Preparation of 1,5-Disubstituted Pyrrolidin-2-ones

Alan R. Katritzky,* Shamal Mehta, Hai-Ying He, and Xilin Cui

Center for Heterocyclic Chemistry, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

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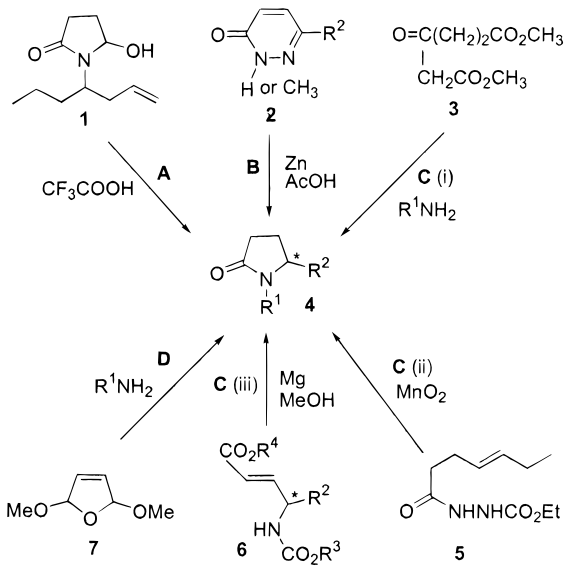
1,5-Disubstituted pyrrolidin-2-ones **18a**−**g**, **19a**−**h,** and **20a**−**f** were synthesized in good to excellent yields via the nucleophilic substitution of 5-(benzotriazol-1-yl)-1-substituted-pyrrolidin-2-ones **9** with allylsilanes, organozinc reagents, and phosphorus compounds. Compounds **9** and 5-(benzotriazol-2-yl)-1-substituted-pyrrolidin-2-one isomers **10** are readily prepared in total 70−84% yields from 2,5-dimethoxy-2,5-dihydrofuran (**7**), primary amines **8,** and benzotriazole; **9** and **10** react identically with nucleophiles.

Introduction

Pyrrolidin-2-ones possess varied biological activity and have been used as pharmaceuticals.[1,2] Consequently, there has been an ongoing interest in the synthesis of substituted pyrrolidin-2-ones. They are also effective intermediates for the synthesis of pyrrolidine alkaloids and γ-amino acids.[3] Although the preparation of pyrrolidin-2-ones has been much studied,[4] it remains of considerable interest to explore new synthetic routes. We now report the novel synthesis of 1,5-disubstituted pyrrolidin-2-ones via benzotriazole methodology.[5]

Typical routes to 1,5-disubstituted pyrrolidin-2-ones can be classified as follows (Scheme 1): (A) treatment of carbinolamide (**1**) with CF_3COOH gave a ring-closure product **4** [R^1, R^2 = $-CH(CH_2CH_2CH_3)CH_2CH(O_2CCF_3)-CH_2-$];[6] **(**B) reductive ring-contraction of pyridazin-3-ones **2** by Zn in AcOH formed **4** (R^1 = H, R^2 = aryl);[7] (C) ring-closure reactions of (i) dimethyl 3-oxohexanedioate (**3**) with primary amines to **4** (R^1 = H or alkyl, R^2 = $CH_2CO_2CH_3$),[8] (ii) γ,δ-unsaturated hydrazide (**5**) with active MnO_2 to **4** (R^1 = $NHCO_2Et$, R^2 = $CH{=}CHCH_3$),[9] and (iii) γ-amino-α,β-unsaturated carboxylate **6** with magnesium in methanol to **4** (R^1 = H, R^2 = alkyl);[10]

Scheme 1



(D) reaction of 2,5-dimethoxy-2,5-dihydrofuran (**7**) and primary amines in refluxing acetic acid produced **4** (R^2 = alkoxy) (Scheme 1).[11,12]

The reported methods generally introduce R^2 (alkyl or aryl) group into the pyrrolidin-2-one ring directly from the starting material. Because of the strong C−C bond, it is difficult to replace such R^2 groups substituted by any other functionality. The weaker C−N bond of *N*-substituted benzotriazoles should allow easy replacement of a Bt group via nucleophilic substitution, elimination, reduction, and cyclization, etc.[5] We report herein the synthesis of 5-benzotriazolyl-1-substituted-pyrrolidin-2-ones as versatile synthons and their novel reactions with allylsilanes, organozinc reagents, and phosphorus compounds to generate 1,5-disubstituted pyrrolidin-2-ones.

