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Diastereocontrolled Synthesis of Enantioenriched 3,4-Disubstituted β-Prolines

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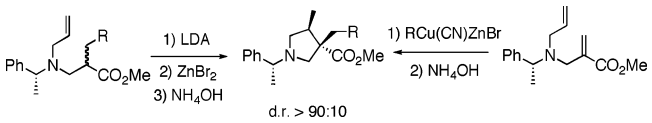

Enantioenriched 3,4-disubstituted β-prolines have been prepared with a high diastereocontrol through a carbometalation reaction or through a domino Michael addition/carbometalation reaction.

Introduction

Oligo-(β-aminoacids), also known as β-peptides, have raised considerable interest[1] over the past decade. These oligomers have shown enhanced resistance toward hydrolysis by proteases and greater conformational stability than the most widely known α-peptides. These interesting properties have led to numerous synthetic studies[2] toward new and efficient preparations of their building blocks, β-amino acids. Among the latter, β-proline ((*S*)-pyrrolidine-3-carboxylic acid) has been shown to be an interesting synthetic target: oligomers of β-proline have been found to possess a rigid secondary structure[3,4] and endomorphin-1 analogues containing β-proline are μ-opioid receptor agonists and display an enhanced enzymatic hydrolysis resistance.[5] Whereas several enantioselective syntheses of β-proline itself are reported,[3,6] few studies have been devoted to the stereoselective and enantioselective synthesis[7] of 4-substituted β-prolines (mainly through enantioselective [2 + 3] azomethine ylide cycloadditions)[8] and, to the best of our knowledge, even fewer[9] to 3,4-disubstituted β-prolines. We would like to report our results concerning the diastereoselective synthesis of enantiopure 3-substituted and 3,4-disubstituted β-prolines.

Results and Discussion

Enantiopure β-Proline through Carbocyclization of β-*N*-Allyl Amino Ester Zinc Enolates. We have shown recently[10] that 3,4-disubstituted 3-carbomethoxypyrrolidines can be obtained in good yields from zinc enolates derived from β-*N*-allyl amino esters **1**. The carbometalation reaction observed from these enolates has been shown to involve a C-centered zinc

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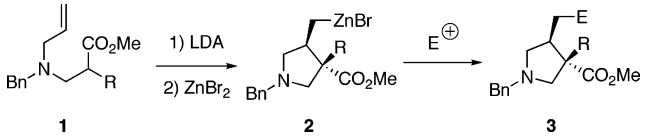
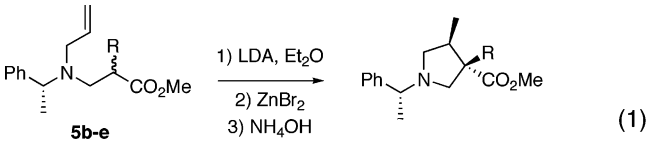
SCHEME 1. Diastereoselective Synthesis of 3,3,4-Trisubstituted Pyrrolidines



enolate (Scheme 1)[11] and to lead highly stereoselectively to the corresponding metalated pyrrolidines **2** that react further with various electrophiles to give diversely substituted pyrrolidines **3** in good to excellent yields (Scheme 1).

An enantioselective version of this carbometalation reaction could thus be envisioned by using a chiral auxiliary either on the ester moiety or on the nitrogen atom. In the related carbocyclization reaction of α-amino zinc enolates, attempts to induce stereoselectivity by means of a chiral ester (menthyl or phenylmenthyl) or chiral amide (camphorsultam) have been reported[12] to be unsuccessful (limited diastereoselectivities or lack of reactivity). By contrast, very high levels of stereoinduction have been achieved using the inexpensive, readily available (in both enantiomeric forms) α-methylbenzylamino group as stereoinductor.[12,13] We have thus examined the behavior of enantiopure *β-N*-allylamino esters **5a**−**e** (Scheme 2) as starting materials for the carbocyclization reaction. **5b**−**e** were easily prepared, as a mixture of two diastereomers, through alkylation of the parent unsubstituted *β-N*-allylamino ester **5a**.

We first studied the behavior of the zinc enolate derived from *β-N*-allylamino ester **5a** which was prepared by deprotonation with LDA followed by zinc salt addition at −60 °C. Upon warming, when $ZnBr_2$ was used, *β*-elimination occurred and only amine **4** was recovered after aqueous workup. This side reaction could be partially avoided by performing the transmetalation step with ZnI_2 (instead of $ZnBr_2$). Under these conditions, a smooth carbocyclization reaction took place upon warming, affording after aqueous workup pyrrolidine **6a** (Scheme 3) in fair yield and to our delight in diastereomerically pure form (based on ^1H and ^{13}C NMR of the crude reaction product).

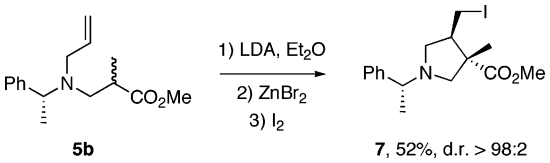


(1)

R = Me: **6b**, 77%, d.r. > 98:2
R = *n*-Pentyl: **6c**, 74%, d.r. > 98:2
R = Allyl: **6d**, 78%, d.r. > 98:2
R = Bn: **6e**, 59%, d.r. > 98:2

By contrast, *β*-elimination was not a problem starting from the substituted *β-N*-allylamino esters **5b**−**e**. Using $ZnBr_2$, we did not detect the free amine and we obtained the corresponding pyrrolidines after aqueous workup in good yields and as diastereo- and enantiomerically pure compounds (eq 1). These results closely parallel our findings on the benzylamino series (zinc enolates derived from **1**) where *β*-elimination was only detected in the case of the unsubstituted zinc enolates (derived from **1** with R = H in Scheme 1).[10] We attribute this to a higher reactivity correlated with a higher substitution pattern.[14]

One of the most interesting features of the carbocyclization of zinc enolates is the resulting organometallic species that can be further functionalized with various electrophiles. The pyrrolidinylmethylzinc species obtained after the carbocyclization reaction from *β-N*-allylamino ester **5b** could be quenched with iodine (eq 2), and the resulting iodide **7** could be isolated in fair yield and as a diastereomerically pure compound.



(2)

The sense of the stereoinduction was determined through chemical correlation in the case of **6b** (Scheme 4). Cleavage of the chiral auxiliary was achieved through hydrogenolysis, and the amino moiety was benzylated under standard conditions to afford chiral pyrrolidine **8** in 74% overall yield. This pyrrolidine was spectroscopically (^1H and ^{13}C NMR) identical to the trans racemic pyrrolidine we reported previously,[10] and the trans relationship between the carbomethoxy group in C-3 and the C-4 methyl group was thus secured. The ester moiety was reduced to alcohol **9**. Reduction of the corresponding mesylate into a methyl group proved to be rather difficult but was finally achieved with triethylborohydride to give (−)-**10** in 41% yield. The enantiomeric compound has been reported[15] previously with a +11.1 optical rotation. We could thus determine the absolute configuration in C-4 and deduce the sense of the stereoinduction in **6b**. The absolute configurations in **6a** and **6c**−**e** were assumed to be identical to that of **6b**.

Having in hand an efficient methodology for the preparation of enantiopure 3,4-disubstituted *β*-proline esters, we turned our attention to the possible stereoselective formation of two contiguous quaternary carbon centers. Deprotonation of *β-N*-methallyl aminoester **11** (Scheme 5) followed by transmetalation with zinc iodide afforded after carbocyclization and hydrolysis the corresponding tetrasubstituted pyrrolidine **12** in 63% isolated yield as a mixture of two diastereomers (dr = 86:14). Iodolysis of the pyrrolidinylzinc intermediate gave the corresponding iodopyrrolidine **13** with a moderate stereoselectivity as a mixture of four diastereomers (dr = 70:11:10:9). Unfortunately, the major diastereomer could not be isolated by flash chromatography, and only a mixture of two diastereomers could be obtained (43%, dr = 90:10). The absolute configurations of the two quaternary carbon centers of this major diastereomer could thus not be determined unambiguously. They are assumed to be as depicted in Scheme 5 by analogy with the stereochemical behavior of *N*-allyl esters reported above.

