A New Palladium-Catalyzed Intramolecular Allylation to Pyrrolidin-2-ones[1]

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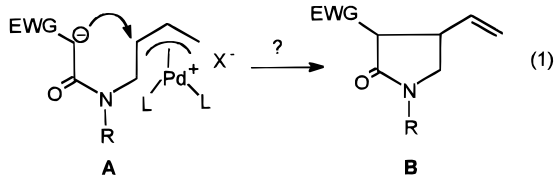
A novel palladium(0)-catalyzed cyclization to 3,4-disubstituted pyrrolidin-2-ones has been developed. The new approach relies upon the concomitant generation of stabilized acetamide enolate anions and of a π-allyl−palladium appendage, properly tethered by a nitrogen atom. Reaction conditions have been optimized for the methoxycarbonyl-stabilized model reaction **[(*Z*)-2 → 3]** and then applied to other substrates. A broad range of acetamide anion stabilizers was shown to allow the desired intramolecular C−C bond formation (MeO_2C, MeCO, NC, $(EtO)_2PO$, $PhSO_2$). The cyclizations gave exclusively 5-*exo*-trig ring closure, thereby affording γ-lactams. All the cyclizations gave the corresponding 3,4-disubstituted pyrrolidin-2-ones with total diastereoselection. Complete trans preference was unequivocally demonstrated for the model reaction via a NOESY experiment.

The γ-lactam skeleton is commonly found in molecules with great value in medicinal chemistry as psychotropic agents,[2] muscarinic acid antagonists,[3] and antihypertensive agents.[4] Furthermore, pyrrolidones can be easily converted into other bioactive molecules via reduction to the corresponding pyrrolidines[5] or cleavage of the amide bond to afford open γ-amino acids such as the GABA analogue Baclofen[6] or the gastroprotective substance AI-77-B.[7] In particular, C-3 and/or C-4[8] substituted γ-lactams are present in several biologically interesting compounds such as in the hepatoprotective agent Clausenamide,[9] in some hypolipidemic agents,[10] in conformationally constrained peptide mimics,[11] in glycine antagonists,[12] and in the neurotrophic agent lactacystin.[13] Therefore, the search for new procedures for the stereoselective synthesis of 3,4-disubstituted γ-lactams appears to be highly desirable.

Following our interest in these heterocycles,[14] we wish to report our latest results toward the synthesis of 3,4-disubstituted γ-lactams exploiting π-allyl palladium chemistry.[15] The synthetic plan we conceived relies on the concomitant generation of a stabilized acetamide enolate anion and a π-allyl appendage, properly tethered by a nitrogen atom, so as to trigger an intramolecular allylic alkylation.[16]



(1)

Although such an approach is, to our knowledge, still unexplored,[17,18] it is interesting to note that keto ana-

(1) This work has been presented, in part, at the 9th IUPAC Symposium on Organometallic Chemistry, OMCOS 9, Göttingen, Germany, July 20−25, 1997.

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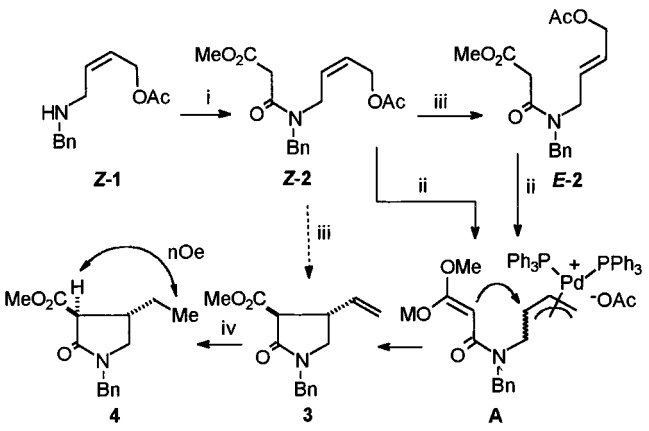
Scheme 1[a]



[a] Key: (i) MeO_2CCH_2COCl, NEt_3, CH_2Cl_2 (74%); (ii) $Pd_2(dba)_3$, (0.05 equiv), PPh3, (0.5 equiv), BSA (1.2 equiv), AcOK (0.1 equiv), THF, 70 °C, 12 h, (69%); (iii) $Pd_2(dba)_3$, (0.05 equiv), PPh_3, (0.5 equiv), THF, 70 °C, 12 h, (*E*)-**2**: 51%, **3**: 13%). (iv) H_2, (1 atm), 10% Pd/C Cat., MeOH (86%).

