Stereoselective Addition of Grignard-Derived Organocopper Reagents to *N*-Acyliminium Ions: Synthesis of Enantiopure 5- and 4,5-Substituted Prolinates

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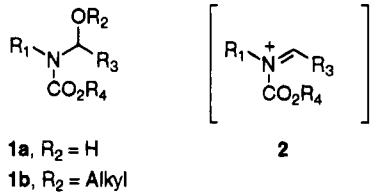
Alkylation of nonracemic *N*-acyliminium ions derived from proline and 4-substituted prolines has been extended to different types of Grignard-derived organocopper reagents. The reaction proceeds with high yield and stereoselectivity to yield 5-mono- and 4,5-disubstituted prolinates. The stereochemistry is controlled by the formation of a RCu-π complex intermediate between the *N*-acyliminium ion, the carbonyl group of the ester, and the copper species.

Reactions for the introduction of functional groups at the α-position of cyclic amines are of great interest due to the large number of natural products having this substitution pattern.[1] One of the most useful ways to obtain this type of functionalization is the nucleophilic addition to *N*-acyliminium ions **2** (Figure 1), which have been shown to have great synthetic potential.[2] *N*-Acyliminium ions can be generated from α-alkoxy *N*-(alcoxycarbonyl)amines[3] **1**, obtained either from the corresponding amines by electrochemical oxidation[4] or from lactams by partial reduction to the hemiaminal.[5] Compounds **1** have been reacted with various nucleophiles[6] or trapped intramolecularly by alkenes, alkynes,[7] arenes,[8] or heteronucleophiles,[9] in the presence of Lewis acids.

Wistrand and co-workers have reported that the highly diastereoselective addition of alkylcopper reagents to the optically active *N*-acyliminium ions derived from proline[6f-i] and pipecolic acid[6j] occurs with a high degree of *trans* selectivity. Only *n*-alkyl and 2-methyl-1-propenyl cuprates derived from the corresponding alkyllithium were used. In these studies, a mechanism involving nucleophilic attack on the less hindered face of a sterically biased *N*-acyliminium ion–copper complex was proposed to explain the stereochemical reaction outcome. In this paper, we report on a more general reaction of chiral *N*-acyliminium ions derived from ethyl (2*S*)-*N*-Boc-5-methoxyprolinates (**5a–c**) with an organocopper reagent, generated from the more readily available Grignard reagents (Scheme 1). The stereoselectivity found in the reaction with chiral 4-substituted prolinates (**5b,c**) gave us further evidence for the mechanism previously proposed by Wistrand *et al.*[6g,h]

The required aminals **5a–c** were prepared from ethyl *N*-Boc-pyroglutamate **3a**.[10] Thus, aldol condensation[11] or



1a, R_2 = H
1b, R_2 = Alkyl

2

Figure 1.

alkylation[12] of the lactam enolate derived from **3a** gave rise to ethyl (4*S*)-4-benzyl-*N*-Boc-pyroglutamate (**3b**) and ethyl (4*R*)-4-benzyl-*N*-Boc-pyroglutamate (**3c**), respectively, as we have previously reported. Selective reduc-

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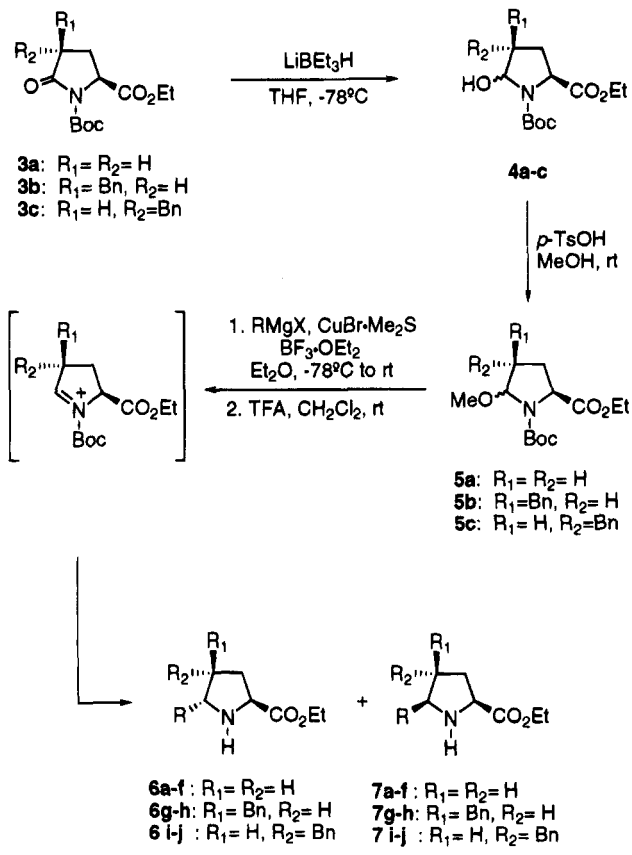
Scheme 1