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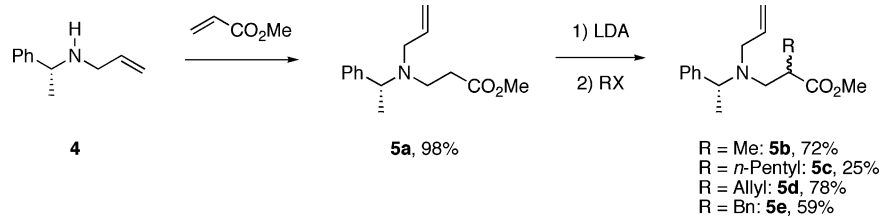
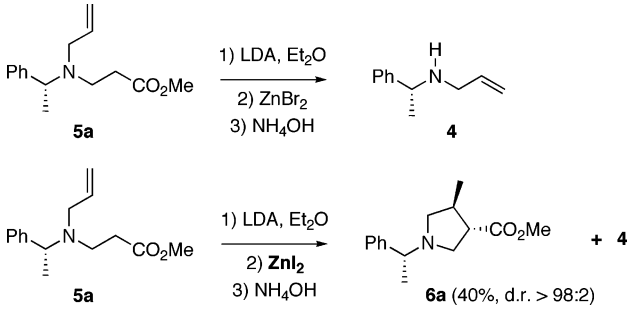
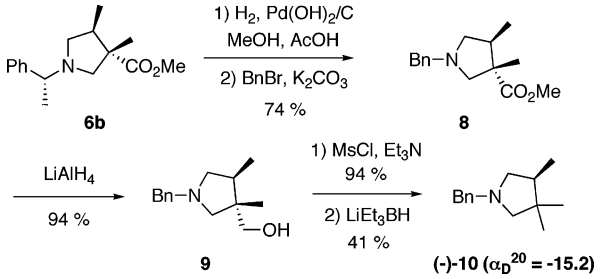
SCHEME 2. Preparation of β-Amino Esters 5a−e



SCHEME 3. Reaction of Zinc Enolate Derived from β-*N*-Allylamino Ester 5a

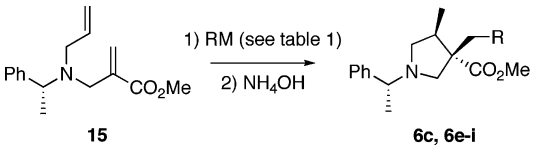


SCHEME 4. Chemical Correlation for Pyrrolidine 6b



Enantiopure β-Proline through Domino Michael Addition/Carbometalation Reaction. We have also shown recently[16] that disubstituted pyrrolidines can be obtained through a domino Michael addition/carbometalation process starting from the β-*N*-allyl amino enoate **14** (Scheme 6). The diastereoselectivity is excellent, and the resulting metalated carbomethoxypyrrolidine intermediates can be further functionalized with various electrophiles.

Following our good results in the enantioselective carbocyclization of zinc enolates depicted above, we have thus examined the possible stereocontrol exerted by the α-methylbenzylamino group in our domino reaction by using acrylic ester **15** (eq 3). Our first trials were made with *n*-BuCu(CN)ZnBr. As reported previously in this type of domino reaction, a strong salt effect was observed on the relative stereoselectivity between the two newly formed carbon centers. Moreover, we also noticed a strong impact of the presence and the nature of salts on the chirality transfer from the chiral auxiliary (eq 3, Table 1). As a general trend, we noticed that the conditions leading to a good stereocontrol in the achiral version also resulted in good chirality transfer. Our best results were obtained using organocopper/zinc mixed reagents prepared from 3 equiv of zinc salts and salt-free organolithium compounds (Table 1, entry 3). To our delight, these conditions showed to be general and the addition/cyclization of several alkyl groups was performed with high stereoselectivity (Table 1, entries 3−5). The reasons for this strong salt effect still remain unclear. Indeed, no zinc salt addition was necessary in the reaction of sp^2 organometallics (phenyl, cyclohexenyl, and 2-propenyl), and the corresponding pyrrolidines were obtained with high diastereoselectivity (Table 1, entries 6−8). The compound obtained after *n*-butyl (respectively, phenyl) group addition was identical to compound **6c** (respectively, **6e**) obtained previously (see above) from **5c** (respectively, **5e**).



(3)

Diastereoselectivity in the Carbometalation Reaction. In the carbometalation of zinc enolates derived from β-aminoesters **1**, the diastereoselectivity has been previously explained[11] by a transition state involving a C-metalated zinc enolate **16** (Figure 1). Due to an extra chelation with zinc salts between the nitrogen atom and the carbomethoxy group, the latter adopts a pseudo-axial position leading to the trans substituted pyrrolidine. In the case of zinc enolates **5a**−**e** bearing an α-methylbenzylamino group, the trans relative configuration between C-3 and C-4 centers tends to prove that here again a N−Zn−O bridge is being formed in the corresponding transition states.

However, in this case the nitrogen becomes stereogenic as a result of complexation to the zinc salt. Such diastereoselective complexation to nitrogen has already been reported[17] and involved in diastereoselective transformations. A stereodifferentiation (whatever its origin) could be imagined at this stage, and transition state **17** could be favored over **18** (Figure 1). To gain further insight in the role played by this chelation and to determine whether the complexation is diastereoselective or not, we thus examined spectroscopically the reaction of unsubstituted starting material **5a** (as a model of the lithium enolate) with zinc salts in various solvents. Addition of ZnI_2 (5 equiv) to β-amino ester **5a** in acetone-d_6 resulted in a rapid (15 min) formation of a complex that could be observed by ^{1}H NMR. However, two sets of signals were detected (in a 58:42 ratio), attributable to the two possible diastereomers. Addition of ZnI_2 (5 equiv) to **5a** in ether resulted in the rapid precipitation of a solid that, after filtration and drying, gave also two sets of signals in acetone-d_6, with a diastereomeric ratio of 55:45. These NMR experiments show that the formation of a complex indeed takes

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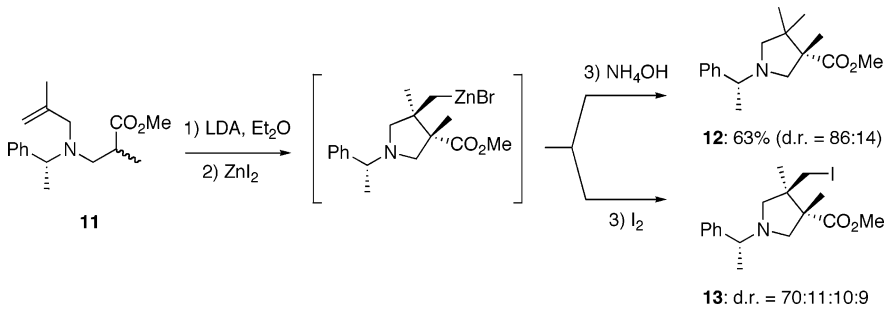
SCHEME 5. Formation of Two Consecutive Quaternary Carbon Centers