Table 1. Study of Cyclization of (*E*)-2 and (*Z*)-2

entry	precursor	catalyst	enolization system	**3** (%)	(*E*)-**2** (%)
1	(*Z*)−**2**	$Pd_2(dba)_3$	NaH	50[a]	
2	(*Z*)−**2**	$Pd_2(dba)_3$	BSA/AcOK	69	
3	(*Z*)−**2**	$Pd(PPh_3)_4$	BSA/AcOK	70	
4	(*Z*)−**2**		BSA/AcOK	0	
5	(*Z*)−**2**	$Pd_2(dba)_3$		13	51
6	(*E*)−**2**	$Pd_2(dba)_3$	BSA/AcOK	73	

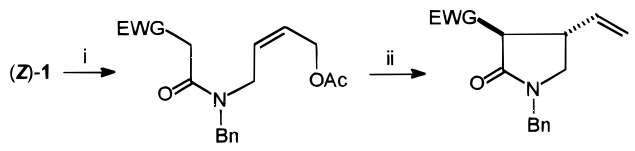
[a] Spectroscopic yield.

logues of amide derived from **A** have been reported to cyclize giving mixtures of 5-exo-trig and 7-endo-trig products.[19]

According to the envisioned synthetic plan, a model cyclization precursor was first prepared. Benzylamine was allylated with (*Z*)-1-acetoxy-4-chloro-butane[20] to give the allylic amine (*Z*)-1 whose acylation with methyl malonyl chloride gave the amide (*Z*)-**2** in high yield (Scheme 1).

The crucial cyclization step has been studied next (Table 1). First trials by treatment of (*Z*)-**2** with NaH in THF at 70 °C, in the presence of $Pd_2(dba)_3$ and PPh_3, gave indeed the expected cyclized product, as detected by ^{1}H NMR of the crude material. However, contamination by some intractable byproducts did not allow a clean isolation of the product (entry 1). We found later that by using BSA/AcOK as the enolization system,[21] the cyclization product was cleanly obtained in 69 and 70% yields, by employing $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ as catalysts, respectively (entries 2 and 3). Further corollary experiments were also of help for a better understanding. The presence of palladium (entry 4) appeared essential for the success of the cyclization, thereby confirming the true palladium catalysis of the cyclization. However, when the π-allyl−palladium complex was generated in the absence of any base (entry 5), to obtain isomerization of

Table 2. Amidation of (*Z*)-1 to 5−10 and Their Cyclizations to 3,4-Disubstituted Pyrrolidin-2-ones 11−16[a]



entry	EWG	amid (%)	yield (%)	cycliz product	yield (%)
1	MeCO	(*Z*)−**5**	61	11	77
2	NC	(*Z*)−**6**	93	12	70
3	$PhSO_2$	(*Z*)−**7**	78	13	78
4	PhS	(*Z*)−**8**	83	−	0
5	$(EtO)_2PO$	(*Z*)−**9**	75	14	80
6	Cl	(*Z*)−**10**	73	*b*	0

[a] Key: (i) (*Z*)-**1** → (*Z*)-**5**: 2,6,6-trimethyl-4*H*-1,3-dioxin-4-one, toluene, 110 °C, 3 h; (*Z*)-**1** → (*Z*)-**6**: $NCCH_2CO_2H$, DCC, THF, rt, 10 h; (*Z*)-**1** → (*Z*)-**7**: $PhSO_2CH_2CO_2H$, DCC, THF, rt, 10 h; (*Z*)-**1** → (*Z*)-**8**: $PhSCH_2COCl$, NEt_3, CH_2Cl_2, 0 °C → rt, 4 h; (*Z*)-**1** → (*Z*)-**9**: $(EtO)_2POCH_2CO_2H$, DCC, THF, rt, 10 h; (*Z*)-**1** → (*Z*)-**10**: $ClCH_2COCl$, NEt_3, CH_2Cl_2, 0 °C → rt, 4 h. (ii) All the cyclizations have been performed in THF in the presence of $Pd_2(dba)_3$ (0.05 equiv), PPh_3, (0.5 equiv), BSA (1.2 equiv), AcOK (0.1 equiv) and refluxed at 70 °C for 12 h. [b] The acyclic 1,3-diene **15** was obtained in 68% yield (eq 2).