Results and Discussion

Preparation of 5-Benzotriazolyl-1-substituted-pyrrolidin-2-ones 9 and 10. The reaction of 2,5-dimethoxy-

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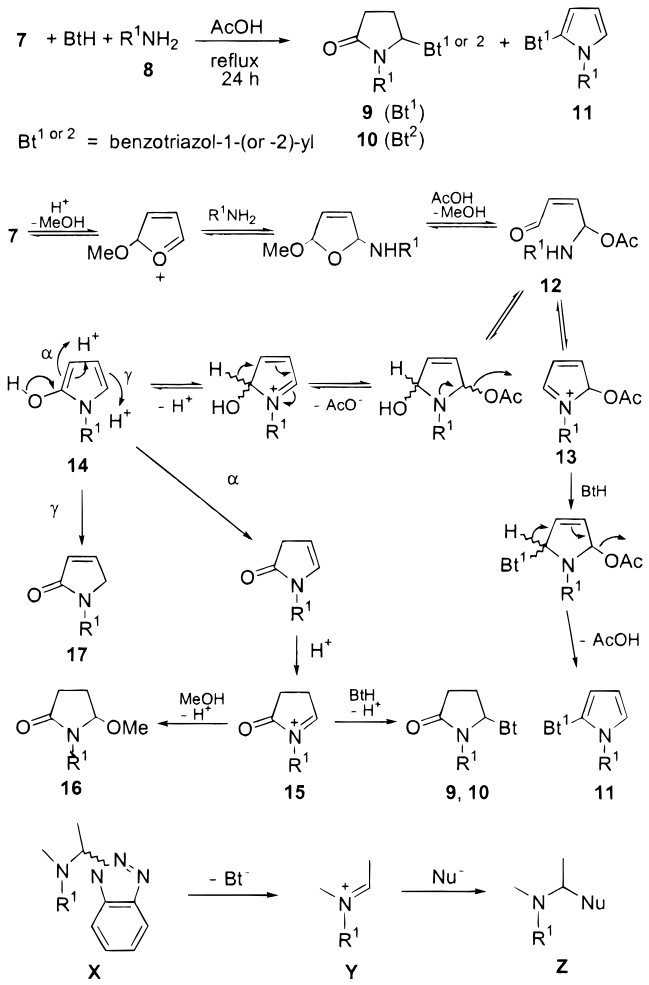
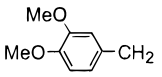
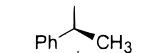
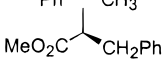
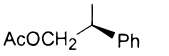
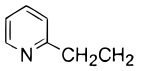
Scheme 2



2,5-dihydrofuran (**7**), benzotriazole, and primary amine **8** in refluxing AcOH for 24 h gave 5-(benzotriazol-1-yl)-1-substituted-pyrrolidin-2-one **9** and 5-(benzotriazol-2-yl)-1-substituted-pyrrolidin-2-one **10**, along with a minor byproduct 1-(1-substituted-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole **11** (Scheme 2). Bt^1 isomer **9** and Bt^2 isomer **10** were separated by column chromatography (silica gel), with the Bt^1 isomer as the major constituent. Although some of the intermediates, e.g., **9a**,**c**,**f**,**g**,**i**−**k** and **10b**,**f**−**k**, were not fully characterized possibly due to easy oxidation, they had clear ^{1}H and ^{13}C NMR spectra, and their nucleophilic reactions with allylsilanes, organozinc reagents, and phosphorus compounds also afforded the fully characterized expected 1,5-disubstituted pyrrolidin-2-ones. The total yields for **9** and **10** are from good to excellent (Table 1). Methyl (2*S*)-2-amino-3-phenylpropanoate gave the expected intermediate **9i**, which indicates that easily obtained chiral amino acid esters could be used for the preparation of 1,5-disubstituted pyrrolidin-2-ones, although no expected product was isolated using (2*S*)-2-amino-3-phenylpropanoic acid. From chiral primary amines, the intermediates **9h**−**j** and **10h**−**j** were obtained with little chiral control at the 5-position as shown by the ^{1}H and ^{13}C NMR spectra.