tion of the lactam group of **3a–c** with $LiBEt_3H$[6a] in THF at −78 °C and subsequent reaction of the hemiaminals **4a–c** in methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the corresponding aminals **5a–c** in quantitative yields. These compounds were used without any further purification.

The reaction of **5a** with 4 equiv of $RCu{\cdot}MgX_2$ gave after deprotection of nitrogen a mixture of 5-substituted prolinates **6a–f** and **7a–f** (Table 1, entries a–f) in good yields.[13] The organocopper reagent was generated *in situ* from stoichiometric amounts of a Grignard reagent, copper(I) bromide–dimethyl sulfide complex,[14] at −40 °C for 45 min. The reaction mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ was added. After 30 min, the aminal **5a** was subsequently added and the mixture allowed to react from −78 °C to room temperature. The diastereoisomeric ratio of the crude reaction mixture was determined by NMR, the major isomer being *trans*.[15] Both isomers were easily separated by flash chromatography, and the major one was characterized.

Table 1 shows that a variety of Grignard reagents can be successfully used, demonstrating the general application of these organometallic species in this reaction. Therefore, the use of the readily available Grignard reagents to generate the alkylcopper makes them the reagent of choice compared with their alkyllithium counterparts. The stereoselectivity of the reaction for **5a**[16] is excellent and equally as stereoselective as those reported using the lithium-derived alkylcopper reagent (Table 1, entries b and d).

We also performed the Grignard-derived alkylcopper reaction on chiral 4-substituted 5-methoxy prolinates **5b** and **5c**, in order to study the stereochemical reaction outcome and as a way to obtain 4,5-disubstituted prolines. Thus, when **5b** was reacted with 4 equiv of RCu generated from the corresponding Grignard reagents, $CuBr{\cdot}Me_2S$ and $BF_3{\cdot}OEt_2$, *trans* prolinates **6g,h** were exclusively obtained after *N*-Boc deprotection[13] (Table 1, entries g and h). When **5c** was reacted under the same conditions, **6i** was exclusively obtained, whereas **6j** was the major component in the reaction mixture. The stereochemistries of prolinates **6g–j** were assigned by NOE experiments (Figure 2).

Although much work has been published regarding the reaction of monosubstituted *N*-acyliminium ions derived from proline with several nucleophiles,[6] the only precedent of this reaction with chiral 4-substituted prolinates was with silanes.[6w,x] Furthermore, Wistrand has reported that neither *N*-(methoxycarbonyl)-4-*O*-acetyl nor 4-*O*-TBDMS prolinates react with lithium-derived organocopper reagents.[6h] Our results are in sharp contrast with these precedents, suggesting that the nature of the substituent at the C-4 position plays an important role in the reaction.

As mentioned above, an explanation for the observed stereoselectivity in the addition of RCu to *N*-acyliminium ions derived from proline has been proposed by Wistrand and co-workers.[6g,h] They have suggested the formation of a complex between the *N*-acyliminium ion, the carbonyl group of the ester, and the copper species (**I**) (Figure 3). Then, selective *trans* attack by another RCu moiety from the opposite less hindered face (*re*) would account for the stereochemical outcome of the reaction. The diastereoselective reaction of the organocopper reagents with the intermediate (**II**), where no ester group is present, has been explained[6h] simply by steric factors. In this way, the *trans* isomers have been obtained with higher stereoselectivity depending on the increased bulkiness of the R group.

The stereochemical reaction outcome observed for **5b** and **5c** which exhibited opposite configuration at the prolinate C-4 position has allowed us to quantify the influence of the formation of the RCu-π complex *versus* the 1,2-asymmetric induction of the substituent at C-4 on the reaction stereoselectivity. In the case of the *cis*-4-benzyliminium ion **III** derived from **5b**, both factors force the attack of the organocopper reagent to be

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(13) *N*-Boc deprotection was required due to doubling of the ^1H NMR signals because of rotamers, which makes the proton assignment very complex: Hondrelis, J.; Lonergan, G.; Voliotis, S.; Matsoukas, J. *Tetrahedron* **1990**, *46*, 565. This signal splitting is also observed in the NMR spectra of compounds **4a–c** and **5a–c**.