(*Z*)-**2** to (*E*)-**2**, 13% of the cyclized product **3** was also detected. Cyclization of (*E*)-**2**, under otherwise identical conditions (entry 6) gave essentially the same outcome as (*Z*)-**2**. Since the rate-determining step in allylic alkylations is expected to be the oxidative addition,[22] and given the high rate of a 5-exo-trig cyclization, we surmise that cyclization of (*Z*)-**2** and (*E*)-**2** involves immediate trapping of the anti and the syn π-allyl−palladium complexes, respectively, as soon as they are formed.

Only the trans diasteroisomer **3** was always detected as the cyclized product. Its stereochemistry was unambiguously assigned on the basis of the NOESY spectrum of the hydrogenated product **4**.[23] Whether the observed trans diastereoselectivity is attained during the C−C bond formation or after equilibration of the cyclized material is still a matter of investigation.[24]

Having in hand the optimized conditions for the cyclization step, we next evaluated other EWG moieties as acetamide anion stabilizers. Accordingly, the acyclic precursors **5**−**10** have been prepared from (*Z*)-**1** using standard procedures, and then submitted to the above cyclization conditions. The acetyl-, cyano-, phenylsulfonyl-, and diethylphosphonyl moieties all were able to promote the cyclizations (Table 2). Again, the five-membered rings were always and exclusively obtained, the alternative 7-endo-trig process being evidently highly disfavored. Interestingly, this result differs from what observed by Tsuji[19] in the case of the corresponding acyclic keto precursors. In contrast to the above results, the sulfenyl- and the chloro-stabilized acetamides **8** and **10** failed to cyclize. Seemingly, such substrates are not activated enough to be enolized by the BSA/AcOK system. In the latter case oxidative addition of Pd(0) on the C−Cl

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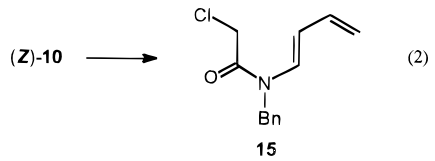
(23) Direct assignment of the relative stereochemistry on compound **3** turned out to be unfeasible owing to signal overlaps in the ^{1}H-NMR spectrum.

(24) Since in the isomerization of (*Z*)-**2** to (*E*)-**2** (Table 1, entry 5), where a potentially enolizing base is absent and **3** was again obtained in trans stereochemistry, we favor the first hypothesis.

bond did not compete,[25] and clean elimination to the corresponding 1,3-diene[26] **15** was observed.



In conclusion, we have illustrated a new and stereoselective intramolecular cyclization to 3,4-disubstituted pyrrolidin-2-ones based on π-allyl−palladium chemistry. The method is flexible enough to encompass a broad range of acetamide anion stabilizers. Given the mild conditions required and the high yields and selectivities attained, this new approach appears to be synthetically attractive and a useful alternative to the existing methods.[17,18] Asymmetric modifications of the methodology are currently underway.

Experimental Section

General Methods. THF and toluene were dried by distillation from sodium/benzophenone under nitrogen atmosphere, and CH_2Cl_2 was dried by distillation from CaH_2. All moisture and air-sensitive reactions were carried out in predried glassware under a positive nitrogen atmosphere. Final product solutions were dried over Na_2SO_4, filtered, and evaporated under reduced pressure on a rotary evaporator.

