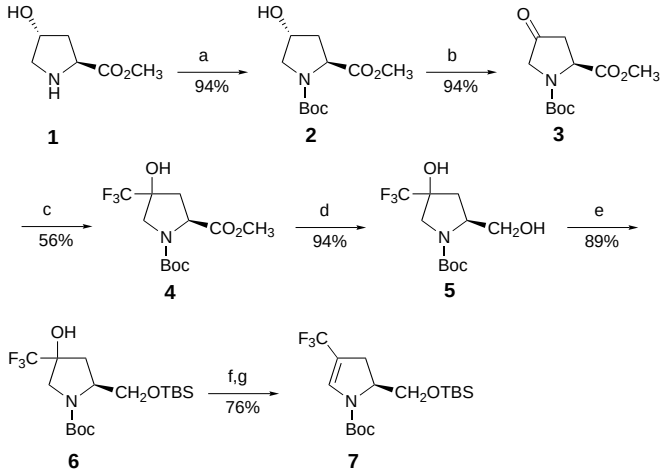


Scheme 3. Reagents and conditions: a) Boc_2O, triethylamine (TEA), CH_2Cl_2, 18 h; b) Trichloroisocyanuric acid, TEMPO (cat.), CH_2Cl_2, 20 min, 0 °C; c) 2 equiv CF_3TMS (TMS = trimethylsilyl), 2.1 equiv TBAF (tetrabutylammonium fluoride), 0 °C → RT, 24 h; d) $NaBH_4$, LiCl, EtOH:THF (2:1), RT, 18 h; e) TBDMSCl, TEA, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, RT, 18 h; f) TosCl (Tos = tosyl), NaH, THF, 0 °C → RT, 2 h; g) 2 equiv *t*BuOK, THF, −40 °C, 2 h.

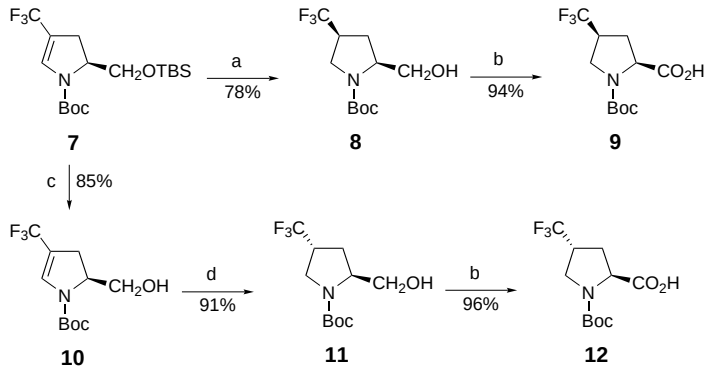
The dehydration of **4** posed a challenge as few reports deal with the effects of trifluoromethyl groups on this transformation. In our initial efforts, reaction of **4** with $SOCl_2$/pyridine, *para*-toluenesulfonic acid/benzene, and $POCl_3$/DBU yielded none of the desired product. A study on the dehydration of tertiary α-trifluoromethyl alcohols carried out by Nagai and co-workers[25] found that base-promoted elimination of the corresponding tosylates gave the desired olefins in satisfactory yield. Therefore, **4** was treated with lithum borohydride and the resulting primary alcohol was selectively protected as the *tert*-butyl trimethylsilyl (TBDMS) ether to give **6**. Tosylation of the tertiary alkoxide of **6** proceeded normally and treatment of the product with potassium *tert*-butoxide furnished the key pyrroline intermediate **7** in good yield. Analysis of the crude product mixture revealed a small amount (8%) of the 3,4-olefin that was removed during purification.

Heterogenous hydrogenation of **7** was carried out under a variety of conditions (Table 1). Curiously, hydrogenations with Pd/C resulted in nearly complete removal of the TBDMS protecting group. Despite this, good facial selectivities were observed with the sterically directed *cis* 2*S*,4*S* isomer **8** as the major product in each case. The best selectivity, a 15:1 *cis*:*trans* ratio, was obtained by using 5% Pd/C in ethyl acetate. The minor diastereomer can be removed by column chromatography to give the *cis* product **8** in 78% isolated yield and >98% diastereomeric excess (Scheme 4).

Table 1. Hydrogenations of pyrroline **7**.

Catalyst	Solvent	*cis*:*trans*[a]	Yield[b]
10% Pd/C	THF	90:10	86%
5% Pd/C	EtOH	92:8	81%
5% Pd/C	EtOAc	94:6	85%
Rh/C	EtOAc	78:22	UD

[a] Determined by ^{19}F NMR analysis of crude mixtures. [b] Crude combined yield (**8** + **11**). UD = undetermined.