(14) It should be noted that, when the reaction is run in the absence of the copper salt or with the hemiaminal (**4a–c**) as the substrate, the reaction does not take place.

(15) To assign the stereochemistry, *cis* isomers **7a**, **7b**, and **7f** were prepared by an independent route. Thus, nucleophilic ring opening of **3a** with 1 equiv of the corresponding Grignard reagent (Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; García Navío, J. L.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **1993**, *34*, 6317) followed by *N*-Boc deprotection gave the corresponding Δ^1-pyrroline which was further hydrogenated exclusively to the *cis* proline (Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147). H-2 and H-5 signals for the *cis* isomers are always shifted to downfield compared with the corresponding ones for their *trans* counterparts.

(16) In order to study the effect of the steric bulkiness of the ester group on the reaction stereoselectivity, the α-methoxy-*N*-Boc *tert*-butyl prolinate analogue was also prepared, but no change was observed in the stereochemical outcome of the reaction.

Table 1

entry (substrate)	RMgX	**6/7** ratio (de)[a]	% yield[b]	$[\alpha]_D$[c]
a (**5a**)	PhMgBr	≥98.5:≤1.5 (≥97%)	87	−86.7 (c = 0.7)
b (**5a**)	nBuMgCl[d]	95:5 (90%)	78	−33.5 (c = 1.0)
c (**5a**)	cyclo-C_6H_{11}MgCl	93:7 (86%)	79	−26.8 (c = 0.77)
d (**5a**)	CH_2=CHMgBr[e]	94:6 (88%)	80	−34.7 (c = 0.85)
e (**5a**)	MeMgBr	89:11 (78%)	73	−38.9 (c = 0.95)
f (**5a**)	$PhCH_2MgCl$	95.5:4.5 (91%)	78	−15.4 (c =1.0)
g (**5b**)	PhMgBr	≥98.5:≤1.5 (≥97%)	82	−3.4 (c = 0.45)
h (**5b**)	nBuMgCl	≥98.5:≤1.5 (≥97%)	79	+39.8 (c = 0.6)
i (**5c**)	PhMgBr	≥98.5:≤1.5 (≥97%)	84	−44.4 (c = 1.1)
j (**5c**)	nBuMgCl	92.5:7.5 (85%)	74	−19.7 (c = 1.0)

[a] The diastereomeric excess was determined by ^{1}H NMR analysis (200 MHz). The detection limit was established to be ≥97 by doping experiments. [b] Isolated yields of the major isomer after column chromatography. [c] Specific optical rotation values for the major isomer in $CHCl_3$. [d] When the lithium-derived organocopper reagent was used, the relative ratio was 96:4 (de = 92%).[6f,g] [e] When (2-methyl-1-propenyl)lithium was used to generate the corresponding organocopper species, the relative ratio was also 94:6.[6h]

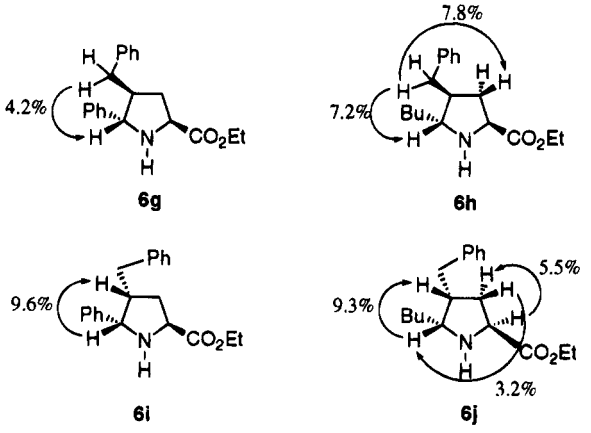
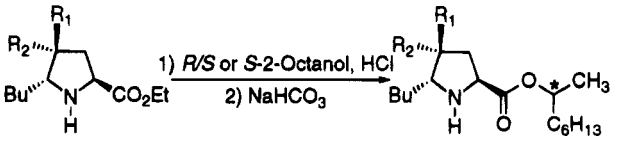


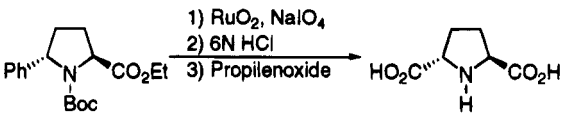
Figure 2.

