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Locked Conformations for Proline Pyrrolidine Ring: Synthesis and Conformational Analysis of *cis*- and *trans*-4-*tert*-Butylprolines

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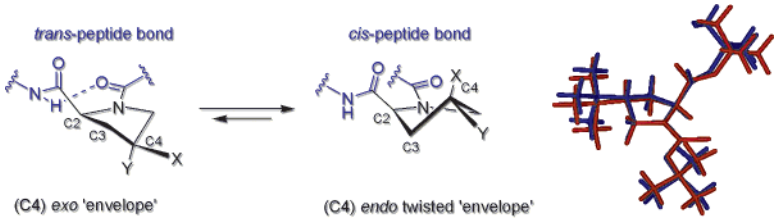
Received April 26, 2005



The motional restrictions of the proline pyrrolidine ring allow this secondary amine amino acid to act as a turn inducer in many peptides and proteins. The pyrrolidine ring is known to exhibit two predominant pucker modes (i.e., C-4 (C^{γ}) *exo* and *endo* envelope conformers whose ratio can be controlled by proper substituents in the ring). In nature, the *exo* puckered 4(*R*)-hydroxy-L-proline plays a crucial role as a building block in collagen and collagen-like structures. It has been previously concluded that the electronegativity of the 4-cis-substituent increases the *endo* puckering while the electronegativity of the 4-trans-substituent favors the *exo* puckering. Here, we have introduced a sterically demanding *tert*-butyl group at C-4 in trans- and cis-configurations. In the case of trans-substitution, the induced puckering effect on the pyrrolidine ring was studied with X-ray crystallography and ^{1}H NMR spectral simulations. Both *cis*- and *trans*-4-*tert*-butyl groups strongly favor pseudoequatorial orientation, thereby causing opposite puckering effects for the pyrrolidine ring, *cis-exo* and *trans-endo* for L-prolines, in contrast to the effects observed in the case of electronegative C-4 substituents. The syntheses and structural analysis are presented for the conformationally constrained 4-*tert*-butylprolines. The prolines were synthesized from 4-hydroxy-L-proline, substitution with *t*-BuCuSPhLi being the key transformation. This reaction gave *N*-Boc-*trans*-4-*tert*-butyl-L-proline *tert*-butyl ester in 94% ee and 57% de. Enantioselectivity was increased to 99.2% ee by crystallization of *N*-Boc-*trans*-4-*tert*-butyl-L-proline in the final step of the synthesis.

Introduction and Background

Due to the conformational restrictions imposed by its pyrrolidine ring, the proteinogenic amino acid proline has an exceptional tendency to act as a turn inducer in peptides and proteins.[1] The pyrrolidine ring exhibits two predominant pucker modes: C-4 (C^{γ}) *exo* and *endo* envelope conformers, that is, "up" and "down", respectively (Figure 1).[2] In the case of unsubstituted proline, the *endo* puckering mode is favored over the *exo* mode. The puckering propensity can be controlled by proper choice of ring substituents. In collagen structures, the nonproteinogenic amino acid, 4-(*R*)-hydroxyl-L-proline (trans-substituted), is equipped with a C-4 (*R*) OH group that makes the *exo* puckering prevailing (Y = OH, X = H, Figure 1).[3]

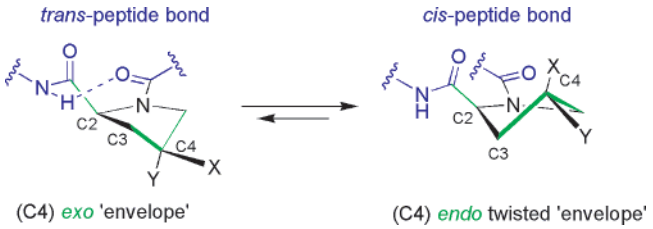


FIGURE 1. Proline ring pucker modes are generally referred to C-4 (C^{γ}) "*endo*" (or "down") and "*exo*" (or "up"). Notations arise from the N1 − C4 pseudorotation angles; *endo* is associated to the *gauche*+ and *exo* to the *gauche*- torsion rotamer. The substitution of C-4 affects not only the *endo* and *exo* puckering but also the trans and cis peptide bonding.

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10.1021/jo050838a CCC: $30.25
Published on Web 07/01/2005

Synthetic C-4 fluoroprolines have been used to elucidate the puckering effect of electronegative substituent where *trans*-fluoroprolines promote *exo* envelope and *cis*-fluoroprolines promote the *endo* envelope conformers.[3,4] Extensive computational and NMR studies have suggested that the conformational effects of the electronegative substituent is dictated by inductive and stereoelectronic factors. Moreover, it has been concluded that the peptide cis/trans-isomerism in collagen triple helix structure is dictated by the stereochemistry (*R*/*S*) of the C-4 substituent (OH, F).[5] It has also been suggested that the 4-hydroxyproline stabilized ring pucker is a key determinant endowing collagen its stability.[3c]

Although 4-substituted prolines have gained considerable synthetic interest,[6−8] the conformational restrictions caused by this substitution have not been considered in the context of peptide secondary structures. As an exception, Koskinen et al. have synthesized conformationally constrained C-4 methyl prolines for peptidomimetics with the purpose of increasing conformational stability through only a minor chemical change on the natural amino acid.[6b,9] Secondary structure constrainment was observed for the open chain 4-methylproline tetrapeptides (Ala-(C-4)MePro-Gly-Ala) in a conformational NMR study.[10]