The mechanism for the reaction of **7** and R^1NH_2 was previously supposed to involve a competitive α- and γ-tautomerization of the transient 2-hydroxypyrrole (**14**), leading to the formation of 5-methoxypyrrolidin-2-one **16** and the conjugated pyrrolinone **17**, respectively (Scheme 2).[12] We believe, in our reaction, 2-hydroxypyrrole (**14**) forms the same transient iminium cation **15**, which immediately reacts with BtH to produce 5-benzotriazolyl-1-substituted-pyrrolidin-2-ones **9** and **10**.[13] No conjugated pyrrolinone **17** was detected in our reaction. In addition, the intramolecular condensation of the formyl group and the secondary amine in the transient **12** generates the intermediate iminium cation **13**, which reacts with BtH and subsequently eliminates AcOH to afford the minor product α-(benzotriazol-1-yl)pyrrole **11**.

Table 1. Isolated Yields of 9−11

No.	R^1	9	10	11
a	Ph	70	[a]	10
b	$PhCH_2$	69	10	5
c	$PhCH_2CH_2$	66	14	1
d	*p*-$MeOC_6H_4CH_2$	64	14	[a]
e	*p*-$MeOC_6H_4CH_2CH_2$	63	9	[a]
f [b]	$CH_3COOCH_2CH_2$	65 [d]	16 [d]	[a]
g		74	9	[a]
h		67	15	2
i		66	18	[a]
j [c]		60	13	5
k		66	14	[a]

[a] No detectable amount of the product was isolated. [b] $HOCH_2$-CH_2NH_2 was used, but **9f** and **10f** were obtained as esters due to the presence of CH_3COOH. [c] (*S*)-$PhCH(CH_2OH)NH_2$ was used, but **9j**, **10j**, and **11j** were obtained as esters due to the presence of CH_3COOH. [d] Yields estimated by ^{1}H NMR spectrum.

Our previous work[14] has demonstrated that (i) Bt^1 and Bt^2 groups are both good leaving groups and can be replaced by a nucleophile, and (ii) the mechanism of nucleophilic substitution of the Bt group from the adduct **X** involves a planar iminium salt **Y** as intermediate (Scheme 2). Therefore, the position at which the substituent is attached to the benzotriazole ring is not important. Thus, the mixture of intermediates **9** and **10** could be used for the subsequent nucleophilic substitutions with allylsilanes, organozinc reagents and phosphorus compounds.

Substitution of the Benzotriazole Group from 9 Using Allylsilanes. Initially, it was desired to confirm that there was no difference in the reactivity of the Bt^1 isomer **9** and the Bt^2 isomer **10**. Hence, **9b** (R^1 = $PhCH_2$), **9c** (R^1 = $PhCH_2CH_2$), and **10b** (R^1 = $PhCH_2$), **10c** (R^1 = $PhCH_2CH_2$) were each separately used to react with allyl(trimethyl)silane in the presence of $BF_3{\cdot}Et_2O$. The yields of **18a**, generated from **9b** and **10b**, were 90% and 87%, respectively, while the yields of **18b**, generated from **9c** and **10c**, were 90% and 90%, respectively (Scheme 3). These examples prove that the Bt^1 isomer and Bt^2 isomer have no significant difference in their reactivities and