Scheme 2



6h R_1= Bn, R_2= H — **8**
6j R_1= H, R_2= Bn — **9**

Scheme 3



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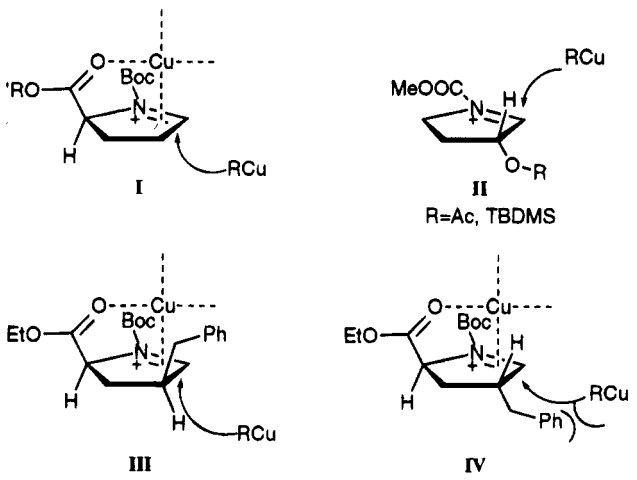

Figure 3.

exclusively by the *re* face. However, in the case of the *trans*-4-benzyliminium ion **IV** derived from **5c**, each factor would deliver the opposite result. While the substituent at the C-4 position would direct the organocopper attack by the *si* face, the RCu-π complex would induce the opposite configuration of the newly generated stereogenic center. From our results, it can be established that the steric effect induced by the formation of the RCu-π complex is responsible for the observed stereoselectivity, showing that when both factors compete the coordination effect is more important than the 1,2-asymmetric induction.

The determination of enantiomeric purity for the final prolinates was performed by conversion of **6h** and **6j** to their (*R*/*S*)-2-octanol and (*S*)-2-octanol esters (**8** and **9**, Scheme 2).[17] ^{1}H NMR spectra showed the presence of only one diastereoisomer, when compared with the racemic mixture, and thus **6a–j** are of high enantiomeric purity (ee >97%).[18]

Furthermore, *N*-Boc-protected **6a** was oxidized to (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid **10** (Scheme 3). Comparison of the spectroscopic data (^{1}H and ^{13}C NMR) and optical rotation data with the reported literature values for the natural product[19] shows that no epimerization has taken place in any reaction of the whole synthetic sequence.

In conclusion, the alkylations of the *N*-acyliminium ions generated from **5a–c** in the presence of BF_3·OEt_2 with a variety of Grignard-derived organocopper compounds proceed with a high degree of *trans* selectivity. In the cases of the chiral 4-benzyl prolinate iminium ions derived from **5b** and **5c**, regardless of the *cis*/*trans* stereochemistry of the substituent, the more important factor governing the diastereoselectivity is the steric hindrance of the attack to the RCu-π complex intermediate.

Experimental Section[20]

Ethyl (2*S*)-1-(*tert*-Butoxycarbonyl)-5-methoxyprolinates (5a–c). To a solution of 7.8 mmol of **3a–c** in 60 mL of dry THF was added 9.4 mL (9.4 mmol) of a solution of 1 M lithium triethylboron hydride (Super-Hydride) at −78 °C under

(17) The corresponding Mosher amides derived from **6h** and **6j** could not be analyzed by ^{1}H NMR due to the complexity of the spectra caused by the presence of rotamers.

(18) Unfortunately, it has been impossible to find suitable HPLC or GC conditions for the direct determination of the ee.

(19) Impellizzeri, G.; Mangiafico, S.; Oriente, G.; Piateli, M.; Scinto, S. *Phytochemistry* **1975**, *14*, 1549.

(20) For general information, see ref 11.

N_2. After the mixture was stirred for 30 min at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and the mixture was allowed to stand until the temperature reached 0 °C. Then, 50 drops of H_2O_2 (33%) were added, and the mixture was stirred for 20 min. The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was dissolved in MeOH (25 mL), and *p*-TsOH·H_2O (0.8 mmol) was added. The solution was stirred overnight, and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). After MeOH was removed, the aqueous layer was extracted with ether (3 × 10 mL). The combined organic phases were dried over anhyd Na_2SO_4 and evaporated to dryness. The crude aminals **5a–c**, obtained in quantitative yields, were used in the following step without any further purification.