The sterically bulky *tert*-butyl group is commonly used to lock a ring conformation, due to its tendency to orient equatorially for spatial and entropic reasons. For prolines, this approach has been applied at the C-3 and C-5 positions.[11,12] Several synthetic routes toward C-4 alkylation have been explored,[6−9] but to our knowledge no synthetic pathway has been reported for 4-*tert*-butyl prolines. Yet, introduction of this bulky group specifically on carbon C-4 is attractive as it can be expected that the steric control takes place via pyrrolidine ring while the *tert*-butyl substituents at both C-3 and C-5 positions sterically interfere with the backbone peptide bonds.

In addition to the C-4 *tert*-butyl prolines, a number of 4-alkyl substituted prolines have already been synthesized[6−9] and are widely used in pharmaceutical industry, such as angiotensin-converting enzyme (ACE) inhibitors and potential inhibitors of proline dehydrogenase.[7h] Our primary synthetic interest was the preparation of *trans*-4-*tert*-butyl-L-proline. We present herein the synthetic access to all the C-4 *tert*-butyl and C-2 CO_2-*t*Bu epimers. In this work, we also present a conformational study of the C-4 *tert*-butylprolines based on X-ray diffraction data and ^{1}H NMR spectroscopy.

Results and Discussion

Among the reported syntheses toward C-4 alkyl substituted prolines, the routes involving glutamate or pyroglutamate intermediates have proven to be successful in γ-alkylations. The alkyl groups have usually been introduced as electrophiles on glutamate enolates.[6] However, the poor electrophilic nature of *tert*-butyl group precludes this type of synthetic strategy for 4-*tert*-butylprolines. Many alkylation routes involve synthetic steps via α-vinylic bonds and subsequent catalytic hydrogenation.[7] Unfortunately, this type of synthetic route would involve unfavorable high energy intermediates caused by the allylic strain involving the *tert*-butyl group. Alkyl cuprate substitutions of prolines at the C-4 position appealed to us as an intriguing approach.[7]

Our synthesis began with the preparation of intermediate **4** starting from *trans*-4-hydroxyproline using literature procedures (Scheme 1).[7h,k] The hydroxyprolinate **4** was then submitted to a Mitsunobu-type bromination, yielding the bromo prolinate **5**, key intermediate in this synthesis route.[13] Bromide was substituted with a *tert*-butyl group in a Corey−House reaction using *tert*-butylcuprate as the nucleophile.[14] The alkylation reaction was attempted with several types of *tert*-butyl cuprates: Gilman (*t*-Bu_2CuLi),[8,14,15] cyano (*t*-$Bu_2CuCNLi_2$),[14] and thiophenol (*t*-BuCuSPhLi)[17] reagents under various reaction conditions.[16] We found out that the Posner *tert*-butyl thiophenolcuprate procedure proved to be most efficient in the substitution.[17] The substitution reaction proceeded

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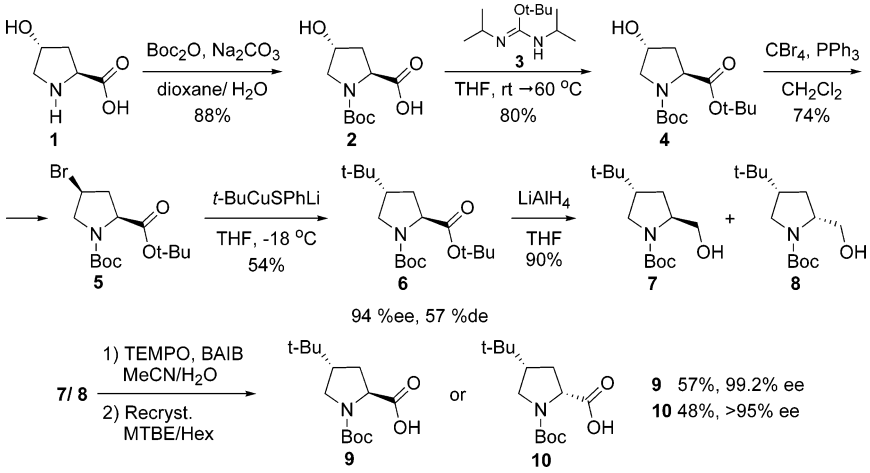
(16) See Supporting Information for optimization of the reaction conditions.

SCHEME 1. Synthesis of *N*-Boc-Protected 4-*tert*-Butylprolines



in THF at −18 °C in acceptable yield (54%) and gave 4-*tert*-butylprolinate **6** in 94% ee and 57% de. The yield was satisfactory, taking into account the reported modest yields for *tert*-alkylcuprates in general. This was especially the case, while our electrophile, inactivated secondary halogen in the 5-ring, is a poor candidate for substitution reactions.

The reason for the observed C-2 epimerization lies in the applied basic reaction conditions that led to enolate equilibrium and thus loss in diastereoselectivity. This was especially pronounced when the reaction times were prolonged.