SCHEME 6. Diastereoselective Domino 1,4-Addition/Carbocyclization Reaction

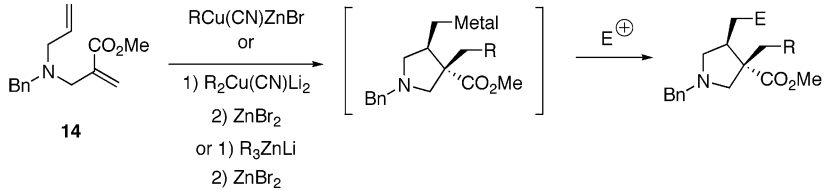


TABLE 1. Diastereoselectivity in the Domino Michael Addition/Carbocyclization Reaction with Organocopper Zinc Mixed Species

entry	RM	additive	product	dr[a]	yield (%)[b]
1	*n*-BuCu(CN)ZnBr-LiBr[c]	$ZnBr_2$ (1 equiv)	**6c**	62:22:16	n.d.
2	*n*-BuCu(CN)ZnBr-LiBr[c]	$ZnBr_2$ (2 equiv), LiBr (1 equiv)	**6c**	49:29:22	n.d.
3	*n*-BuCu(CN)ZnBr-LiBr[c]	$ZnBr_2$ (3 equiv)	**6c**	>95:5	57
4	EtCu(CN)ZnBr-LiBr[c]	$ZnBr_2$ (3 equiv)	**6f**	91:9	62
5	*n*-HexCu(CN)ZnBr-LiBr[c]	$ZnBr_2$ (3 equiv)	**6g**	>95:5	54
6	PhCu(CN)ZnBr-3LiBr[d]		**6e**	>95:5	57
7	1-cyclohexenylCu(CN)ZnBr-3LiBr[d]		**6h**	>95:5	51
8	1-propenylCu(CN)ZnBr-3LiBr[d]		**6i**	>95:5	58

[a] Determined by ^{1}H NMR on the crude reaction mixture. [b] Isolated yield. [c] Prepared from salt-free organolithium species, CuCN and $ZnBr_2$. [d] The organolithium species was prepared through I−Li exchange with *t*-BuLi (2 equiv).

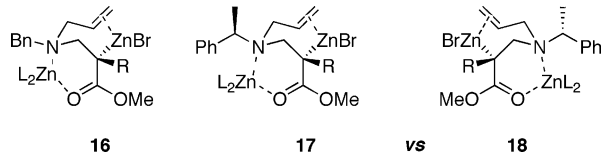
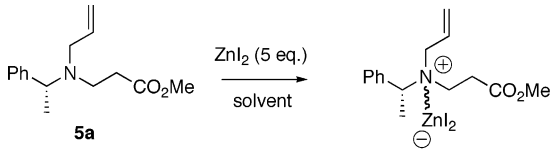


FIGURE 1. Possible intermediates in the carbocyclization reaction from zinc enolates.

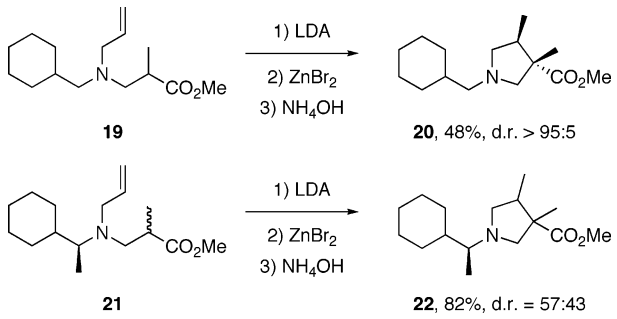
place, but that the α-methylbenzyl group is not capable of inducing diastereoselective complexation of ZnI_2 to the adjacent nitrogen (eq 4). Although these NMR experiments have been performed on aminoester **5a** and not on its lithium enolate, the excellent diastereoselectivity observed in the carbocyclization process does not seem compatible with the stereorandom formation of the complex **5a**−ZnI_2.



(4)

We next turned our attention to the study of the influence of structural parameters on diastereoselectivity and in particular to the role played by the aromatic ring. We thus examined the diastereoselectivity in the reactions starting from the cyclohexyl and (*S*)-α-methylcyclohexyl analogues **19** and **21** (Scheme 7).

SCHEME 7. Carbocyclizations Starting from Aminoesters 19 and 21



Starting from β-amino ester **19**, the carbocyclization reaction gave the corresponding pyrrolidine **20** with an excellent diastereoselectivity (>95:5), albeit in moderate yield. This dr, similar to those reported from **1**, shows that the simple diastereoselection of the carbocyclization step (i.e., the trans relationship between C-3 and C-4) is not related to the aromaticity of the nitrogen substituent. This simple diastereoselection arises from the intrinsic nature of the transition state involving a C-centered zinc enolate (**16** in Figure 1) which *does not involve* the aromatic moiety.

By contrast, the carbocyclization reaction starting from **21** gave the corresponding pyrrolidine **22** in good yield but with very poor stereoselectivity (dr = 58:42). It should be noted that, although the starting material **21** is engaged as a mixture of two diastereomers, the stereocenter α to the ester moiety is lost

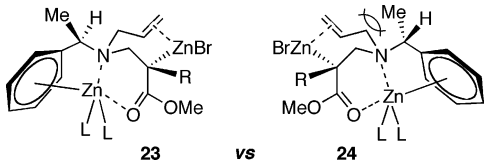


FIGURE 2. Origin of the chirality transfer in the carbocyclization reaction from zinc enolates.

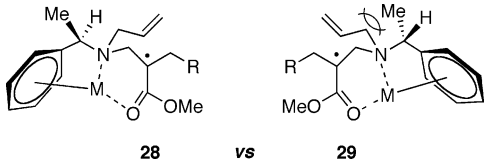


FIGURE 3. Origin of the chirality transfer for the radical cyclization in the domino reaction.

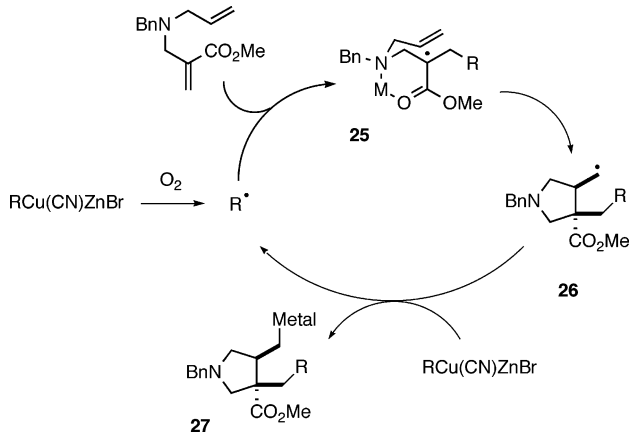
during the deprotonation step, and the resulting zinc enolate is thus enantiomerically pure. Two new stereocenters are created in this carbocyclization step, and four possible diastereomers can be obtained. Only two were observed by ^{1}H NMR, but unfortunately we could not ascertain the relative stereochemistries of the two newly formed stereocenters. However, this result compared to the excellent diastereoselectivity obtained from **19** strongly suggests that the simple diastereoselection (i.e., the trans relationship between C-3 and C-4) is maintained in the cyclization step, but the enantioselectivity transfer is almost inexistent when a cyclohexyl is used instead of a phenyl moiety. The aromaticity thus seems to be strongly involved in the enantioselectivity transfer between the α-methylbenzyl group and the two newly formed stereogenic centers C-3 and C-4.

Zinc(II)−Ar interactions have been largely involved[13c,18] in organozinc chemistry and can be invoked to explain the diastereoselectivity of the carbocyclization reaction. An interaction between the aromatic moiety and the zinc salt chelated by the carbomethoxy and the nitrogen moieties would lead to diastereomeric transition states **23** and **24** (Figure 2). The steric interaction between the methyl group and the allyl moiety in transition state **24** makes it less favorable than **23** which gives the observed products.