General Procedure for Reaction of 5a–c with Grignard-Derived Organocopper Reagents. To a stirred suspension of CuBr·Me_2S (4 mmol) in dry ether (8 mL), at −40 °C under N_2, was added dropwise a solution of the corresponding Grignard reagent (4 mmol). After stirring for 45 min, the mixture was cooled to −78 °C, and BF_3·OEt (4 mmol) was added dropwise. After 30 min, a solution of **5a–c** (1 mmol) in dry ether (1.5 mL) was added dropwise. The mixture was stirred for 15 min and allowed to reach rt over a period of 3 h. After 1 h at rt, the reaction was quenched with a mixture of an aqueous saturated NH_4Cl solution and concd NH_3 (1:1) (5 mL) and the mixture stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution (5 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (15–25% ethyl acetate/hexane), yielding the corresponding mixture of diastereoisomers of 5-monosubstituted or 4,5-disubstituted *N*-Boc-protected prolinates.[21] To this mixture of diastereoisomers in CH_2Cl_2 (20 mL) was added TFA (10 mmol), and the reaction mixture was stirred overnight. The reaction solution was washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), dried over anhyd Na_2SO_4, and evaporated to dryness to afford the corresponding mixture of diastereoisomers **6/7**. The major diastereoisomer was separated and purified by column chromatography as indicated in each particular case.[22]

Ethyl (2*S*,5*S*)-5-phenylprolinate (6a): CH_2Cl_2/MeOH (40:1) as eluent; yield 87% from **3a**; oil; $[\alpha]^{25}_D$ −86.7 (*c* = 0.7, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.17 (m, 5H), 4.35 (dd, 1H, *J* = 6.4 and 8.4 Hz), 4.19 (c, 2H, *J* = 7.1 Hz), 4.01 (dd, 1H, *J* = 5.7 and 8.3 Hz), 2.59 (br s, 1H), 2.41–2.10 (m, 2H), 2.04–1.87 (m, 1H), 1.80–1.62 (m, 1H), 1.28 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.9, 144.4, 128.2 (2C), 126.8, 126.4 (2C), 61.6, 60.9, 59.5, 34.6, 29.7, 14.2; HRMS (*m/z*) calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1259, found 219.1254.

Ethyl (2*S*,5*R*)-5-butylprolinate (6b): CH_2Cl_2/MeOH (40:1) as eluent; yield 78% from **3a**; oil; $[\alpha]^{25}_D$ −33.5 (*c* = 1.0, $CHCl_3$); IR (film) 3350, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (c, 2H, *J* = 7.1 Hz), 3.79 (dd, 1H, *J* = 5.8 and 8.3 Hz), 3.17–3.07 (m, 1H), 2.30–2.11 (m, 1H), 2.18 (br s, 1H), 1.95–1.71 (m, 2H), 1.48–1.12 (m, 7H), 1.24 (t, 3H, *J* = 7.1 Hz), 0.89–0.83 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 175.9, 60.8, 59.2, 58.5, 36.4, 31.6, 29.7, 29.5, 22.8, 14.2, 14.1; HRMS (*m/z*) calcd for $C_{11}H_{20}NO_2$ (M^+ − 1) 198.1494, found 198.1491.

Ethyl (2*S*,5*S*)-5-cyclohexylprolinate (6c): CH_2Cl_2/MeOH (40:1) as eluent; yield 79% from **3a**; oil; $[\alpha]^{25}_D$ = −26.8 (*c* = 0.77, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (c, 2H, *J* = 7.1 Hz), 3.72 (dd, 1H, *J* = 6.1 and 8.2 Hz), 2.86–2.75 (m, 1H), 2.34 (br s, 1H), 2.25–2.06 (m, 1H), 1.91–1.56 (m, 7H), 1.52–1.26 (m, 1H), 1.20 (t, 3H, *J* = 7.1 Hz), 1.13–0.75 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.9, 63.7, 60.7, 59.1, 44.1, 30.8, 30.1, 29.6, 29.4, 26.4, 26.0, 25.9, 14.1; HRMS (*m/z*) calcd for $C_{13}H_{22}NO_2$ (M^+ − 1) 224.1650, found 224.1652.