(*Z*)-4-(Benzylamino)but-2-enyl Acetate ((*Z*)-1). To a solution of (*Z*)-2-butene-1,4-diol (0.607 g, 6.89 mmol) in CH_2Cl_2 (40 mL) are added sequentially triethylamine (0.72 mL, 5.17 mmol) and acetic anhydride (0.49 mL, 5.17 mmol). After 6 h stirring, the mixture is treated with H_2O (10 mL), the organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (3 × 20 mL). The organic phases are collected, washed with a small portion of H_2O, and dried, and the solvent is evaporated. To the resulting crude monoacetate are added pyridine (1.67 mL, 20.67 mmol) and thionyl chloride (1.50 mL, 20.67 mmol), and stirring is continued for 3 h. After treatment with saturated aqueous Na_2CO_3 (15 mL), the reaction mixture is extracted with CH_2Cl_2 (3 × 10 mL), and the collected organic phases are dried and evaporated in vacuo. The resulting monoacetate monochloride is then immediately dissolved in acetonitrile (20 mL), benzylamine (1.13 mL, 10.34 mmol) is added, and the mixture is brought to reflux for 12 h. The mixture is then treated with saturated aqueous Na_2CO_3 (10 mL) and submitted to standard extractive workup with CH_2Cl_2 (3 × 10 mL). Flash chromatography (hexanes:ethyl acetate: triethylamine 75:25:4%) gives the pure amine amine (*Z*)-**1** (237 mg, 39%, starting from the diol 69% considering the recovered diol), and the corresponding (*Z*)-diacetate $AcOCH_2CH{=}CHCH_2OAc$ (67 mg, 11%). ^{1}H NMR ($CDCl_3$): δ = 7.33−7.27 (5H), 5.85−5.56 (2H), 4.60 (d, 2H, J = 6.4 Hz), 3.79 (s, 2H), 3.34 (d, 2H, J = 6.4 Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, selected data): δ = 20.93, 45.65, 53.42, 60.25, 125.56, 127.07, 128.18, 128.47, 133.06, 140.01. IR ($CDCl_3$): 3005, 2930, 1731 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.47; H, 7.96; N, 6.17.

General Procedure for the Synthesis of (*Z*)-[Benzyl-(malonyl)amino]but-2-enyl Acetate ((*Z*)-2), (*Z*)-4-[Benzyl[2-(phenylthio)acetyl]amino]but-2-enyl Acetate ((*Z*)-8), and (*Z*)-4-[Benzyl(2-chloroacetyl)amino]but-2-enyl Acetate ((*Z*)-10). To a solution of (*Z*-1) (1.0 mmol) in CH_2Cl_2 (11 mL) are dropwise added at 0 °C NEt_3 (0.21 mL, 1.5 mmol) and the proper acid chloride (1.5 mmol) sequentially. After 6 h stirring at rt, the reaction mixtures are treated with water (5 mL) and extracted with CH_2Cl_2. The collected organic layers are dried and evaporated in vacuo. Flash chromatography of the crude products (AcOEt:hexanes) gives the pure amides as oils ((*Z*)-**2**, 74%, (*Z*)-**8**, 83%, (*Z*)-**10**, 73%). (*Z*)-**2**: ^{1}H NMR ($CDCl_3$): δ = 7.37−7.17 (5H), 5.78−5.43 (2H), 4.62−4.42 (4H), 4.10 (d, 2H, 55%, J = 5.9 Hz), 3.93 (d, 2H, 45%, J = 5.9 Hz), 3.76 (s, 3H, 45%), 3.72 (s, 3H, 55%), 3.53 (s, 2H, 45%), 3.48 (s, 2H, 55%), 2.03 (s, 3H, 45%), 2.00 (s, 3H, 55%). ^{1}H NMR (DMSO, 70 °C, 300 MHz): δ = 7.40−7.19 (5H), 5.63−5.51 (2H), 4.53 (s, 2H), 4.49 (d, 2H, J = 6.3 Hz), 3.98 (d, 2H, J = 6.2 Hz), 3.65 (s, 3H), 3.11 (s, 2H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 20.70, 20.74, 40.99, 42.59, 44.70, 48.45, 51.16, 52.38, 59.37, 59.72, 126.50, 127.32, 127.43, 127.54, 127.89, 128.09, 128.63, 128.87, 129.00, 129.23, 135.84, 136.66, 166.19, 166.37, 167.90, 168.07, 170.55, 170.60. IR ($CDCl_3$): 3007, 2955, 2856, 1733, 1643 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.01; H, 6.60; N, 4.51. (*Z*)-**8**: ^{1}H NMR ($CDCl_3$): δ = 7.53−7.17 (10H), 5.77−5.50 (2H), 4.60−4.43 (4H), 4.07 (d, 2H, 50%, J = 4.3 Hz), 3.98 (d, 2H, 50%, J = 3.9 Hz), 3.82 (s, 2H, 50%), 3.76 (s, 2H, 50%), 2.04 (s, 3H, 50%), 1.99 (s, 3H, 50%). Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.19; H, 6.21; N, 3.82. (*Z*)-**10**: ^{1}H NMR ($CDCl_3$): δ = 7.38−7.18 (5H), 5.78−5.50 (2H), 4.60−4.48 (4H), 4.14−4.00 (4H), 2.04 (s, 3H, 50%), 2.00 (s, 3H, 50%). ^{13}C NMR ($CDCl_3$): δ = 20.80, 41.26, 42.97, 44.39, 48.75, 50.95, 59.43, 59.76, 126.54, 127.67, 127.80, 128.08, 128.20, 128.45, 128.78, 129.13, 129.25, 133.72, 133.91. IR ($CHCl_3$): 3006, 2945, 1737, 1650 cm^{-1}. Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.97; H, 6.21; N, 4.67.