In all cuprate reactions, some ring-opened *N*-Boc allyl glycine *tert*-butyl ester was found as a side product. This is most likely formed through direct transmetalation, and similar observations have been reported in the literature.[8c]

The diastereo- and enantioselectivities were determined by gas chromatography. Unfortunately, only the trans-enantiomers of *tert*-butylproline **6** of the four epimers were fully separable in chiral GC. The poor chromatographic separation of the product mixture was solved by reduction of the ester to an alcohol group with lithium aluminum hydride to give a diastereomer mixture of prolinols **7** and **8** in excellent yield (90%). These diastereomers were separable by flash chromatography. The absolute stereochemistries in prolinols **7** and **8** were determined through the corresponding Mosher esters. The enantiopurity of **8** was also determined through the Mosher ester. The final step in the synthesis involved TEMPO-catalyzed oxidation of the primary alcohols back to the corresponding substituted prolines **9** and **10**.[18] Although the oxidation proceeded in 80% (for **9**) and 76% (for **10**) yields and gave NMR pure samples, these products were recrystallized to improve enantiopurity, lowering the total yields to 57 and 48%, respectively. A small amount of proline **9** was esterified using isourea **3** to determine the enantiopurity with GC, and it was found to be excellent (99.2% ee).

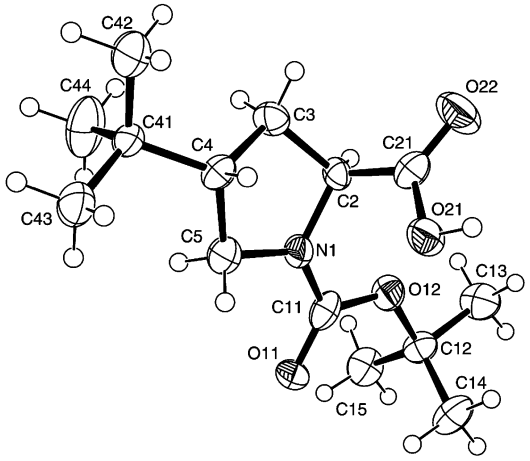


FIGURE 2. ORTEP plot of the X-ray crystal structure of proline **9**.

An X-ray structure of proline **9** proved that the *tert*-butyl substituent is trans to the carboxyl group and occupies a pseudoequatorial position in the crystal (Figure 2).

Determination of the enantiopurity also required the other enantiomers for accurate chiral GC analysis. Synthesis of the enantiomer for prolinate **6** was performed starting from the intermediate **11**, which was prepared from *trans*-4-hydroxy-L-proline using literature procedures (Scheme 2).[19] The stereochemistry at C-4 was inverted using a Mitsunobu reaction to give **12** in good yield (82%). The fully protected hydroxyproline **12** was hydrolyzed (1 M sodium hydroxide) to give *N*-Boc-*trans*-4-hydroxy-D-proline **ent-2** in quantitative yield. Subsequent esterification with isourea **3** proceeded in 79% yield. The hydroxyprolinate **ent-4** was brominated using Mitsunobu-type reaction with inversion at C-4. This key intermediate was then alkylated using the same conditions as for its enantiomer **5** using *t*-BuCuSPhLi. The reaction gave prolinate **ent-6** in acceptable yield (34%) and in selectivity similar (92% ee, 68% de) to that of its enantiomer **6**.

Pure trans-epimer of **6** was crystallized from freezer cold (−18 °C) isooctane, and the crystallographic structure was determined (Figure 3).

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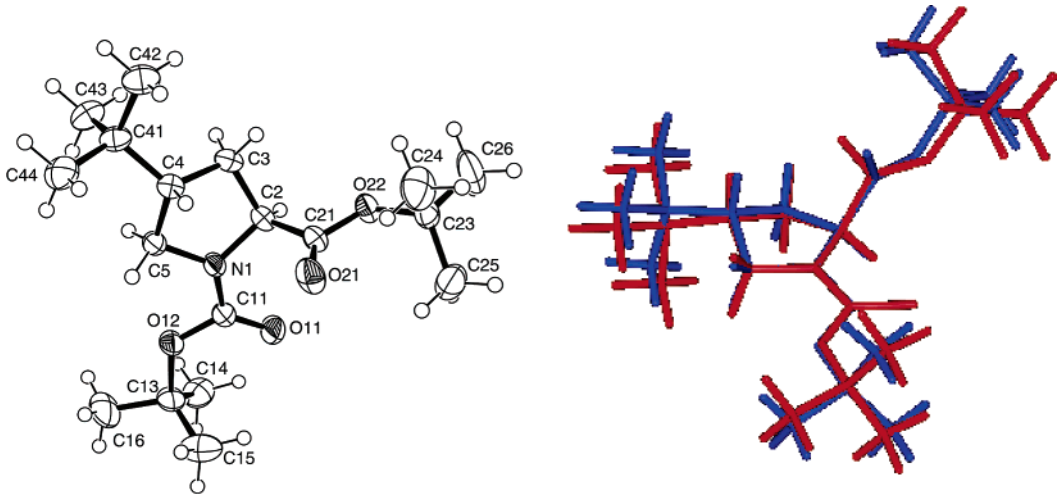

FIGURE 3. ORTEP plot of the X-ray crystal structures of proline **6** and 3D plot of the RMS fit of its crystal structure (blue) and solution structure (red).