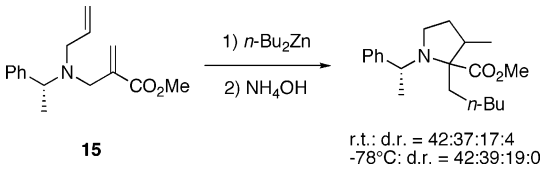
Diastereoselectivity in the Domino Reaction. We have recently demonstrated that our domino reaction follows a radical/polar crossover mechanism.[19] The cyclization step occurs through a radical pathway (Scheme 8), and the diastereoselectivity has been explained by the cyclization of the radical intermediate **25** obtained after radical Michael addition. Pyrrolidinylmethyl radical **26** is then obtained, giving the observed trans organometallic species **27** after reduction.

In such a mechanism, the high diastereoselectivity observed in the case of copper−zinc mixed reagents when using an α-methylbenzyl group instead of a benzyl group can be again explained by an Ar−metal interaction (Figure 3). The radical

SCHEME 8. Radical/Polar Mechanism of the Domino Reaction



SCHEME 9. Domino Reaction on Michael Acceptor 15



intermediate **28** (similar to organometallic intermediate **23** in Figure 2) should be favored over intermediate **29** (similar to organometallic intermediate **24**). The bases of the chirality transfer are thus the same in both polar and radical/polar mechanisms, although the enantioselectivity and the diastereoselectivity of both reactions are decided through the reaction of a different intermediate (organometallic or radical species).

We have shown recently that when dialkylzincs are used instead of copper−zinc mixed reagents in the domino reaction, it still follows a radical/polar mechanism.[19] But in this case, presumably due to the lower Lewis acidity of dialkylzincs, no chelation to the carbomethoxy moiety is observed, and the latter adopts a pseudoequatorial position in the radical intermediate leading to the *cis* product. It was thus interesting to test the possible chirality transfer by using the α-methylbenzyl group as chiral auxiliary in such a reaction. Unfortunately, when performed with *n*-Bu_2Zn at room temperature on chiral Michael acceptor **15**, the domino reaction showed no chirality transfer (Scheme 9), as a mixture of the four possible diastereomers was obtained. A similar result was observed at a lower temperature. Although this result precludes the enantioselective synthesis of *cis* 3,4-disubstituted *β*-prolines by using the starting material **15**, it is in agreement with our hypothesis of a direct interaction between the α-methybenzyl group, a metal salt, and the carbomethoxy moiety.

Conclusion

3,4-Disubstituted *β*-prolines can be easily prepared in a stereoselective and enantioselective fashion through a carbometalation reaction or a domino radical/polar crossover reaction. The α-methylbenzylamino auxiliary has proven to be highly efficient in such reactions, allowing the possibility to control the enantioselective formation of two contiguous quaternary carbon centers. A domino version of this carbometalation reaction has been also reported. The mechanism of this reaction (a radical/polar crossover mechanism) is entirely different from

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(19) (a) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043−4046. (b) Denes, F.; Perez-Luna, A.; Cutri, S.; Chemla, F. *Chem.−Eur. J.* **2006**, *12*, 6506−6513.

the one of the carbometalation reaction. However, the stereo- and enantiocontrol is still excellent and allows the enantioselective preparation of diversely substituted β-prolines in high yield.

Experimental Section

(1*R*)-Methyl 3-(*N*-Allyl-*N*-(1-phenylethyl)amino)-propanoate 5a. To a stirred solution of amine **4** (8.05 g, 50 mmol) in MeOH (120 mL) was added methyl acrylate (8.60 g, 100 mmol, 2 equiv) at room temperature. The solution was stirred at room temperature until completion (72 h). The solvent and the excess of the methyl acrylate were removed under reduced pressure to give the title compound (12.1 g, 98%), which was used for further transformation without purification. $[\alpha]^{20}_D$ +17.1 (*c* 1.17, $CHCl_3$); IR (neat): 3062, 2973, 2814, 1736, 1435, 1194, 915, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, d, *J* = 7.1 Hz), 2.44 (2H, t, *J* = 7.4 Hz), 2.76 (1H, dt, *J* = 13.2, 7.4 Hz), 2.88 (1H, dt, *J* = 13.2, 7.4 Hz), 3.02 (1H, dd, *J* = 14.2, 6.1 Hz), 3.12 (1H, dd, *J* = 14.2, 6.6 Hz), 3.64 (3H, s), 3.86 (1H, q, *J* = 6.8 Hz), 5.08−5.18 (2H, m), 5.81 (1H, ddt, *J* = 17.3, 10.2, 6.6 Hz), 7.20−7.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 33.3, 45.5, 51.5, 53.3, 59.0, 116.7, 126.8, 127.6 (2C), 128.1 (2C), 136.7, 143.9, 173.2; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.79; H, 8.68; N, 5.64.

General Procedure for Alkylation. To a solution of LDA (12 mmol) in THF (16 mL) was added dropwise a solution of ester (10 mmol) in THF (10 mL) at −78 °C. The solution was stirred at −78 °C for 1 h. A solution of alkyl halide (12 mmol) in THF (10 mL) was added slowly at −78 °C. The solution was stirred at −78 °C for 2 h. The cold bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with NH_4Cl/NH_3 (2:1). Et_2O (30 mL) was added, and the layers were separated, the aqueous one being extracted three times with Et_2O. The combined organic layers were washed with brine and dried over K_2CO_3, and the solvents were evaporated under reduced pressure.

(1′*R*)-Methyl 3-(*N*-Allyl-*N*-(1′-phenylethyl)amino)-2-methyl-propanoate 5b. 5b was prepared according to the general procedure from **5a** (2.47 g, 10 mmol) and methyl iodide (747 μL, 12 mmol). Purification by flash chromatography (cyclohexane/ethyl acetate = 90:10) afforded the title compound (1.88 g, 72%, dr = 63:37) as a colorless oil. IR ($CHCl_3$): 2973, 2814, 1735, 1493, 1195, 1155, 915, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.08 (3H-major, d, *J* = 6.8 Hz), 1.14 (3H-minor, d, *J* = 6.8 Hz), 1.35 (3H-minor, d, *J* = 6.8 Hz), 1.36 (3H-major, d, *J* = 7.1 Hz), 2.34 (1H-major, dd, *J* = 12.6, 6.6 Hz), 2.52 (1H-minor, dd, *J* = 11.9, 5.4 Hz), 2.64−2.78 (1H and 1H-minor, m), 2.85 (1H-major, dd, *J* = 12.9, 8.6 Hz), 2.97−3.15 (2H, m), 3.63 (3H-minor, s), 3.69 (3H-major, s), 3.92 (1H-major, q, *J* = 6.8 Hz), 3.94 (1H-minor, q, *J* = 6.8 Hz), 5.15−5.20 (2H, m), 5.65−5.85 (1H, m), 7.21−7.30 (1H, m), 7.30−7.36 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.2, 15.8, 39.2, 39.4, 51.4, 53.3, 53.5, 53.7, 58.4, 58.7, 116.5, 126.6, 126.7, 127.8, 127.9, 128.0, 137.0, 137.1, 143.1, 143.6, 176.5, 176.6; Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.46; H, 8.89; N, 5.39.