General Procedure for the Synthesis of (*Z*)-4-[Benzyl-(cyanoacetyl)amino]but-2-enyl Acetate ((*Z*)-6), (*Z*)-4-[Benzyl[(phenylsulfonyl)acetyl]amino]but-2-enyl Acetate ((*Z*)-7), (*Z*)-4-[Benzyl[(diethylphosphono)acetyl]-amino]but-2-enyl Acetate ((*Z*)-9). To a solution of (*Z*)-**1** (0.5 mmol) and the proper carboxylic acid (0.5 mmol) in THF (32 mL) is added DCC (0.122 g, 0.60 mmol), and the resulting mixture is stirred for 15 h. Hexane (15 mL) is then added so as to precipitate most of the formed dicyclohexyl urea. The reaction mixture is then filtered on a Celite pad washing with hexanes. Evaporation of the solvent gives the crude products which are purified by flash chromatography (AcOEt:hexanes) to give the pure amides as oils ((*Z*)-**6**, 93%; (*Z*)-**7**, 78%; (*Z*)-**9**, 75%). (*Z*)-**6** and (*Z*)-**7** are obtained slightly contaminated by small traces of the dicyclohexylurea byproduct. However, this impurity does not affect the subsequent reactivity of the substrates. (*Z*)-**6**: ^{1}H NMR ($CDCl_3$): δ = 7.40−7.15 (5H), 5.80−5.40 (2H), 4.61−4.47 (4H), 4.14 (d, 2H, 50%, J = 6.6 Hz), 3.96 (d, 2H, 50%, J = 5.5 Hz), 3.59 (s, 2H, 50%), 3.48 (s, 2H, 50%), 2.04 (s, 3H, 50%), 2.00 (s, 3H, 50%). ^{13}C NMR ($CDCl_3$): δ = 20.80, 25.19, 43.63, 44.85, 49.55, 51.26, 59.27, 59.65, 113.82, 114.07, 126.23, 128.03, 128.27, 128.38, 128.47, 128.89, 129.38, 134.99, 135.97, 156.72, 162.23, 166.05, 170.73. IR ($CHCl_3$): 3009, 2937, 2858, 2261, 1734, 1665 cm^{-1} (*Z*)-**7**: ^{1}H NMR ($CDCl_3$): δ = 7.92 (2H), 7.68−7.53 (3H), 7.37−7.14 (5H), 5.68 (m, 1H), 5.57 (m, 1H), 4.71−4.47 (4H), 4.31−4.04 (4H), 2.05 (s, 3H, 50%), 1.99 (s, 3H, 50%) ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.82, 24.93, 25.60, 33.92, 43.23, 45.27, 49.15, 51.46, 59.49, 59.72, 59.83, 60.00, 126.41, 127.71, 127.78, 127.87, 128.13, 128.20, 128.40, 128.58, 128.76, 129.02, 129.16, 129.20, 134.24, 134.30, 135.61, 136.21, 138.85, 166.66, 170.71. IR ($CDCl_3$): 3072, 3034, 2936, 2858, 1732, 1652 cm^{-1} (*Z*)-**9**: ^{1}H NMR ($CDCl_3$): δ = 7.36−7.16 (5H), 5.75−5.46 (2H), 4.66 (s, 2H, 50%), 4.61 (s, 2H, 50%), 4.50 (d, 2H, J = 5.9 Hz), 4.23−4.07 (6H), 3.11 (d, 2H, 50%), 3.04 (d, 2H, 50%), 2.03 (s, 3H, 50%), 1.99 (s, 3H, 50%), 1.32 (t, 6H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ = 16.25, 16.36, 20.80, 32.25, 32.36, 34.89, 35.00, 42.86, 45.10, 48.65, 51.44, 59.56, 59.80, 62.62, 126.45, 127.34, 127.51, 127.82, 127.98, 128.64, 129.00, 129.11, 129.49, 136.17, 136.77, 165.34, 165.45, 170.69. IR ($CDCl_3$): 3032, 2983, 2931,