SCHEME 2. Synthesis of the Enantiomeric Pair for the Ester 6

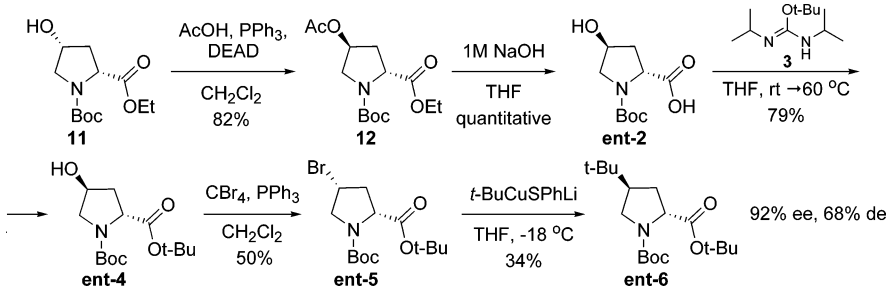

TABLE 1. Simulated and Calculated $^3J_{H-H}$ Couplings for *trans*-4-*tert*-Butylproline

coupled protons	simulated $^3J_{H-H}$ couplings (Hz)[a] NMR at 25 °C	NMR at 110 °C	$^3J_{H-H}$ couplings (Hz) calculated from structural parameters[b] X-ray	DFT *endo* pucker	DFT *exo* pucker
H^2-H^{3a}	9.26	9.13	9.55	8.16	8.52
H^2-H^{3e}	1.13	1.54	0.91	0.45	9.03
$H^{3a}-H^4$	12.57	11.43	12.25	12.59	9.08
$H^{3e}-H^4$	6.65	7.18	6.03	5.42	0.45
$H^{5a}-H^4$	10.09	9.49	11.20	10.62	8.22
$H^{5e}-H^4$	8.49	8.45	6.64	7.36	0.80

[a] Based on spectral iteration (see Experimental Section). [b] Calculated from torsion parameters using the Haasnoot−Altona equation (including the β-substituent correction).

TABLE 2. Simulated and Calculated $^3J_{HH}$ Couplings for *cis*-4-*tert*-Butylproline

coupled protons	simulated $^3J_{H-H}$ couplings (Hz)[a] NMR at 25 °C	$^3J_{H-H}$ couplings (Hz) calculated from structural parameters[b] DFT *exo*	DFT *endo*
H^2-H^{3a}	9.08	9.96	10.20
H^2-H^{3e}	7.99	7.96	6.48
$H^{3a}-H^4$	12.17	12.61	11.50
$H^{3e}-H^4$	6.98	5.40	4.53
$H^{5a}-H^4$	11.24	11.25	10.10
$H^{5e}-H^4$	7.47	6.50	2.33

[a] Based on spectral iteration (see Experimental Section). [b] Calculated from torsion parameters using the Haasnoot−Altona equation (including the β-substituent correction).

Solution structures were determined relying on vicinal ($^3J_{H-H}$) coupling constants, which were obtained from spectral simulations. The simulated couplings were first converted into H−C−C−H torsion angles exploiting the Haasnoot−Altona equation (including the β-substituent correction) (Tables 1 and 2).[20,21] The reciprocal use of this formula yielded the estimated $^3J_{H-H}$ coupling constants from the corresponding structural dihedral parameters (Tables 1 and 2).

In the case of *trans*-4-*tert*-butyl-L-proline, the calculated dihedrals were set as constraints in the geometry optimization (MM+ force field). As a result, unambiguous *endo* puckering could be deduced for this proline. By comparing the simulated $^3J_{H-H}$ couplings at 25 and 110 °C, we found that there is still strong preference for *endo* puckering mode even at elevated temperatures (Table 1).

The 4-*tert*-butyl-proline ring conformations were also studied computationally using B3LYP at 6-31G* level of theory.[22] For density functional theory (DFT) modeling, the structures were truncated from the peripheral *tert*-butyl ester and Boc-group for computational reasons (Figures 4 and 5). In the case of *trans*-4-*tert*-butyl-L-proline geometry optimization, both *exo* and *endo* conformers were found as energy minima of which the *endo* mode was energetically favored by 2.5 kcal/mol over its *exo* counterpart. On the basis of the $^3J_{H-H}$ couplings

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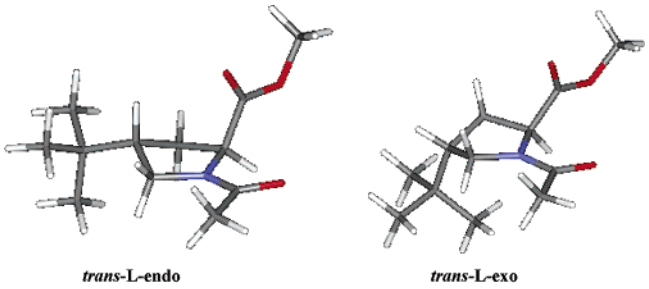

FIGURE 4. DFT B3LYP 6-31G* geometry optimized *endo* (left) and *exo* (right) puckering modes for *N*-Ac methyl *trans*-4-*tert*-butyl-l-prolinate. The *endo* is the global minimum conformer with a 2.5 kcal/mol relative energy preference.