(1′*R*)-Methyl 2-[*N*-Allyl-*N*-(1′-phenylethyl)-aminomethyl]-heptanoate 5c. 5c was prepared according to the general procedure from **5a** (2.47 g, 10 mmol) and bromopentane (1.81 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (cyclohexane/ethyl acetate = 90:10) afforded the title compound (793 mg, 25%, dr = 59:41) as a colorless oil. IR ($CHCl_3$): 2928, 2857, 1736, 1493, 1372, 1201, 1165, 914, 826, 735, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3H, m), 1.20−1.50 (11H, m), 2.33 (1H-major, dd, *J* = 12.3, 5.3 Hz), 2.53 (1H-minor, dd, *J* = 12.3, 5.3 Hz), 2.63 (1H, m), 2.74 (1H-minor, dd, *J* = 12.2, 9.3 Hz), 2.82 (1H-major, dd, *J* = 12.8, 9.5 Hz), 2.96 (1H-major, ddbr, *J* = 14.6, 6.6 Hz), 3.03 (2H-minor, d, *J* = 6.3 Hz), 3.14 (1H-major, ddbr, *J* = 14.6, 6.0 Hz), 3.64 (3H-minor, s), 3.70 (3H-major, s), 3.89 (1H-major, q, *J* = 6.9 Hz), 3.96 (1H-minor, q, *J* = 6.8 Hz), 5.08−5.18 (2H, m), 5.74−5.86 (1H, m), 7.21−7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 14.4, 16.6, 22.5, 27.1, 27.2, 30.3, 30.4, 31.7, 45.4, 45.7, 51.3, 52.3, 52.7, 53.1, 53.5, 57.9, 59.0, 116.5, 126.6, 126.7, 127.8, 127.9, 128.0, 137.0, 137.1, 142.8, 143.8, 176.1, 176.3; Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.31; H, 9.76; N, 4.48.

(1′*R*)-Methyl 2-[*N*-Allyl-*N*-(1′-phenylethyl)-aminomethyl]-pent-4-enoate 5d. 5d was prepared according to the general procedure from **5a** (2.47 g, 10 mmol) and allylbromide (885 μL, 12 mmol). Purification by flash chromatography (cyclohexane/ethyl acetate = 90:10) afforded the title compound (2.24 g, 78%, dr = 55:45) as a colorless oil. IR ($CHCl_3$): 3077, 2973, 2815, 1736, 1641, 1193, 914, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (3H-minor, d, *J* = 6.8 Hz), 1.36 (3H-major, d, *J* = 6.8 Hz), 2.22 (2H-major, m), 2.28 (2H-minor, m), 2.42 (1H-major, dd, *J* = 12.6, 5.8 Hz), 2.58 (1H-minor, m), 2.68−2.78 (1H and 1H-minor, m), 2.83 (1H-major, dd, *J* = 12.6, 9.0 Hz), 2.99 (1H-major, ddm, *J* = 14.4, 6.6 Hz), 3.04 (2H-minor, dbr, *J* = 6.1 Hz), 3.14 (1H-major, ddm, *J* = 14.4, 6.3 Hz), 3.64 (3H-minor, s), 3.69 (3H-major, s), 3.91 (1H-major, q, *J* = 6.8 Hz), 3.96 (1H-minor, q, *J* = 6.8 Hz), 4.96−5.20 (4H, m), 5.62−5.86 (2H, m), 7.21−7.35 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.7, 16.2, 34.4, 34.5, 45.1, 45.4, 51.3, 51.8, 52.1, 53.2, 53.4, 58.1, 58.9, 116.5, 116.6, 116.7, 126.6, 126.7, 127.8, 127.94, 127.96, 135.4, 135.5, 136.8, 137.0, 142.9, 143.6, 175.2, 175.4; Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.07; H, 8.91; N, 4.81.

(1′*R*)-Methyl 3-(*N*-Allyl-*N*-(1′-phenylethyl)amino)-2-benzyl-propanoate 5e. 5e was prepared according to the general procedure from **5a** (2.47 g, 10 mmol) and benzylbromide (2.05 g, 12 mmol). Purification by flash chromatography (cyclohexane/ethyl acetate = 90:10) afforded **5e** (1.99 g, 59%, dr = 61:39) as a colorless oil. IR ($CHCl_3$): 3026, 2971, 1735, 1202, 1159, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H-major, d, *J* = 6.8 Hz), 1.35 (3H-minor, d, *J* = 6.8 Hz), 2.45 (1H-minor, dd, *J* = 12.1, 4.9 Hz), 2.62 (1H-major, dd, *J* = 12.9, 5.8 Hz), 2.76−3.00 (4H and 1H-minor, m), 3.05 (2H-major, dbr, *J* = 6.3 Hz), 3.15 (1H-minor, dd, *J* = 14.4, 6.3 Hz), 3.56 (3H-major, s), 3.62 (3H-minor, s), 3.91 (1H-minor, q, *J* = 6.8 Hz), 3.95 (1H-major, q, *J* = 6.8 Hz), 5.09−5.16 (2H, m), 5.80 (1H, m), 7.12−7.35 (10H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.8, 16.4, 36.5, 47.5, 47.8, 51.4, 52.2, 52.5, 53.3, 53.5, 58.2, 59.0, 116.8, 126.3, 126.7, 126.8, 127.8, 127.9, 128.0, 128.4, 128.7, 136.8, 136.9, 139.5, 142.8, 143.5, 175.3, 175.4; Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.26; H, 8.21; N, 4.06.

(1′*R*,3*S*,4*S*)-Methyl 4-Methyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6a. To a stirred solution of diisopropylamine (0.8 mL, 5.7 mmol) in Et_2O (20 mL) was added *n*-BuLi (2.2 mL, 2.2 N in hexanes, 4.8 mmol) at −70 °C. After being stirred at −70 °C for 30 min and then at 0 °C for an additional 30 min, the solution was cooled at −78 °C. A solution of ester **5a** (989 mg, 4 mmol) in Et_2O (5 mL) was then added, and the reaction mixture was stirred at −78 °C for 1 h. An ethereal solution of zinc iodide (20 mL, 1 N in Et_2O, 20 mmol) was added dropwise at −70 °C, and the reaction mixture was allowed to warm to room temperature. The biphasic mixture was stirred at room temperature for 20 h. The reaction was hydrolyzed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, and the aqueous one was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (394 mg, 40%) as a pale yellow oil. $[\alpha]^{20}_D$ +17.1 (*c* 1.07, $CHCl_3$); IR (neat): 2967, 2780, 1734, 1452, 1434, 1162, 763, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (3H, d, *J* = 6.6 Hz), 1.34 (3H, d, *J* = 6.6 Hz), 2.22 (1H, dd, *J* = 9.2, 7.1 Hz), 2.37−2.49 (1H, m), 2.48−2.55 (1H, m), 2.65−2.69 (2H, m), 2.88 (1H, dd, *J* = 9.2, 6.1 Hz), 3.20 (1H, q, *J* = 6.6 Hz), 3.67 (3H, s),

7.21−7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 23.1, 36.6, 50.4, 51.8, 55.7, 60.5, 65.4, 127.0, 127.3 (2C), 128.3 (2C), 145.5, 175.2; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.78; H, 8.58; N, 5.54.

General Procedure for the Carbocyclization Reaction. To a stirred solution of diisopropylamine (1 mL, 7.1 mmol) in Et_2O (10 mL) was added *n*-BuLi (2.4 mL, 2.5 in hexanes, 6 mmol) at −70 °C. After being stirred at −70 °C for 30 min and then at 0 °C for an additional 30 min, the solution was cooled at −78 °C. A solution of ester (2 mmol) in Et_2O (5 mL) was then added, and the reaction mixture was stirred at −60 °C for 2 h. The cold bath was removed, and the ethereal solution of zinc bromide (6 mL, 1 N in Et_2O, 6 mmol) was added at −40 °C. The trouble mixture was stirred at room temperature for 4 h and hydrolyzed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, and the aqueous one was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were evaporated under reduced pressure.