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1735, 1643 cm^{-1}. Anal. Calcd for $C_{19}H_{28}NO_6P$: C, 57.42; H, 7.10; N, 3.52. Found: C, 57.37; H, 7.12; N, 3.47

(*Z*)-4-[Benzyl(3-oxobutyryl)amino]but-2-enyl Acetate ((*Z*)-5). A solution of (*Z*)-**1** (1.0 mmol) (0.026 g, 0.119 mmol) and 2,6,6-trimethyl-4*H*-1,3-dioxin-4-one (0.019 mL, 0.142 mmol) in toluene (6.0 mL) is heated at reflux. After 3 h stirring, water (3 mL) is added, and the mixture is extracted with Et_2O. The collected organic layers are dried, and the solvent is evaporated in vacuo. Flash chromatography (CH_2Cl_2: MeOH 100:3%) gives pure **5** as an oil.

^1H NMR ($CDCl_3$): δ = 7.40−7.15 (5H), 5.76−5.43 (2H), 4.61−4.43 (4H), 4.10 (d, 2H, 50%, J = 5.8 Hz), 3.90 (d, 2H, 50%, J = 5.8 Hz), 3.63 (s, 2H, 50%), 3.55 (s, 2H, 50%), 2.30 (s, 3H, 50%), 2.25 (s, 3H, 50%), 2.03 (s, 3H, 50%), 2.00 (s, 3H, 50%). ^{13}C NMR ($CDCl_3$): δ = 20.83, 22.01, 30.37, 42.59, 44.77, 48.51, 49.85, 49.94, 51.18, 59.48, 59.78, 126.47, 127.32, 127.49, 127.63, 127.98, 128.10, 128.72, 129.01, 129.09, 129.38, 135.97, 136.66, 166.90, 167.08, 170.71, 202.3, 203.5. IR ($CDCl_3$): 3012, 2970, 2943, 1728, 1667 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.28; H, 7.02; N, 4.67