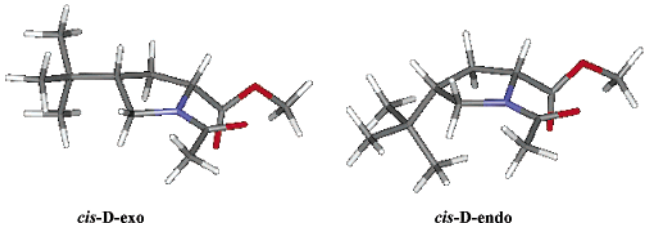

FIGURE 5. DFT B3LYP 6-31G* geometry optimized *exo* (left) and *endo* (right) puckering modes for *N*-Ac methyl *cis*-4-*tert*-butyl-D-prolinate. The *exo* is the global minimum conformer with a 3.3 kcal/mol relative energy preference.

deduced from the X-ray structure and DFT models, it is evident that *trans*-4-*tert*-butylproline exists predominantly in the *endo* puckering conformation.

The DFT modeling of the *cis*-4-*tert*-butyl-D-proline again indicates that pseudoequatorial orientation of the *tert*-butyl group is clearly preferred: the *exo* conformer is 3.3 kcal/mol lower in energy than the *endo* one (Figure 5). It is also worth noticing that in the *endo* conformer the 4-*tert*-butyl group is spatially in a close proximity to the 2-carboxy group. This distorts the pyrrolidine to a nearly planar conformation, where the nitrogen is located slightly below the plane. Inspection of simulated $^3J_{H-H}$ couplings and the calculated ones (Table 2) shows apparent preference for *exo* puckering mode for the *cis*-*tert*-butyl proline, although this was less pronounced than the *endo* puckering in the case of the trans-substitution.

Conclusions

We have developed selective synthetic routes to both *trans*- and *cis*-4-*tert*-butylprolines from *trans*-4-hydroxyproline using *t*-BuCuSPhLi mediated substitution via a secondary bromide. According to ^{1}H NMR-based conformational analysis, molecular modeling, and X-ray structure, the C-4 *tert*-butyl group prefers strongly the pseudoequatorial orientation in the pyrrolidine ring and thereby promotes conformational ring locking for *exo* puckering in the case of cis and *endo* puckering in the case of trans-substituted prolines, in both solution and solid state. As a result of demonstrated conformational locking effect, the C-4 *tert*-butyl-substituted prolines offer potentially very attractive tools to construct short constrained peptide turns. Currently we are investigating structural effects of *trans*-4-*tert*-butylproline in β-turn mimetics.

Experimental Section

(2*S*)-*N*-Boc-*trans*-4-hydroxy-L-proline *tert*-Butyl Ester (4). A solution of proline **2** (3.96 g, 17.1 mmol, 100 mol %) in 60 mL of dry THF was treated with *O*-*tert*-butyl *N*,*N*-diisopropylisourea[23] **3** (5.14 g, 25.7 mmol, 150 mol %) at room temperature and then stirred for 2.5 h at 60 °C. Additional *O*-*tert*-butyl *N*,*N*-diisopropylisourea **3** (3.43 g, 17.1 mmol, 100 mol %) was added to the mixture, and then stirring was continued overnight. Precipitated urea was filtered off through Celite followed by ether washings, and the filtrate was evaporated in vacuo to give an oily white solid. The crude product was purified by flash chromatography (30−50% ethyl acetate/hexanes) to give the corresponding *tert*-butyl ester **4** as a colorless oil (3.93 g, 80%). R_f = 0.45 (ethyl acetate); $[\alpha]_D$ = −57.3 (*c* 1.01, $CHCl_3$); IR (thin film, cm^{-1}): 3437, 2978, 2934, 1742, 1703, 1403, 1367, 1151; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (br s, 1H), [4.28 (t, 7.6 Hz), 4.24 (t, 7.6 Hz) 1H], [3.59 (d, 4.5 Hz), 3.56 (d, 4.3 Hz) 1H], [3.51 (d, 11.5 Hz), 3.39 (d, 11.1 Hz) 1H], [2.62 (s), 2.55 (s) 1H], 2.35−2.17 (m, 1H), 2.10−1.97 (m, 1H), 1.48−1.41 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [172.1, 172.0], [154.4, 154.1], [81.1, 81.0], [80.1, 79.8], [70.0, 69.2], [58.5, 58.4], [54.6, 54.5], [39.1, 38.3], 28.3, [27.9, 27.8]; HRMS (ESI) calcd for $C_{14}H_{25}NO_5Na$, 310.1630; found, 310.1649; Δ = 6.1 ppm. These data match those reported in the literature.[7h,24]