(1′*R*,3*S*,4*S*)-Methyl 3,4-Dimethyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6b. 6b was prepared according to the general procedure from **5b** (522 mg, 2 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (402 g, 77%) as a pale yellow oil. $[\alpha]^{20}_D$ +28.9 (*c* 1.16, $CHCl_3$); IR (neat): 3025, 2971, 2932, 2874, 2780, 1732, 1452, 1209, 1124, 765, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, d, *J* = 7.1 Hz), 1.20 (3H, s), 1.34 (3H, d, *J* = 6.6 Hz), 2.15 (1H, t, *J* = 8.5 Hz), 2.27 (1H, d, *J* = 9.6 Hz), 2.55−2.64 (1H, m), 2.75 (1H, t, *J* = 8.5 Hz), 3.23 (1H, q, *J* = 6.6 Hz), 3.35 (1H, d, *J* = 9.6 Hz), 3.68 (3H, s), 7.21−7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.5, 23.2, 38.7, 50.2, 52.0, 59.6, 63.6, 65.4, 126.9, 127.3 (2C), 128.4 (2C), 145.7, 178.0; Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.52; H, 8.99; N, 5.35.

(1′*R*,3*S*,4*S*)-Methyl 4-Methyl-3-pentyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6c. 6c was prepared according to the general procedure from **5c** (634 mg, 2 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (469 mg, 74%) as a pale yellow oil. $[\alpha]^{20}_D$ +33.8 (*c* 1.03, $CHCl_3$); IR (neat): 2951, 2932, 2864, 2777, 1734, 1452, 1196, 1131, 764, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7.0 Hz), 1.00 (3H, d, *J* = 7.6 Hz), 1.03−1.22 (2H, m), 1.23−1.33 (4H, m), 1.36 (3H, d, *J* = 6.6 Hz), 1.45 (1H, dt, *J* = 12.4, 4.6 Hz), 1.72 (1H, dt, *J* = 12.4, 4.6 Hz), 2.02 (1H, t, *J* = 8.8 Hz), 2.23 (1H, d, *J* = 9.6 Hz), 2.39−2.49 (1H, m), 2.75 (1H, dd, *J* = 8.8, 7.3 Hz), 3.22 (1H, q, *J* = 6.6 Hz), 3.53 (1H, d, *J* = 9.6 Hz), 3.68 (3H, s), 7.18−7.23 (1H, m), 7.24−7.27 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.0, 22.5, 23.1, 25.1, 32.4, 32.9, 39.5, 51.7, 54.2, 59.9, 60.1, 65.4, 126.8, 127.1 (2C), 128.2 (2C), 145.8, 177.2; Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.53; H, 9.91; N, 4.45.

(1′*R*,3*S*,4*S*)-Methyl 3-Allyl-4-methyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6d. 6d was prepared according to the general procedure from **5d** (574 mg, 2 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (448 mg, 78%) as a pale yellow oil. $[\alpha]^{20}_D$ +35.9 (*c* 1.00, $CHCl_3$); IR (neat): 2970, 2776, 1729, 1452, 1207, 1130, 763, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = Hz), 1.33 (3H, d, *J* = 6.6 Hz), 2.11 (1H, t, *J* = 8.5 Hz), 2.22 (1H, dd, *J* = 13.7, 8.1 Hz), 2.32 (1H, d, *J* = 9.7 Hz), 2.47−2.52 (2H, m), 2.73 (1H, t, *J* = 8.5 Hz), 3.21 (1H, q, *J* = 6.4 Hz), 3.33 (1H, d, *J* = 9.7 Hz), 3.67 (3H, s), 4.99−5.06 (2H, m), 5.55−5.65 (1H, m), 7.20−7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 23.0, 37.1, 39.4, 51.6, 53.9, 59.4, 59.5, 65.2, 117.6, 126.7, 127.0 (2C), 128.1 (2C), 134.3, 145.4, 176.2; Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.21; H, 8.91; N, 4.73.

(1′*R*,3*S*,4*S*)-Methyl 3-Benzyl-4-methyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6e. 6e was prepared according to the general procedure from **5e** (674 mg, 2 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (398 mg, 59%) as a pale yellow oil. $[\alpha]^{20}_D$ +36.6 (*c* 1.15, $CHCl_3$); IR (neat): 3061, 2971, 2933, 2874, 2780, 1727, 1603, 1452, 1208, 1099, 765, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, d, *J* = 7.0 Hz), 1.39 (3H, d, *J* = 6.4 Hz), 2.37−2.43 (1H, m), 2.45 (1H, d, *J* = 10.1 Hz), 2.47−2.57 (1H, m), 2.81−2.84 (2H, m), 3.08 (1H, d, *J* = 10.1 Hz), 3.18 (1H, d, *J* = 13.1 Hz), 3.30 (1H, q, *J* = 6.4 Hz), 3.62 (3H, s), 7.07−7.09 (2H, m), 7.18−7.27 (4H, m), 7.31−7.36 (2H, m), 7.38−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.8, 37.8, 40.5, 51.5, 55.2, 58.4, 59.3, 65.3, 126.4, 126.9, 127.3 (2C), 128.1 (2C), 128.2 (2C), 129.6 (2C), 138.2, 145.4, 176.2; Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.32; H, 8.04; N, 4.07.

(3*S*,4*S*)-Methyl 4-(Iodomethyl)-3-methyl-1-((*R*)-1-phenylethyl)-pyrrolidine-3-carboxylate 7. Diisopropylamine (0.22 mL, 1.6 mmol) was added to *n*BuLi (2.3 M in hexanes, 0.63 mL, 1.45 mmol). Once the gummy mixture formed, Et_2O (2 mL) was added and the solution was cooled to −78 °C. An Et_2O (2 mL) solution of ester **5b** (130 mg, 0.50 mmol) was added dropwise, and the mixture was allowed to warm to −30 °C over 3 h before being cooled back to −60 °C. $ZnBr_2$ (1 M in Et_2O, 2.0 mL, 2.0 mmol) was added, and once a white suspension formed the cooling bath was removed. The biphasic mixture was stirred at room temperature (RT) for 16 h and then cooled to −20 °C. A THF (3 mL) solution of I_2 (509 mg, 2.0 mmol) was added dropwise, and the cooling bath was removed. The mixture was stirred at RT for 3 h and then hydrolyzed with a saturated aqueous solution of $Na_2S_2O_3$ (3 mL) followed by an aqueous solution of NH_4Cl/NH_4OH (2:1) (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (pentane/ether = 90:10) afforded the title compound (96 mg, 52%) as a colorless oil. $[\alpha]^{20}_D$ −13.5 (*c* 0.99, $CHCl_3$); IR (neat): 2970, 2780, 1729, 1491, 1452, 1371, 1259, 1109, 763, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, s), 1.30 (3H, d, *J* = 6.6 Hz), 2.40 (1H, d, *J* = 9.4 Hz), 2.50 (1H, dd, *J* = 9.4, 7.2 Hz), 2.91 (1H, m), 2.99 (1H, m), 3.04−3.11 (2H, m), 3.25 (1H, q, *J* = 6.6 Hz), 3.33 (1H, dd, *J* = 9.1, 4.4 Hz), 3.66 (3H, s), 7.20−7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.6, 18.4, 23.0, 46.8, 50.7, 52.3, 58.6, 63.9, 64.7, 127.0, 127.1 (2C), 128.3 (2C), 145.1, 176.5. HRMS calcd for $C_{16}H_{23}INO_2$ $[M - H]^+$: 388.0768. Found: 388.0766.