Ethyl (2*S*,5*S*)-5-vinylprolinate (6d): CH_2Cl_2/MeOH (40:1) as eluent; yield 80% from **3a**; oil; $[\alpha]^{25}_D$ −34.7 (*c* = 0.85, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76 (ddd, 1H, *J* = 6.9, 10.1, and 17.1 Hz), 5.13 (ddd, 1H, *J* = 1.1, 1.6 and 17.1 Hz), 4.98 (ddd, 1H, *J* = 0.9, 1.6, and 10.1 Hz), 4.14 (c, 2H, *J* = 7.1 Hz), 3.83 (dd, 1H, *J* = 5.5 and 8.5 Hz), 3.76–3.66 (m, 1H), 2.23 (br s, 1H), 2.32–2.13 (m, 1H), 1.99–1.75 (m, 2H), 1.60–1.46 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.7, 140.8, 114.5, 60.9, 60.8, 59.1, 31.8, 29.4, 14.1; HRMS (*m/z*): calcd for $C_9H_{14}NO_2$ (M^+ − 1) 168.1025, found 168.1026.

Ethyl (2*S*,5*R*)-5-methylprolinate (6e): CH_2Cl_2/MeOH (30:1) as eluent; yield 73% from **3a**; oil; $[\alpha]^{25}_D$ = −38.9 (*c* = 0.95, $CHCl_3$); IR (film) 3320, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (c, 2H, *J* = 7.1 Hz), 3.81 (dd, 1H, *J* = 5.4 and 8.7 Hz), 3.36–3.20 (m, 1H), 2.27–2.13 (m, 1H), 2.24 (br s, 1H), 1.93–1.72 (m, 2H), 1.37–1.20 (m, 1H), 1.22 (t, 3H, *J* = 7.1 Hz), 1.09 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 175.8, 60.8, 59.3, 53.8, 33.4, 29.9, 21.4, 14.2; HRMS (*m/z*): calcd for $C_8H_{14}NO_2$ (M^+ − 1) 156.1025, found 156.1024.

Ethyl (2*S*,5*S*)-5-Benzylprolinate (6f). In this case, a temperature of −25 °C was required during organocopper formation: CH_2Cl_2/MeOH (50:1) as eluent; yield 78% from **3a**; oil; $[\alpha]^{25}_D$ = −15.4 (*c* = 1.0, $CHCl_3$); IR (film) 3320, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.13 (m, 5H), 4.16 (c, 2H, *J* = 7.1 Hz), 3.87 (dd, 1H, *J* = 5.4 and 8.7 Hz), 3.58–3.44 (m, 1H), 2.79 and 2.71 (2H, AB part of ABX system, J_{AB} = 13.3 Hz, J_{AX} = 6.9 Hz, J_{BX} = 6.8 Hz), 2.35–2.10 (m, 1H), 2.20 (br s, 1H), 1.96–1.77 (m, 2H), 1.59–1.33 (m, 1H), 1.26 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.8, 139.8, 128.9 (2C), 128.3 (2C), 126.1, 60.8, 59.8, 59.1, 42.8, 31.1, 29.3, 14.2; HRMS (*m/z*): calcd for $C_{14}H_{18}NO_2$ (M^+ − 1) 232.1338, found 232.1337.

Ethyl (2*S*,5*R*)-5-phenylprolinate (7a): $[\alpha]^{25}_D$ +9.7 (*c* = 0.9, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.16 (m, 5H), 4.19 (c, 2H, *J* = 7.1 Hz), 4.16 (dd, 1H, *J* = 5.5 and 9.4 Hz), 3.87 (dd, 1H, *J* = 5.1 and 8.3 Hz), 2.34 (br s, 1H), 2.29–1.98 (m, 3H), 1.78–1.56 (m, 1H), 1.26 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.1, 143.3, 128.4 (2C), 127.1, 126.7 (2C), 63.6, 60.9, 60.1, 34.2, 30.6, 14.2; HRMS (*m/z*): calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1259, found 219.1258.