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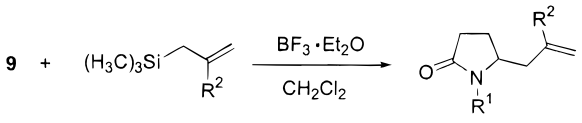
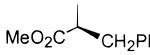
Scheme 3

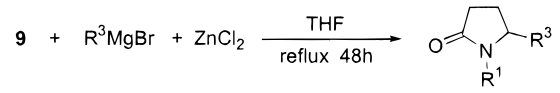


18a-g

18	R^1	R^2	yield (%)
a	$PhCH_2$	H	90 (87)[a]
b	$PhCH_2CH_2$	H	90 (90)[a]
c	$PhCH_2CH_2$	CH_3	84
d	*p*-$MeOC_6H_4CH_2$	CH_3	80
e	*p*-$MeOC_6H_4CH_2CH_2$	H	85
f	*p*-$MeOC_6H_4CH_2CH_2$	CH_3	80
g		H	49

[a] The yield in brackets was obtained from Bt^2 isomer **10**.

Scheme 4

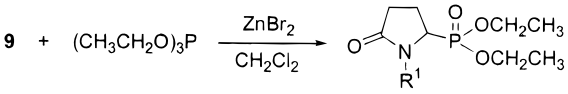


19a-h

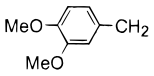
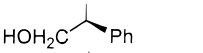
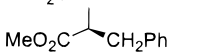
19	R^1	R^3	yield (%)
a	$PhCH_2$	$CH_3C{\equiv}C$	49
b	*p*-$MeOC_6H_4CH_2CH_2$	$CH_3C{\equiv}C$	71
c	*p*-$MeOC_6H_4CH_2CH_2$	$CH_2{=}CH$	80
d	*p*-$MeOC_6H_4CH_2CH_2$	$CH_3CH{=}CH$	52
e	*p*-$MeOC_6H_4CH_2CH_2$	$PhCH_2$	50
f	*p*-$MeOC_6H_4CH_2CH_2$	*cyclo*-C_5H_9	57
g	*p*-$MeOC_6H_4CH_2CH_2$	*n*-C_5H_{11}	73
h[a]	*p*-$MeOC_6H_4CH_2CH_2$	$CH(COOEt)_2$	67

[a] Reaction condition for **19h**: $BrCH(COOEt)_2$, Zn

Scheme 5



20a-f

20	R^1	yield (%)
a	$HOCH_2CH_2$	49
b	*p*-$MeOC_6H_4CH_2$	79
c		78
d	*p*-$MeOC_6H_4CH_2CH_2$	76
e		85
f		67

lead to the same products in very similar yields. To compare and discuss different reactions, the same experiments were carried out by using the pure Bt^1 isomer **9** as the starting material.

Treatment of intermediates **9b**−**e**,**i** with 4 equiv of trimethylallyl- or trimethyl(2-methylallyl)silane in the presence of $BF_3{\cdot}Et_2O$ at 0 °C furnished 1-substituted-5-allylpyrrolidin-2-ones **18a**−**f** in 80−90% yield and **18g** in 49% yield (Scheme 3). The structures of **18a**−**g** were confirmed by the ^1H, ^{13}C NMR spectra and high-resolution mass spectra (HRMS). The Bt group of **9** serves as a good leaving group and is easily eliminated in the presence of $BF_3{\cdot}Et_2O$ to generate iminium cation **Y**, which is subsequently attacked by the nucleophile allylsilane to afford the 1-substituted-5-allylpyrrolidin-2-ones **18a**−**g**. Thus, by using benzotriazole methodology, an allyl group is easily introduced into the 5-position of the pyrrolidin-2-one ring. However, **18g** was obtained as diastereoisomers with no control by the *N*-(chiral)-substituted group of the 5-position chiral center.