(1′*R*, 3*S*)-Methyl 1-(1′-Phenylethyl)-3,4,4-trimethylpyrrolidine-3-carboxylate 12. To a solution of LDA (1.6 mmol) in Et_2O (2 mL) was added dropwise an Et_2O (2 mL) solution of ester **11** (120 mg, 0.44 mmol) at −78 °C. Once the addition was completed, the mixture was allowed to warm to −30 °C over 3 h before being cooled to −60 °C. ZnI_2 (1 M in Et_2O, 1.8 mL, 1.8 mmol) was added, and once a white suspension formed the cooling bath was removed. The biphasic mixture was stirred at room temperature for 16 h and then hydrolyzed with an aqueous solution of NH_4Cl/NH_4OH (2:1) (4 mL). The aqueous layer was extracted with Et_2O (20 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate = 85:15) afforded the title compound (colorless oil, 76 mg, 63%) as an unseparated diastereomeric mixture (dr = 86:14). IR ($CHCl_3$): 2968, 2873, 1728, 1491, 1139, 1096, 762, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereoisomer): δ 1.00 (3H, s), 1.12 (3H, s), 1.30 (3H, s), 1.33 (3H, d, *J* = 6.6), 2.44 (1H, d, *J* = 9.9 Hz), 2.48 (1H, d, *J* = 8.8 Hz), 2.69 (1H, d, *J* = 8.8 Hz), 3.31 (1H, d, *J* = 9.9 Hz), 3.43 (1H, q, *J* = 6.8 Hz), 3.68 (3H, s), 7.20−7.30 (1H, m), 7.30−7.39 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereoisomer): 21.3, 23.3, 23.5, 25.6, 42.8, 51.3, 53.7, 61.7, 65.0, 65.3, 126.6, 127.2 (2C), 128.2 (2C), 146.3, 176.6; Anal. calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.06; H, 9.15; N, 4.91.

(1′*R*,3*S*,4*R*)-Methyl 3,4-Dimethyl-4-iodomethyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 13. To a solution of LDA (1.6 mmol) in Et_2O (2 mL) was added dropwise an Et_2O (2 mL) solution of ester **11** (120 mg, 0.44 mmol) at −78 °C. Once the addition was completed, the mixture was allowed to warm to −30 °C over

3 h before being cooled to −60 °C. ZnI_2 (1 M in Et_2O, 1.8 mL, 1.8 mmol) was added, and once a white suspension formed the cooling bath was removed. The biphasic mixture was stirred at room temperature for 16 h and then cooled to −50 °C. I_2 (509 mg, 2.0 mmol) in THF (3 mL) was added dropwise, and the cooling bath was removed. The mixture was stirred at RT for 4 h and then hydrolyzed with a saturated aqueous solution of $Na_2S_2O_3$ (3 mL) followed by an aqueous solution of NH_4Cl/NH_4OH (2:1) (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the crude (dr = 70:11:10:9) by flash chromatography (cyclohexane/ethyl acetate = 85:15) afforded the title compound (pale yellow oil, 74 mg, 43%) as an unseparated mixture of two diastereoisomers (dr = 90:10). IR ($CHCl_3$): 2969, 2815, 1727, 1491, 1452, 1373, 1286, 1211, 762, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major diastereoisomer): δ 1.15 (3H, s), 1.32 (3H, s), 1.35 (3H, d, J = 6.6 Hz), 2.51 (1H, d, J = 9.5 Hz), 2.60 (1H, d, J = 9.9 Hz), 3.06 (1H, d, J = 9.5 Hz), 3.24 (1H, d, J = 9.9 Hz), 3.40−3.47 (2H, m), 3.65−3.69 (4H, m), 7.20−7.30 (1H, m), 7.30−7.39 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereoisomer): δ 18.1, 21.0, 23.2, 24.9, 45.3, 51.7, 52.8, 61.9, 63.9, 64.5, 126.8, 127.1 (2C), 128.3 (2C), 145.5, 175.4; HRMS calcd for $C_{17}H_{25}INO_2$ $[M - H]^+$: 402.0930. Found: 402.0922.

General Procedure for the Domino Conjugate Addition/Cyclization with Zinc−Copper Mixed Reagents. To a suspension of copper cyanide (197 mg, 2.2 mmol) in Et_2O (10 mL) was added dropwise an ethereal solution of zinc bromide (2.2 or 8 mL, 1 M in Et_2O, 2.2 or 8 mmol, see text), followed by RLi (2.2 mmol) at −10 °C. The reaction mixture was stirred at 0 °C for 1 h, and a solution of **15** (2 mmol) in Et_2O was added dropwise at 0 °C. The cold bath was removed, and the biphasic mixture was stirred at room temperature for 1−12 h. The reaction was hydrolyzed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, and the aqueous one was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were evaporated under reduced pressure.

(1′*R*,3*S*,4*S*)-Methyl 4-Methyl-1-(1′-phenylethyl)-3-propylpyrrolidine-3-carboxylate 6f. 6f was prepared according to the general procedure from **15** (579 mg, 2 mmol) using an ethereal solution of zinc bromide (8.2 mL, 1 M in Et_2O, 8.2 mmol) and EtLi (1.60 mL, 1.26 M in Et_2O, 2.2 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (359 mg, 62%) as a pale yellow oil. $[\alpha]^{20}_D$ +33.9 (*c* 1.03, $CHCl_3$); IR (neat): 3025, 2959, 2932, 2872, 2777, 1732, 1452, 1130, 764, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz), 1.00 (3H, d, J = 7.1 Hz), 1.04−1.31 (2H, m), 1.36 (3H, d, J = 6.6 Hz), 1.38−1.47 (1H, m), 1.65−1.74 (1H, m), 1.96−2.02 (1H, m), 2.22 (1H, d, J = 9.6 Hz), 2.39−2.48 (1H, m), 2.75 (1H, dd, J = 8.9, 7.3 Hz), 3.21 (1H, q, J = 6.6 Hz), 3.54 (1H, d, J = 9.6 Hz), 3.69 (3H, s), 7.20−7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.7, 18.8, 23.1, 35.4, 39.5, 51.7, 54.2, 60.0, 60.2, 65.4, 126.8, 127.2 (2C), 128.2 (2C), 145.8, 177.3; Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.65; H, 9.55; N, 4.80.

(1′*R*,3*S*,4*S*)-Methyl 3-Heptyl-4-methyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6g. 6g was prepared according to the general procedure from **15** (519 mg, 2 mmol) using an ethereal solution of zinc bromide (8.2 mL, 1 M in Et_2O, 8.2 mmol) and HexLi (0.88 mL, 2.5 M in hexane, 2.2 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (373 mg, 54%) as a pale yellow oil. $[\alpha]^{20}_D$ +30.3 (*c* 1.07, $CHCl_3$); IR (neat): 3025, 2931, 2856, 2777, 1734, 1452, 1208, 1131, 764, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 6.9 Hz), 1.00 (3H, d, J = 7.1 Hz), 1.05−1.20 (2H, m), 1.25−1.32 (8H, m), 1.35 (3H, d, J = 6.5 Hz), 1.44 (1H, dt, J = 12.6, 4.5 Hz), 1.71 (1H, dt J = 12.6, 5.4 Hz), 2.00 (1H, t, J = 8.8 Hz), 2.22 (1H, d, J = 9.6 Hz), 2.38−2.48 (1H, m), 2.74 (1H, dd, J = 8.8, 7.3 Hz), 3.21 (1H, q, J = 6.5 Hz), 3.52 (1H, d, J = 9.6 Hz), 3.69 (3H, s), 7.20−7.23 (1H, m), 726−7.35 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.2, 22.7, 23.2, 25.5, 29.2, 30.2, 31.9, 33.1, 39.5, 51.8, 54.2, 60.0, 60.2, 65.4, 126.8, 127.2 (2C), 128.2 (2C), 145.8, 177.3; Anal. Calcd for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21; N, 4.05. Found: C, 76.46; H, 10.36; N, 4.06.