(2*S*)-*N*-Boc-*cis*-4-bromo-L-proline *tert*-Butyl Ester (5). Hydroxyproline **4** (4.61 g, 16.0 mmol, 100 mol %) and tetrabromomethane (16.23 g, 48.9 mmol, 305 mol %) were dissolved in 40 mL of dry dichloromethane. The mixture was cooled to 0 °C, and triphenylphosphine (13.09 g, 49.9 mmol, 310 mol %) was added carefully. The reaction was stirred at room temperature for 15 h. Ethanol (4 mL) was added, and the solution was stirred for 2 h. Ether (40 mL) was added dropwise to precipitate the phosphine oxide, which was filtered off, the filter cake was washed with dichloromethane (2 × 30 mL), and the filtrate was evaporated in vacuo to give a brown oil. Purification by flash chromatography (20−30% ether/hexanes) gave bromide **5** (4.17 g, 74%) as a colorless oil. R_f = 0.43 (50% ether in hexanes); $[\alpha]_D$ = −38.1 (*c* 1.00, $CHCl_3$); IR (thin film, cm^{-1}): 2978, 2932, 1746, 1704, 1395, 1367, 1151; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33−4.15 (m, 2H), [4.05 (dd, 6.4 Hz, 11.8 Hz), 3.99 (dd, 6.4 Hz, 11.7 Hz) 1H], [3.69 (dd, 5.8 Hz, 12.0 Hz), 3.65 (dd, 6.0 Hz, 11.9 Hz) 1H], 2.89−2.72 (m, 1H), 2.42−2.30 (m, 1H), [1.47 (s), 1.46 (s) 9H], [1.45 (s), 1.42 (s) 9H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [170.5, 170.3], [153.4, 153.2], [80.3, 80.2], [58.8, 58.7], [55.6, 55.3], [42.2, 41.5], [41.0, 40.0], [28.3, 28.2], 27.9; HRMS (ESI) calcd for $C_{14}H_{24}NO_4NaBr$, 372.0786; found, 372.0777; Δ = 2.4 ppm.

(2*S*)-*N*-Boc-*trans*-4-*tert*-butyl-L-proline *tert*-Butyl Ester (6). A suspension of copper(I) thiophenolate[17b] (1.47 g, 8.52 mmol, 600 mol %) in 30 mL of dry THF was cooled to −20 °C and treated with careful addition of 1.85 M *tert*-butyllithium in pentane (4.6 mL, 8.52 mmol, 600 mol %). This black solution was stirred for 20 min, and a precooled (−20 °C) solution of bromide **5** (0.50 g, 1.42 mmol, 100 mol %) in dry THF (5 mL) was added. The reaction was stirred at −18 °C for 16 h and quenched by pouring into a solution of saturated aqueous NH_4Cl (30 mL). The aqueous mixture was stirred vigorously until the black color disappeared. Solids were filtered off, and the phases were separated. The aqueous phase was extracted with ether, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4.

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Evaporation of solvent in vacuo gave a yellow oily solid. Silica gel chromatography (5−10% ether/hexanes) yielded prolinate **6** (0.253 g, 54%, 95% ee, 57% de) as an oily white solid. R_f = 0.54 (50% ether in hexanes).

***trans*-L-6:** IR (thin film, cm^{-1}): 2965, 1742, 1704, 1394, 1366, 1176, 1153, 1124; ^1H NMR (400 MHz, $CDCl_3$): δ [4.24 (d, 7.8 Hz), 4.15 (d, 8.6 Hz) 1H], [3.58 (dd, 8.6 Hz, 10.2 Hz), 3.48 (dd, 8.7 Hz, 10.6 Hz) 1H], [3.10 (t, 10.2 Hz), 3.03 (t, 10.2 Hz) 1H], 2.23−2.06 (m, 1H), 2.20−1.80 (m, 2H), [1.46 (s), 1.44 (s), 1.42 (s) 18H], 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [172.3, 172.2], [154.4, 154.0], [80.8, 80.8], [79.5, 79.4], [60.1, 59.9], [47.5, 47.3], [47.5, 46.6], 31.7, [30.9, 30.8], [28.4, 28.3], 28.0, 27.3; HRMS (ESI): calcd for $C_{18}H_{33}NO_4Na$, 350.2307; found, 350.2312; Δ = 1.4 ppm; GC t_r = 79.4 min.

***cis*-D-6:** ^1H NMR (400 MHz, $CDCl_3$): δ [4.11 (dd, 7.3 Hz, 8.6 Hz), 4.07 (dd, 8.2 Hz,8.8 Hz) 1H], [3.66 (dd, 7.8 Hz, 9.8 Hz), 3.49 (dd, 7.5 Hz, 10.0 Hz) 1H], [3.10 (t, 11.0 Hz), 3.08 (t, 10.6 Hz) 1H], 2.29−2.18 (m, 1H), 2.06−1.91 (m, 1H), 1.65−1.55 (m, 1H), [1.46 (s), 1.45 (s), 1.45 (s), 1.43 (s) 18 H], [0.90 (s), 0.89 (s) 9H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 154.0, 80.7, 79.7, [60.0, 60.0], [49.0, 48.2], [47.9, 47.8], 32.2, [31.1, 30.9], [28.4, 28.3], [28.0, 27.9], [27.5, 27.4]; GC t_r = 94.5 min.

(2*S*)-*N*-Boc-*trans*-4-*tert*-butyl-L-prolinol (7) and (2*R*)-*N*-Boc-*cis*-4-*tert*-butyl-D-prolinol (8). A solution of ester **6** (0.496 g, 1.51 mmol, 100 mol %) in dry THF was treated with careful addition of lithium aluminum hydride (0.23 g, 6.06 mmol, 400 mol %) at room temperature and then was stirred for 40 min. The reaction was finished using the three-step quench method: addition of distilled water (0.23 mL), 15 wt % NaOH solution (0.23 mL), and distilled water (0.69 mL) to a precooled solution (0 °C). The mixture was allowed to warm to room temperature and was stirred for 20 min, then dried over Na_2SO_4 and filtered. The filtrate was again dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure to give a yellow oil. Silica gel chromatography (5−15% ethyl acetate/hexanes) yielded fraction A: alcohol **8** (0.045 g, 11%), fraction B: alcohols **8** and **7** (0.020 g, 5%), fraction C: alcohol **7** (0.353 g, 74%).