Scheme 4. Reagents and conditions: a) H_2 (1 atm), Pd/C, EtOAc, RT, 8 h, 99:1 d.r. after flash chromatography (See Table 1); b) NaClO, $NaClO_2$, TEMPO, MeCN:pH 6.7 NaH_2PO_4 buffer (0.67 M), 45 °C, 24 h; c) TBAF, THF, RT, 30 min; d) H_2 (1 atm), 2 mol% $[Ir(cod)(py)PCy_3]$, CH_2Cl_2, RT, 4 h, 158:1 d.r. (see Table 2).

Oxidation of **8** was carried out using a slight modification to the method described by Zhao et al.[26] The Boc-amino acid **9** was sufficiently pure after work up for use in peptide synthesis. The absolute stereochemistry of Boc-(4*S*)-trifluoromethyl-L-proline (**9**) was confirmed by X-ray diffraction (Figure 1).

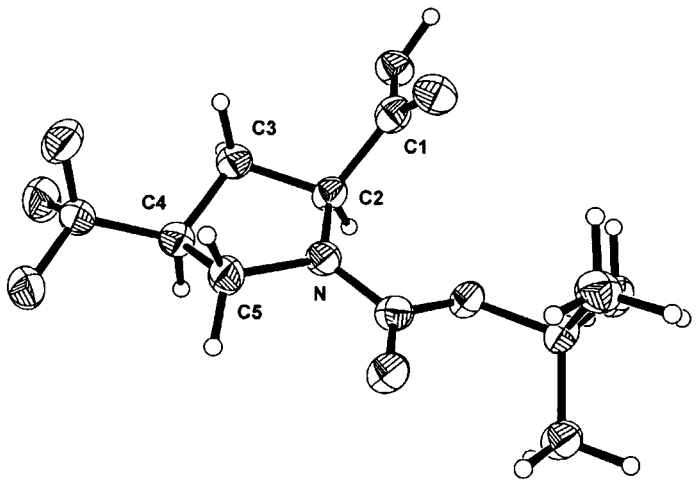


Figure 1. Crystal Structure of **9**.

To prepare the pyrroline intermediate for hydroxy-directed asymmetric hydrogenation, **7** was deprotected to unmask the primary alcohol. The results of the hydrogenations of **10** are summarized in Table 2.

Prior to attempting homogenous reduction, some heterogeneous catalysts were tested. Because the previous hydro-

Table 2. Hydrogenation of pyrroline **10**.

Catalyst	Solvent	*cis*:*trans*[a]	Yield[b]
Raney-Ni	MeOH	70:30	98%
5% Pd/C	PhH	52:48	92%
5% Pd/C	EtOAc	55:45	95%
$[Ir(cod)(py)PCy_3]$[c]	CH_2Cl_2	5:95	96%
$[Ir(cod)(py)PCy_3]$[d]	CH_2Cl_2	1:158	95%

[a] Determined by ^{19}F NMR analysis of crude mixtures. [b] Crude combined yield (**8** + **11**). [c] 15 mol% catalyst. [d] 2 mol% catalyst.

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genations with Pd/C heavily favored the *cis* product despite loss of the TBDMS group, we did not expect a significant coordination of the hydroxy group to the palladium catalyst. Nevertheless, reduction of **10** with 5% Pd/C gave appreciable amounts of the *trans* isomer. After careful chromatographic separation the 1:1 diastereomeric ratio rendered these conditions suitable for preparing both isomers simultaneously. In attempting homogenous hydrogenation, however, we found a divergent approach to be equally practical for the preparation of these building blocks.

Among the numerous catalysts available for homogenous hydrogenation,[27, 28] the Ir^I compound introduced by Crabtree et al.[29] has consistently shown excellent selectivity in the hydroxy-directed reduction of cyclic olefins.[30–32] By employing the Ir^I complex, we observed a dramatic increase in the *trans* selectivity.[33] Under optimal conditions, treatment of **10** with 2 mol% of [Ir(cod)(py)PCy_3] (cod = cyclootadiene, py = pyridine) under H_2 resulted in complete conversion into the desired product. The *trans*:*cis* ratio was 158:1, measured by ^{19}F NMR spectroscopy. Subsequent removal of the catalyst by filtration through a plug of silica gel provided Boc-(4*R*)-trifluoromethyl-L-prolinol (**11**) in a diastereomerically pure form.

Prolinol **11** was oxidized as described above in 96% yield. The ^{19}F NMR spectrum of **12** contained two doublet signals in a 1.5:1 ratio. Incremental increases in temperature resulted in the gradual coalescence of the NMR peaks of **12**, confirming the rotamer effect and ruling out epimerization during the oxidation. Thus, the *trans* isomer, Boc-(4*R*,2*S*)-trifluoromethylproline, was synthesized in good overall yield and with complete diastereoselectivity, from hydroxyproline.

In summary, we have described the preparation of both *cis* and *trans*-4-trifluoromethyl-L-proline employing stereoselective substrate-directed hydrogenation reactions. Most noteworthy is the outstanding facial selectivity achieved in the reduction of **10** with the Crabtree catalyst (158:1 d.r.). These results will be applied in the synthesis of various substituted prolines for incorporation into peptides and peptidomimetics.

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