(1′*R*,3*S*,4*S*)-Methyl 3-(Cyclohex-1-enyl)methyl-4-methyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6h. 6h was prepared according to the general procedure from **15** (519 mg, 2 mmol) using an ethereal solution of zinc bromide (4 mL, 1 M in Et_2O, 4 mmol) and cyclohexenyllithium (2.26 mL, 1.77 M in Et_2O, 4 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (348 mg, 51%) as a pale yellow oil. $[\alpha]^{20}_D$ +38.1 (*c* 1.01, $CHCl_3$); IR (neat): 2932, 2835, 1730, 1452, 1203, 1100, 764, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (3H, d, J = 6.9 Hz), 1.36 (3H, d, J = 6.6 Hz), 1.43−1.57 (4H, m), 1.69−1.86 (2H, m), 1.93−2.00 (2H, broad s), 2.11−2.16 (2H, m), 2.36 (1H, d, J = 9.8 Hz), 2.36−2.43 (1H, m), 2.48 (1H, d, J = 13.9 Hz), 2.73 (1H, dd, J = 8.8, 7.9 Hz), 3.23 (1H, q, J = 6.6 Hz), 3.38 (1H, d, J = 9.8 Hz), 3.66 (3H, s), 5.40 (1H, broad s), 7.20−7.23 (1H, m), 7.27−7.31 (2H, m), 7.32−7.36 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 22.2, 23.0, 23.1, 25.4, 28.9, 40.8, 41.0, 51.6, 53.3, 59.2, 59.5, 65.5, 124.5, 126.7, 127.2 (2C), 128.1 (2C), 134.4, 145.7, 177.2; Anal. Calcd for $C_{22}H_{31}NO$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.33; H, 9.18; N, 4.03.

(1′*R*,3*S*,4*S*)-Methyl 4-Methyl-3-(2-methylallyl)-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate 6i. 6i was prepared according to the general procedure from **15** (519 mg, 2 mmol) using an ethereal solution of zinc bromide (4 mL, 1 M in Et_2O, 4 mmol) and isopropenyllithium (3.51 mL, 1.14 M in Et_2O, 4 mmol). Purification by flash chromatography (cyclohexane/AcOEt = 80:20) afforded the title compound (350 mg, 58%) as a pale yellow oil. $[\alpha]^{20}_D$ +38.7 (*c* 1.10, $CHCl_3$); IR (neat): 3074, 2970, 2932, 2779, 1731, 1452, 1199, 764, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (3H, d, J = 7.1 Hz), 1.36 (3H, d, J = 6.6 Hz), 1.64 (3H, s), 2.09 (1H, m), 2.21 (1H, d, J = 14.2 Hz), 2.36 (1H, d, J = 9.9 Hz), 2.43 (1H, m), 2.56 (1H, d, J = 14.2 Hz), 2.75 (1H, dd, J = 9.1, 7.3 Hz), 3.24 (1H, q, J = 6.6 Hz), 3.50 (1H, d, J = 9.9 Hz), 3.69 (3H, s), 4.66 (1H, s), 4.78 (1H, s), 7.20−7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 23.1, 23.4, 40.6, 40.8, 51.8, 53.1, 59.5, 59.6, 65.4, 113.4, 126.8, 127.3 (2C), 128.2 (2C), 142.4, 145.7, 177.1; Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.61; H, 9.09; N, 4.54.

(3S*,4S*)-Methyl 1-Cyclohexylmethyl-3,4-dimethylpyrrolidine-3-carboxylate 20. To a stirred solution of diisopropylamine (1 mL, 7.1 mmol) in Et_2O (10 mL) was added *n*-BuLi (2.4 mL, 2.5 in hexanes, 6 mmol) at −70 °C. After being stirred at −70 °C for 30 min and then at 0 °C for an additional 30 min, the solution was cooled at −78 °C. A solution of aminoester **19** (507 mg, 2 mmol) in Et_2O (5 mL) was then added, and the reaction mixture was stirred at −60 °C for 2 h. The cold bath was removed, and the ethereal solution of zinc bromide (6 mL, 1 N in Et_2O, 6 mmol) was added at −40 °C. The trouble mixture was stirred at room temperature for 4 h and hydrolyzed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, and the aqueous one was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. Purification by flash chromatography (cyclohexane/ethyl acetate = 80:20) afforded the title compound as a pale yellow oil (243 mg, 48%); IR (neat): 2932, 2854, 1732, 1667, 1450, 1275, 1128, 917, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.79−0.88 (2H, m), 0.97 (3H, d, J = 7.1 Hz), 1.17 (3H, s), 1.14−1.24 (2H, m), 1.33−1.42 (1H, m), 1.64−1.82 (6H, m), 2.07−2.19 (3H, m), 2.27 (1H, dd, J = 11.7, 8.1 Hz), 2.56−2.65 (1H, m), 2.88 (1H, t, J = 8.4 Hz), 3.27 (1H, d, J = 9.7 Hz), 3.67 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.2, 26.3, 27.0, 31.8, 32.0, 38.7, 50.3, 52.0, 61.9, 63.7, 65.1, 178.0; Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.04; H, 10.76; N, 5.41.

Methyl 1-(1′-Cyclohexylethyl)-3,4-dimethylpyrrolidine-3-carboxylate 22. To a stirred solution of diisopropylamine (1 mL, 7.1 mmol) in Et_2O (10 mL) was added *n*-BuLi (2.4 mL, 2.5 in hexanes, 6 mmol) at −70 °C. After being stirred at −70 °C for 30 min and then at 0 °C for an additional 30 min, the solution was cooled at −78 °C. A solution of ester **21** (535 mg, 2 mmol) in Et_2O (5 mL) was then added, and the reaction mixture was stirred at −60 °C for 2 h. The cold bath was removed, and the ethereal solution of zinc bromide (6 mL, 1 N in Et_2O, 6 mmol) was added at −40 °C. The trouble mixture was stirred at room temperature for 4 h and hydrolyzed with an aqueous solution of NH_4Cl/NH_4OH (2:1). The layers were separated, and the aqueous one was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. Purification by flash chromatography (cyclohexane/ethyl acetate = 80:20) afforded the title compound as a mixture of inseparable diastereomers (439 mg, 82%, dr = 57:43). IR (neat): 2932, 2854, 1732, 1667, 1450, 1275, 1128, 917, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85−1.43 (6H, m), 0.90 (3H-minor, d, J = 6.6 Hz), 0.92 (3H-major, d, J = 6.6 Hz), 0.98 (3H, d, J = 7.1 Hz), 1.18 (3H-major, s), 1.19 (3H-minor, s), 1.54−1.80 (5H, m), 2.06−2.17 (1H and 1H-major, m), 2.23 (1H-minor, m), 2.30 (1H-major, d, J = 9.1 Hz), 2.36 (1H-minor, d, J = 9.1 Hz), 2.59 (1H, m), 2.91 (1H-minor, m), 2.98 (1H-major, m), 3.25 (1H-minor, d, J = 9.1 Hz), 3.31 (1H-major, d, J = 9.1 Hz), 3.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 12.5, 13.6, 18.7, 26.6, 26.78, 26.84, 27.0, 27.4, 30.8, 38.2, 41.4, 41.6, 48.8, 51.7, 57.0, 58.0, 61.3, 61.5, 62.3, 62.9, 177.6, 177.7; HRMS calcd for $C_{16}H_{30}NO_2$ $[M - H]^+$: 268.2277. Found: 268.2272.

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Supporting Information Available: Multistep preparation of compounds **11**, **15**, **19**, and **21**, chemical correlation (compounds **8**−**10**) as well as ^1H and ^{13}C spectra for compounds **5a**−**e**, **6a**−**i**, **7**, **9**−**13**, **15**, and **19**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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