7: R_f = 0.44 (50% ethyl acetate in hexanes); $[\alpha]_D$ = +27.8 (*c* 1.00, $CHCl_3$); IR (thin film, cm^{-1}): 3430, 2960, 2874, 1695, 1673, 1404, 1366, 1174, 1127; ^1H NMR (400 MHz, $CDCl_3$): δ 4.07−3.97 (m, 1H), 3.63 (dd, 7.8 Hz, 10.8 Hz, 1H), 3.55 (dd, 4.3 Hz, 10.6 Hz, 1H), 3.6 (dd, 7.8 Hz, 10.6 Hz, 1H), 3.29 (br s, 1H), 2,13−2.00 (m, 1H), 1.77 (dt, 8.7 Hz, 12.6 Hz, 1H), 1.60 (dd, 6.6 Hz, 12.6 Hz, 1H), 1.46 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 80.1, 67.4, 59.7, 48.3, 47.3, 31.0, 29.3, 28.4, 27.4; HRMS (ESI) calcd for $C_{14}H_{27}NO_3Na$, 280.1889; found, 280.1889; Δ = 0 ppm.

8: R_f = 0.51 (50% ethyl acetate in hexanes); $[\alpha]_D$ = −28.2 (*c* 1.00, $CHCl_3$); IR (thin film, cm^{-1}): 3411, 2961, 2872, 1694, 1670, 1409, 1366, 1167, 1119; ^1H NMR (400 MHz, $CDCl_3$): δ 3.96−3.86 (m, 1H), 3.68 (dd, 1.8 Hz, 11.5 Hz, 1H), 3.63−3.43 (m, 3H), 2.95 (t, 10.9 Hz, 1H), 1.99−1.84 (m, 2H), 1.46 (s, 9H), 1.33−1.17 (m, 1H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 80.4, 67.4, 61.2, 48.7, 47.6, 30.7, 30.4, 28.4, 27.5; HRMS (ESI) calcd for $C_{14}H_{27}NO_3Na$, 280.1889; found, 280.1908; Δ = 6.7 ppm.

(2*S*)-*N*-Boc-*trans*-4-*tert*-butyl-L-proline (9). To a flask charged with prolinol **7** (0.263 g, 1.02 mmol, 100 mol %), TEMPO (0.016 g, 0.102 mmol, 10 mol %), and bis-acetoxy-iodobenzene (BAIB) (0.724 g, 2.25 mmol, 220 mol %) was added 2.5 mL of acetonitrile and 2.5 mL of distilled water. The reaction mixture was stirred for 2 h and quenched with saturated aqueous Na_2SO_3 solution (3 mL). Acetonitrile was evaporated under reduced pressure, and the aqueous mixture was basified (pH ≈ 10) with 1 M NaOH solution, washed twice with ether, and acidified with 1 M HCl solution (pH ≈ 3). The acidic aqueous phase was extracted three times with ether. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo to yield proline **9** (0.222 g, 80%) as a white solid. Recrystallization from refluxing MTBE (1 mL)/hexanes (10 mL) gave white crystals (0.160 g, 57%). R_f = 0.11 (50% ethyl acetate in hexanes); mp 140−141 °C; $[\alpha]_D$ = +62.7 (*c* 1.00, $CHCl_3$); IR (thin film, cm^{-1}): 3500−2300 (broad band), 2960, 2894, 1702, 1663, 1478, 1419, 1366, 1257, 1168, 1137; ^1H NMR (400 MHz, $CDCl_3$): δ 10−7.60 (br s, 1H), [4.39 (d, 8.6 Hz), 4.31 (d, 5.3 Hz) 1H], [3.62 (t, 8.2 Hz), 3.42 (t, 8.7 Hz) 1H], [3.12 (t, 9.8 Hz), 3.03 (t, 10.4 Hz) 1H], 2.35−1.90 (m, 3H), [1.48 (s), 1.41 (s) 9H], 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [178.5, 174.5], [156.7, 153.9], [81.6, 80.1], [59.5, 59.2], [48.0, 47.8], [47.3, 46.7], [31.5, 30.9], [30.8, 29.1], [28.3, 28.3], 27.4; HRMS (ESI) calcd for $C_{14}H_{25}NO_4Na$, 294.1681; found, 294.1687; Δ = 2.0 ppm.