Substitution of the Benzotriazole Group from 9 Using Organozinc Reagents. Grignard reagents cannot be directly used for the nucleophilic substitution of **9**, since they react with carbonyl groups. Treatment of **9b** and **9e** with 3 equiv of organozinc reagent, generated by the reaction of the Grignard reagents and zinc chloride, in reflux THF gave 1,5-disubstituted pyrrolidin-2-ones **19a**−**g** in moderate to excellent yields, while treatment of **9e** with 3 equiv of 2-bromomalonate and zinc powder in reflux THF afforded **19h** in 67% yield (Scheme 4). The structures of **19a**−**h** were determined by the ^1H, ^{13}C NMR as well as HRMS. The nucleophilic substitution of **9** with organozinc reagents thus allows the introduction of various substituents, e.g., propynyl, vinyl, propenyl, benzyl, cyclopentyl, pentyl, and ester, into the 5-position of the pyrrolidin-2-one rings.

Substitution of the Benzotriazole Group from 9 by Phosphorus Nucleophiles. In 1997, Maury et al. reported that the cyano group of (3*R*,5*S*,8a*R*)-3-phenylhexahydrooxazolo[3,2-*a*]pyridine-5-carbonitrile, generated from the double condensation of (*R*)-phenylglycinol and glutaraldehyde in the presence of potassium cyanide, could be replaced by a phosphono group using either triethyl- or trimethyl phosphite.[15] In our reaction, avoiding the use of potassium cyanide, the treatment of **9d**−**g**,**i**,**j** in dry THF with triethyl phosphite in the presence of 1 equiv of $ZnBr_2$ produced diethyl 1-substituted-5-oxo-2-pyrrolidinylphosphonates **20a**−**f** in moderate to good yields (Scheme 5). The Bt groups of **9d**−**g**,**i**,**j** are readily replaced with a phosphono group. The intermediates **9f** and **9j**, as esters, were hydrolyzed during the reaction; thus, **20a** and **20e** were obtained as primary alcohols. The structures of **20a**−**f** are determined by ^1H and ^{13}C NMR, and the ^{13}C NMR spectra show that phosphorus has the coupling splitting effect on some carbon peaks. Again, a chiral group at 1-position [R^1 = (*S*)-PhCH(CH_2-OH) or (*S*)-$PhCH_2CH(CO_2Me)$] did not control the chiral center at 5-position, as **20e** and **20f** were obtained as diastereoisomers.

In conclusion, we have described a simple and novel route to 1,5-disubstituted pyrrolidin-2-ones via the benzotriazole methodology. Several advantages for this reaction include the following: (1) the intermediates **9a**−**k** and **10a**−**k** could be obtained in one step; (2) the total yield for Bt^1 and Bt^2 isomers is from good to excellent

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(70% to 84%) and there is no difference for the reactivity of Bt^1 and Bt^2 isomer; (3) the compounds **9a**−**k** and **10a**−**k**, as versatile synthons, can be further transformed to new 1,5-disubstituted pyrrolidin-2-ones via the nucleophilic substitution of benzotriazole group with allylsilanes, organozinc reagents and phosphorus compounds.