Ethyl (2*S*,5*S*)-5-butylprolinate (7b): $[\alpha]^{25}_D$ −13.3 (*c* = 1.9, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (c, 2H, *J* = 7.1 Hz), 3.68 (dd, 1H, *J* = 5.5 and 9.0 Hz), 3.03–2.89 (m, 1H), 2.15–1.76 (m, 3H), 2.02 (br s, 1H), 1.57–1.10 (m, 7H), 1.23 (t, 3H, *J* = 7.1 Hz), 0.89–0.82 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 175.3, 60.9, 60.2, 59.9, 35.5, 31.7, 30.4, 29.5, 22.8, 14.2, 14.0; HRMS (*m/z*): calcd for $C_{11}H_{20}NO_2$ (M^+ − 1) 198.1494, found 198.1493.

Ethyl (2*S*,5*R*)-5-benzylprolinate (7f): $[\alpha]^{25}_D$ −28.7 (*c* = 0.55, $CHCl_3$); IR (film) 3320, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.14 (m, 5H), 4.17 (c, 2H, *J* = 7.1 Hz), 3.72 (dd, 1H, *J* = 5.8 and 8.6 Hz), 3.37–3.23 (m, 1H), 2.88 and 2.72 (2H, AB part of ABX system, J_{AB} = 13.3 Hz, J_{AX} = 7.0 Hz, J_{BX} = 6.8 Hz), 2.17–1.73 (m, 3H), 1.84 (br s, 1H), 1.48–1.33 (m, 1H), 1.25 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.2, 139.6, 128.9 (2C), 128.4 (2C), 126.2, 61.3, 61.0, 59.9, 42.1, 31.2, 30.0, 14.2; HRMS (*m/z*): calcd for $C_{14}H_{18}NO_2$ (M^+ − 1) 232.1338, found 232.1334.

Ethyl (2*S*,4*S*,5*S*)-4-benzyl-5-phenylprolinate (6g): CH_2Cl_2/MeOH (250:1) as eluent; yield 82% from **3b**; oil; $[\alpha]^{25}_D$ −3.4 (*c* = 0.45, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–7.04 (m, 10H), 4.19 (c, 2H, *J* = 7.1 Hz), 4.02–3.94 (m, 2H), 2.80 (dd, 1H, *J* = 3.0 and 12.7 Hz), 2.46–2.21 (m, 4H), 1.75–1.59 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.9, 143.0, 140.4, 128.6 (2C), 128.4 (2C), 128.3 (2C), 127.3 (2C), 127.2, 125.9, 67.9, 61.0, 58.4, 49.9, 38.1, 36.1, 14.2; HRMS (*m/z*): calcd for $C_{20}H_{23}NO_2$ (M^+) 309.1729, found 309.1729.

Ethyl (2*S*,4*S*,5*R*)-4-benzyl-5-butylprolinate (6h): AcOEt/Hexane (1:1) as eluent; yield 79% from **3b**; oil; $[\alpha]^{25}_D$ +39.8 (*c* = 0.6, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.15 (m, 5H), 4.19 (c, 2H, *J* = 7.1 Hz), 3.78 (t, 1H, *J* = 8.8 Hz), 3.45 (br s, 1H), 2.95–2.83 (m, 2H), 2.42 (dd, 1H, *J* = 9.8 and 13.5 Hz), 2.31–2.16 (m, 1H), 2.10–1.90 (m, 1H), 1.65–1.45 (m, 1H), 1.42–1.20 (m, 6H), 1.28 (t, 3H, *J* = 7.1 Hz), 0.91 (br t, 3H); ^{13}C NMR ($CDCl_3$) δ 175.7, 140.6, 128.7 (2C), 128.3 (2C), 125.9, 63.4, 61.0, 58.0, 46.7, 39.3, 36.4, 34.9, 29.4, 22.8,

(21) These experimental conditions (time, temperature, and number of equivalents of each reagent) have been optimized to get both the best chemical yields and stereoselectivities.

(22) Unfortunately, prolinates **6a–j** proved not to be stable enough to get their combustion analyses.

14.1, 14.0; HRMS (*m/z*): calcd for $C_{18}H_{27}NO_2$ (M^+) 289.2042, found 289.2044.