Cyclizations of the Acetates. General Procedure for the Synthesis of (3,4-*trans*)-1-Benzyl-3-(methoxycarbonyl)-4-vinylpyrrolidin-2-one (3), (3,4-*trans*)-3-Acetyl-1-benzyl-4-vinylpyrrolidin-2-one (11), (3,4-*trans*)-1-Benzyl-3-cyano-4-vinylpyrrolidin-2-one (12), (3,4-*trans*)-1-Benzyl-3-(phenylsulfonyl)-4-vinylpyrrolidin-2-one (13), and (3,4-*trans*)-1-Benzyl-3-(diethylphosphoryl)-4-vinylpyrrolidin-2-one (14). To a solution of the acyclic substrate (1.0 mmol) in THF (20 mL) are added bis(trimethylsilyl)acetamide (0.3 mL, 1.2 mmol) and AcOK (10 mg, 0.1 mmol) sequentially with stirring, under nitrogen atmosphere. In a separate flask $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and PPh3 (130 mg, 0.5 mmol) are weighed and added to the reaction vessel, and the resulting mixture is brought to reflux for 12 h. After this period, a saturated aqueous solution of NH_4Cl is added and the organic phase is extracted with Et_2O. The collected organic phases are dried, and the solvent is removed in vacuo. Flash chromatography (hexanes:AcOEt) gives the pure compounds as oils (**3**, 69% from (*Z*)-**2** 73% from (*E*)-**2**), **11**, 77%, **12**, 70%, **13**, 78%, **14**, 80%). **3**: ^1H NMR ($CDCl_3$): δ = 7.34−7.20 (m, 5H), 5.72 (m, 1H), 5.14 (d, 1H, J_{trans} = 10.7 Hz), 5.07 (d, 1H, J_{cis} = 4.1 Hz), 4.46 (s, 2H), 3.80 (s, 3H), 3.44−3.34 (3H), 3.01 (m, 1H). ^{13}C NMR ($CDCl_3$): δ = 40.85, 47.42, 50.48, 53.22, 54.77, 117.88, 128.31, 128.65, 129.29, 136.24, 136.68, 169.45, 170.27. IR ($CHCl_3$): 3005, 2958, 1738, 1688 cm^{-1}. MS *m*/*z* (%): 259 (M^+, 37); 200 (55); 146 (19); 119 (42); 91 (100). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.23; H, 6.66; N, 5.16. **11**: ^1H NMR ($CDCl_3$): δ = 7.39−7.17 (5H), 5.70 (m, 1H), 5.10 (d, 1H, J = 9.5 Hz), 5.03 (d, 1H, J = 4.2 Hz), 4.43 (s, 2H), 3.48−3.35 (3H), 2.99 (m, 1H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 30.65, 37.18, 46.87, 49.78, 61.27, 116.84, 127.83, 128.13, 128.84, 135.79, 137.14, 169.09, 202.92. IR ($CHCl_3$): 3092, 3036, 2927, 1715, 1685 cm^{-1}. MS *m*/*z* (%): 243 (M^+, 12), 200 (47), 91 (100). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.12; H, 7.07; N, 5.69. **12**: ^1H NMR ($CDCl_3$): δ = 7.41−7.21 (5H), 5.73 (ddd, 1H, J = 17.2 Hz, J = 10.2 Hz, J = 6.9 Hz), 5.30 (d, 1H, J = 17.4 Hz), 5.24 (d, 1H, J = 9.7 Hz), 4.56−4.37 (2H), 3.46−3.02 (4H). ^{13}C NMR ($CDCl_3$): δ = 39.93, 42.28, 47.34, 49.60, 119.64, 120.19, 128.25, 128.34, 129.04, 133.15, 133.70, 165.23. IR (CHCl3): 2928, 2248, 1710 cm^{-1}. MS *m*/*z* (%): 226 (M^+, 59), 199 (3), 91 (100). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.39; H, 6.27; N, 12.47. **13**: ^1H NMR ($CDCl_3$): δ = 7.98 (2H), 7.75−7.53 (3H), 7.36−7.15 (5H), 5.78 (ddd, 1H, J = 16.8 Hz, J = 10.4 Hz, J = 7.2 Hz), 5.14 (d, 1H, J_{trans} = 16.8 Hz), 5.13 (d, 1H, J_{cis} = 10.2 Hz), 4.45 (s, 2H), 3.84 (d, 1H, J = 4.4 Hz), 3.67−3.54 (2H), 3.02 (d, 1H, J = 9 Hz). ^{13}C NMR ($CDCl_3$): δ = 36.09, 47.05, 49.87, 71.19, 117.35, 127.94, 128.05, 128.85, 129.05, 129.44, 134.30, 135.21, 136.54, 137.83, 164.79. IR ($CDCl_3$): 3070, 3035, 2928, 1699 cm^{-1}. MS *m*/*z* (%): 342 ($M + 1^+$, 4); 200 (47); 91 (100); 77 (28). Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.83; H, 5.85; N, 4.22. **14**: ^1H NMR ($CDCl_3$): δ = 7.38−7.21 (5H), 5.78 (ddd, 1H, J = 17.2 Hz, J = 9.7 Hz, J = 7.1 Hz), 5.11 (d, 1H, J = 17 Hz), 5.05 (d, 1H, J = 9.1 Hz), 4.46 (s, 2H), 4.30−4.09 (4H), 3.56 (dd, 1H, J = 9 Hz, J = 8.1 Hz), 3.24 (m, 1H), 2.98 (m, 1H), 2.83 (dd, 1H, J = 22 Hz, J = 5.2 Hz), 1.33 (t, 3H, J = 6.6 Hz), 1.32 (t, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ = 16.36, 37.15, 45.81, 46.87, 48.62, 62.29, 62.42, 63.15, 116.13, 127.73, 128.11, 128.73, 135.86, 138.03, 168.60. IR ($CDCl_3$): 2986, 2932, 1686 cm^{-1}. MS *m*/*z* (%): 337 (M^+, 9); 200 (27), 91 (100). Anal. Calcd for $C_{17}H_{24}NO_4P$: C, 60.53; H, 7.17; N, 4.15. Found: C, 60.59; H, 7.17; N, 4.17