Experimental Section

General Procedure for the Preparation of 5-(Benzotriazol-1-yl)-1-substituted-pyrrolidin-2-ones 9 and 5-(Benzotriazol-2-yl)-1-substituted-pyrrolidin-2-ones 10. An appropriate primary amine (25 mmol), 2,5-dimethoxy-2,5-dihydrofuran (**7**) (3.2 g, 25 mmol), and 1*H*-1,2,3-benzotriazole (6.5 g, 55 mmol) were dissolved in acetic acid (25 mL) and refluxed under N_2 for 24 h. After the reaction mixture was cooled, CH_2Cl_2 (50 mL) was added. The organic layer was washed with 2 M NaOH and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was separated by flash chromatography (silica gel) with hexanes−EtOAc (7:3) as eluent to give 5-(benzotriazol-1-yl)-1-substituted-pyrrolidin-2-ones **9** and 5-(benzotriazol-2-yl)-1-substituted-pyrrolidin-2-ones **10**, together with a byproduct 1-(1-substituted-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole **11**.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-benzylpyrrolidin-2-one (9b): brown powder; mp 169.5−170.0 °C; ^{1}H NMR δ 2.40−2.55 (m, 1H), 2.70−2.85 (m, 2H), 3.00−3.15 (m, 1H), 3.53, 4.91 (AB, J = 15.0 Hz, 2H), 6.34 (d, J = 6.6 Hz, 1H), 7.04−7.06 (m, 2H), 7.20−7.22 (m, 4H), 7.37−7.49 (m, 2H), 8.07 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 25.2, 29.4, 44.3, 71.4, 109.0, 120.4, 124.3, 127.9, 128.0, 128.3, 128.6, 131.4, 134.8, 146.3, 174.2. Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.63; H, 5.66; N, 18.93.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-[(1*S*)-1-phenylethyl]-pyrrolidin-2-one (9h). Obtained as diastereoisomers in the ratio 57:43 (minor isomer in the parentheses): yellow oil; ^{1}H NMR δ 0.79 (d, J = 7.2 Hz, 3H), 2.26−2.38 (m, 1H), 2.53−2.77 (m, 2H), 3.12−3.30 (m, 1H), 5.50−5.65 (m, 1H), 6.05−6.15 (m, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.15−7.25 (m, 2H), 7.30−7.53 (m, 5H), 8.10 (d, J = 7.6 Hz, 1H); ^{13}C NMR δ 15.8 (15.1), 26.8 (27.0), 29.7 (29.4), 50.2 (50.5), 69.9 (69.6), 109.3 (109.1), 120.4 (120.1), 124.3 (124.2), 127.6 (127.5), 127.8 (127.6), 128.2 (127.9), 128.9, 131.3, 138.5, 146.1 (147.2), 174.9 (175.2). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.23; H, 6.02; N, 18.46.

Methyl (2*S*)-2-[2-(1*H*-1,2,3-Benzotriazol-1-yl)-5-oxo-1-pyrrolidinyl]-3-phenylpropanoate (9i). Obtained as diastereoisomers in the ratio 59:41 (minor isomer in the parentheses): yellow oil; ^{1}H NMR δ 2.34−2.90 (m, 3H), 2.93−3.15 (m, 2H), 3.49 (d, J = 8.1 Hz, 1H), 3.66 (s, 3H) [3.41 (s, 3H)], 4.79−4.87 (m, 1H), 6.06 (d, J = 5.7 Hz, 1H) [6.30 (d, J = 6.6 Hz, 1H)], 7.00−7.10 (m, 4H), 7.23 (t, J = 6.6 Hz, 2H), 7.46 (t, J = 6.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 26.1 (25.2), 28.7 (28.6), 34.1 (32.9), 52.3 (51.5), 55.9 (54.6), 78.3 (76.3), 103.4, 110.0 (112.8), 117.9 (117.8), 119.4 (120.2), 123.5 (121.9), 126.4 (126.2), 126.8 (126.5), 127.9 (127.8), 128.3 (128.2), 135.3 (132.2), 136.1 (135.8), 143.8 (145.4), 169.7 (169.1), 175.2 (175.3).

(2*S*)-2-[2-(1*H*-1,2,3-Benzotriazol-1-yl)-5-oxo-1-pyrrolidinyl]-2-phenylethyl Acetate (9j). Obtained as diastereoisomers in the ratio 54:46 (minor isomer in the parentheses): yellow oil; ^{1}H NMR δ 1.95 (s, 3H) [1.75 (s, 3H)], 2.25−2.45 (m, 1H), 2.60−2.87 (m, 2H), 3.07−3.32 (m, 1H), 4.00−4.18 (m, 1H) [3.70−3.83 (m, 1H)], 4.48−4.57 (m, 1H) [5.05−5.18 (m, 1H)], 5.20−5.31 (m, 1H) [5.48−5.60 (m, 1H)], 6.67 (J = 6.3 Hz, 1H) [6.25 (d, J = 6.4 Hz, 1H)], 6.80−7.05 (m, 2H), 7.10−7.55 (m, 6H), 7.89 (d, J = 8.2 Hz, 1H) [8.08 (d, J = 8.2 Hz, 1H)]; ^{13}C NMR δ 20.6 (20.3), 25.8 (26.3), 29.6 (29.5), 54.6 (54.2), 61.8 (61.3), 70.7 (71.0), 109.3 (109.2), 120.1 (120.5), 123.9, 124.3, 126.9 (127.4), 127.7, 127.8, 128.0 (128.7), 129.0, 130.8 (130.9), 134.2 (134.6), 146.3 (146.1), 170.0 (170.6), 175.2 (175.1).