Ethyl (2*S*,4*R*,5*S*)-4-benzyl-5-phenylprolinate (6i): CH_2Cl_2/MeOH (250:1) as eluent; yield 84% from **3c**; oil; $[\alpha]^{25}_D$ −44.4 (*c* = 1.1, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46−6.92 (m, 10H), 4.62 (d, 1H, *J* = 6.6 Hz), 4.16 (c, 2H, *J* = 7.1 Hz), 4.09 (dd, 1H, *J* = 5.6 and 8.5 Hz), 2.69−2.52 (m, 1H), 2.30 (dd, 1H, *J* = 4.3 and 13.8 Hz), 2.18−1.86 (m, 3H), 1.24 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2, 141.8, 141.0, 128.8 (2C), 128.2 (2C), 128.1 (2C), 127.3 (2C), 126.8, 125.7, 64.7, 61.0, 58.0, 44.4, 35.8, 34.1, 14.2; HRMS (*m/z*): calcd for $C_{20}H_{23}NO_2$ (M^+) 309.1729, found 309.1720.

Ethyl (2*S*,4*R*,5*R*)-4-benzyl-5-butylprolinate (6j): AcOEt/Hexane (1:1) as eluent; yield 74% from **3c**; oil; $[\alpha]^{25}_D$ = −19.7 (*c* = 1.0, $CHCl_3$); IR (film) 3350, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31−7.13 (m, 5H), 4.12 (c, 2H, *J* = 7.1 Hz), 3.85 (dd, 1H, *J* = 6.7 and 8.7 Hz), 3.27−3.22 (m, 1H), 2.80 (dd, 1H, *J* = 10.4 and 19.4 Hz), 2.44−2.27 (m, 2H), 2.11 (br s, 1H), 2.01−1.88 (m, 1H), 1.82−1.69 (m, 1H), 1.44−1.26 (m, 6H), 1.20 (t, 3H, *J* = 7.1 Hz), 0.90 (br t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 176.1, 141.1, 128.9 (2C), 128.3 (2C), 125.8, 61.2, 60.9, 57.3, 42.6, 34.4, 34.3, 30.7, 29.5, 22.9, 14.2, 14.1; HRMS (*m/z*): calcd for $C_{18}H_{27}NO_2$ (M^+) 289.2042, found 289.2041.

(2′*S*)-2′-Octyl (2*S*,4*S*,5*R*)-4-Benzyl-5-butylprolinate (8). Proline **6h** (1 equiv) in (*S*)-2-octanol (100 equiv) saturated with HCl gas was heated to 100−120 °C for 0.5 h. The solvent was evaporated under a stream of nitrogen, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure:[23] ^1H NMR (C_6D_6) δ 7.19−7.00 (m, 5H), 5.11−4.94 (m, 1H), 3.78 (t, 1H, *J* = 7.7 Hz), 2.91−2.84 (m, 1H), 2.69 (dd, 1H, *J* = 5.2 and 13.4 Hz), 2.26 (dd, 1H, *J* = 8.6 and 13.4 Hz), 2.20−2.06 (m, 1H), 1.95−1.76 (m, 1H), 1.69−1.55 (m, 1H), 1.50−1.19 (m, 16H), 1.07 (d, 3H, *J* = 6.3 Hz), 0.89 (2t, 6H, *J* = 6.3 Hz).

(2′*S*)-2′-Octyl (2*S*,4*R*,5*R*)-4-Benzyl-5-butylprolinate (9). The procedure was as it was described for **8** from **6j**: ^1H NMR (C_6D_6) δ 7.19−6.98 (m, 5H), 5.05−4.92 (m, 1H), 3.93 (dd, 1H, *J* = 6.4 and 8.5 Hz), 3.26−3.16 (m, 1H), 2.67 (dd, 1H, *J* = 4.2 and 12.9 Hz), 2.36 (dd, 1H, *J* = 10.9 and 12.9 Hz), 2.27−2.13 (m, 1H), 2.05−1.80 (m, 2H), 1.49−1.09 (m, 16H), 1.05 (d, 3H, *J* = 6.2 Hz), 0.91 (t, 3H, *J* = 6.5 Hz), 0.87 (t, 3H, *J* = 6.9 Hz).

(2*S*,5*S*)-Pyrrolidine-2,5-dicarboxylic acid (10) was obtained following the standard oxidation procedure:[24] $[\alpha]^{25}_D$ = −110 (*c* = 1.0, H_2O) (lit.[19] −112 (*c* = 1.0, H_2O)); ^1H NMR (D_2O) δ 4.30 (br t, 2H, *J* = 7.0 Hz), 2.40−2.20 (m, 2H), 2.18−1.98 (m, 2H); ^{13}C NMR (D_2O) δ 172.8 (2C), 61.0 (2C), 28.4 (2C).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all compounds lacking elemental analyses (35 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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