(2*R*)-*N*-Boc-*cis*-4-*tert*-butyl-D-proline (10). A suspension of prolinol **8** (28 mg, 0.108 mmol, 100 mol %), TEMPO (1.7 mg, 10.8 μmol, 10 mol %), and BAIB (77 mg, 0.23 mmol, 220 mol %) in acetonitrile (0.5 mL) and distilled water (0.5 mL) was stirred for 21 h at room temperature. The reaction was quenched by addition of saturated aqueous Na_2SO_3 solution until color had disappeared. Acetonitrile was evaporated under reduced pressure, and the aqueous mixture was basified (pH ≈ 10) with 1 M NaOH solution, washed twice with ether, and acidified with 1 M HCl solution (pH ≈ 3). The acidic aqueous phase was extracted three times with ether. The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to yield proline **10** (22 mg, 76%) as a white solid. Recrystallization from refluxing MTBE (0.4 mL)/hexanes (4 mL) gave white crystals (14 mg, 48%). R_f = 0.12 (50% ethyl acetate in hexanes); mp 166−167 °C; $[\alpha]_D$ = −90.8 (*c* 1.00, $CHCl_3$); IR (thin film, cm^{-1}): 3500−2300 (broad band), 2952, 2872, 1731, 1637, 1437, 1405, 1365, 1252, 1167, 774; ^1H NMR (400 MHz, $CDCl_3$): δ [4.30 (t, 8.0 Hz), 4.20 (t, 7.8 Hz) 1H], 3.73−3.54 (m, 1H), [3.15 (t, 10.6 Hz), 3.03 (t, 10.2 Hz) 1H], 2.35−2.15 (m, 1H), 2.10−1.65 (m, 2H), [1.48 (s), 1.42 (s) 9H], 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [178.7, 175.0], [156.5, 153.7], [81.5, 80.4], [59.6, 59.4], 48.5, [48.3, 47.7], [32.3, 30.3], 30.8, [28.3, 28.2], 27.5; HRMS (ESI) calcd for $C_{14}H_{25}NO_4Na$, 294.1681; found, 294.1687; Δ = 2.0 ppm.

(2*R*)-*N*-Boc-*trans*-4-acetoxy-D-proline Ethyl Ester (12). To a solution of prolinate **11** (0.50 g, 1.93 mmol, 100 mol %), triphenyl phosphine (1.01 g, 3.86 mmol, 200 mol %), and glacial acetic acid (0.22 mL, 0.23 g, 3.86 mmol, 200 mol %) in dry THF (5 mL) was added 40% DEAD in toluene (1.67 g, 1.76 mL, 3.86 mmol, 200 mol %) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated, and the residue was purified by silica gel chromatography (20−40% ether/hexanes) to give prolinate **12** (0.482 g, 82%) as a yellow oil. R_f = 0.24 (50% ether in hexanes); $[\alpha]_D$ = +44.0 (*c* 1.00, $CHCl_3$); IR (thin film, cm^{-1}): 2979, 2935, 1744, 1704, 1401, 1367, 1239, 1194, 1160, 1127; ^1H NMR (400 MHz, $CDCl_3$): δ 5.28−5.18 (m, 1H), [4.36 (t 7.6 Hz), 4.29 (8.0 Hz) 1H], 4.25−4.07 (m, 2H), 3.74−3.45 (m, 2H), 2.40−2.28 (m, 1H), 2.21−2.10 (m, 1H), 2.02 (s, 3H), [1.42 (s), 1.39 (s) 9H], [1.24 (t, 7.3 Hz), 1.23 (t, 7.4 Hz) 3H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [172.5, 172.1], [170.3, 170.2], [154.0, 153.5], [80.3, 80.2], [72.6, 71.8], 61.0, [57.8, 57.5], [52.1, 51.9], [36.5, 35.4], [28.2, 28.1], 20.9, [14.1, 14.0]; HRMS (ESI) calcd for $C_{14}H_{23}NO_6Na$, 324.1423; found, 324.1398; Δ = 7.7 ppm.

(2*R*)-*N*-Boc-*trans*-4-hydroxy-D-proline (ent-2). A solution of prolinate **12** (0.424 g, 1.40 mmol) in THF (5 mL) was treated with aqueous 15 wt % NaOH solution and was stirred for 3 h. Most of the THF was evaporated under reduced pressure, and the aqueous mixture was acidified with 6 M HCl to pH ≈ 3. The mixture was extracted with ethyl acetate (10 times) until TLC showed no product in the aqueous phase. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo to give proline **ent-2** (0.325 g, 100%) as a solid. R_f = 0.50 (50% methanol in ethyl acetate); IR (thin film, cm^{-1}): 3500−2300 (broad band), 3419, 2979, 2935, 1725, 1671, 1421, 1197; ^1H NMR (400 MHz, $CDCl_3$): δ 4.55−4.35 (m, 2H), 3.70−3.45 (m, 2H), 2.50−2.05 (m, 2H), [1.47 (s), 1.42 (s) 9H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [177.6, 174.1], [156.7, 154.1], [81.9, 80.9], [69.6, 69.4], 57.8, 54.6, [39.0, 37.2], 28.3; HRMS (ESI) calcd for $C_{10}H_{17}NO_5Na$, 254.1004; found, 254.1005;

$\Delta = 0.4$ ppm. These data are consistent to those reported in the literature for the enantiomer **2**.[25]

Acknowledgment. Financial support from the National Technology Agency of Finland, the Academy of Finland, and EU COST action D28 is gratefully acknowledged.

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Supporting Information Available: Table of the optimization conditions for the *tert*-butyl copper alkylation. Experimental procedures for **ent-4**, **ent-5**, and **ent-6**. Copies of ^{1}H and ^{13}C NMR spectra of compounds **5**−**10**, **12**. GG chromatograms for compounds **6**, **ent-6**, and *tert*-butyl ester derivative **9**. Mosher ester analysis for compound **7** and **8**. Crystallographic collection data and tables for **6** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050838A