(*E*)-[Benzyl(malonyl)amino]but-2-enyl Acetate ((*E*)-2). To a solution of the methyl ester (*Z*)-**2** (0.120 g, 0.376 mmol) in THF (10 mL) are added $Pd_2(dba)_3$ (0.017 g, 0.019 mmol) and PPh_3 (0.049 g, 0.188 mmol), and the resulting mixture is brought to reflux for 12 h. A saturated aqueous solution of NH_4Cl is then added, and the organic phase is extracted with Et_2O. The collected organic phases are dried, and the solvent is removed in vacuo. Flash chromatography (hexanes:AcOEt 60:40) gave pure (*E*)−**2** as an oil (51%) together with a small amount of the cyclized product **3** (13%). ^1H NMR ($CDCl_3$): δ = 7.40−7.11 (5H), 5.73−5.62 (2H), 4.63−4.46 (4H), 4.03 (d, 2H, 45%, J = 3.1 Hz), 3.84 (2H, 55%), 3.76 (s, 3H, 55%), 3.72 (s, 3H, 45%), 3.50 (s, 2H, 55%), 3.48 (s, 2H, 45%), 2.05 (s, 3H, 55%), 2.04 (s, 3H, 45%). ^{13}C NMR ($CDCl_3$): δ = 20.70, 20.73, 40.99, 41.03, 46.70, 48.33, 48.40, 51.17, 52.39, 63.36, 63.76, 126.36, 127.22, 127.47, 127.58, 127.91, 128.19, 128.53, 128.68, 129.08, 134.84, 135.86, 136.36, 166.19, 167.93, 170.55. IR ($CHCl_3$): 3006, 2957, 1738, 1642 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.81; H, 6.67; N, 4.47.

4-[Benzyl(chloroacetyl)amino]buta-1,3-diene (15). The same reaction conditions as those above-described for the cyclizations of compounds **2** and **5**−**10** to give, respectively **3**, and **11**−**14** were applied. Flash chromatography (hexanes: AcOEt 50:50) gives the pure diene **15** as an oil (68%). ^1H NMR ($CDCl_3$): δ = 7.34−7.22 (5H), 6.25−5.94 (3H), 5.36 (dd, 1H, J = 16.1 Hz, J = 2.58 Hz), 5.24 (d, 1H, J = 9.68 Hz), 4.68 (s, 2H), 4.06 (s, 2H). ^{13}C NMR ($CDCl_3$): δ = 42.17, 51.60, 122.57, 126.74, 127.78, 128.60, 128.80, 129.24, 131.18, 136.03, 166.27. IR ($CDCl_3$): 3034, 2929, 1666 cm^{-1}. MS *m*/*z* (%): 235 (M^+, 7); 237 (M^+, 2); 91 (100). Anal. Calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.31; H, 6.07; N, 5.91.

(3,4-*trans*)-1-Benzyl-4-ethyl-3-(methoxycarbonyl)pyrrolidin-2-one (4). To a suspension of 10% Pd/C (2 mg) in MeOH (2.0 mL) is added a solution of compound **3** (0.022 g, 0.085 mmol) in MeOH (3.0 mL) under nitrogen atmosphere. Hydrogen atmosphere is then introduced by means of a three-way tap, and vigorous stirring is started. After 4 h the reaction is filtered through a Celite plug and evaporated. Flash chromatography (hexanes:AcOEt 60:40) gives pure **4** as an oil (76%). ^1H NMR ($CDCl_3$): δ = 7.34−7.20 (5H), 4.46 (s, 2H), 3.79 (s, 3H), 3.42 (dd, 1H, J = 9.5 Hz, J = 8 Hz), 3.19 (d, 1H, J = 7.7 Hz), 2.86 (dd, 1H, J = 9.5 Hz, J = 7 Hz), 2.62 (m, 1H), 1.47 (2H), 0.86 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ = 11.38, 26.75, 37.89, 46.90, 50.60, 52.64, 54.82, 127.74, 128.12, 128.78, 135.95, 169.62, 170.74. IR (CDC_3): 2927, 1714, 1687 cm^{-1}. MS *m*/*z* (%): 261 (M^+, 20), 202 (12), 119 (23), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.02; H, 7.37; N, 5.21.

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