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-benzylpyrrolidin-2-one (10b): yellow oil; ^{1}H NMR δ 2.50−2.67 (m, 3H), 3.08−3.25 (m, 1H), 3.60, 4.94 (AB, J = 14.7 Hz, 2H), 6.22 (d, J = 6.6 Hz, 1H), 7.20−7.29 (m, 5H), 7.40−7.43 (m, 2H), 7.80−7.90 (m, 2H); ^{13}C NMR δ 25.9, 29.0, 44.4, 77.8, 118.4, 126.9, 127.8, 128.5, 128.6, 135.3, 144.4, 175.1.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-[(1*S*)-1-phenylethyl]-pyrrolidin-2-one (10h). Obtained as diastereoisomers in the ratio 53:47 (minor isomer in the parentheses): yellow oil; ^{1}H NMR δ 0.79 (d, J = 7.2 Hz, 3H), 2.13−2.28 (m, 1H), 2.37−2.63 (m, 2H), 3.15−3.35 (m, 1H), 5.52−5.65 (m, 1H), 6.09−6.15 (m, 1H), 7.25−7.51 (m, 7H), 7.83−7.95 (m, 2H); ^{13}C NMR δ 15.3 (14.6), 27.3 (27.1), 29.1 (28.6), 50.1 (50.8), 76.5 (76.1), 118.3 (118.2), 126.7 (126.5), 127.4 (127.2), 127.9, 128.7, 138.9, 144.2 (144.7), 175.3 (175.0).

Methyl (2*S*)-2-[2-(2*H*-1,2,3-Benzotriazol-2-yl)-5-oxo-1-pyrrolidinyl]-3-phenylpropanoate (10i). Obtained as diastereoisomers in the ratio 54:46 (minor isomer in the parentheses): brown oil; ^{1}H NMR δ 2.30−2.67 (m, 3H), 2.90−3.19 (m, 2H), 3.33 (d, J = 8.1 Hz, 1H), 3.41 (s, 3H) [3.66 (s, 3H)], 4.79−4.87 (m, 1H) [4.34−4.41 (m, 1H)], 5.98 (d, J = 6.9 Hz, 1H) [6.56 (d, J = 8.4 Hz, 1H)], 6.92−7.10 (m, 3H), 7.12−7.25 (m, 3H), 7.25−7.51 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 25.1 (24.2), 28.7 (30.3), 34.1 (33.2), 51.6 (52.9), 55.9 (54.9), 72.0 (70.9), 109.1, 119.6 (2), 123.8 (123.7), 126.4 (126.2), 127.4 (126.5), 127.8 (127.5), 127.9 (2), 128.1 (128.0), 128.6, 131.1 (130.6), 136.1 (135.6), 145.7 (145.6), 169.2 (168.8), 174.5 (174.2).

(2*S*)-2-[2-(2*H*-1,2,3-Benzotriazol-2-yl)-5-oxo-1-pyrrolidinyl]-2-phenylethyl Acetate (10j). Obtained as diastereoisomers in the ratio 52:48 (minor isomer in the parentheses): yellow oil; ^{1} H NMR 1.66 (s, 3H) [1.87 (s, 3H)], 2.35−2.75 (m, 3H), 3.17−3.42 (m, 1H), 3.90−4.12 (m, 1H), 4.48−4.62 (m, 1H) [5.01−5.17 (m, 1H)], 5.24−5.40 (m, 1H) [5.55−5.67 (m, 1H)], 6.22 (d, J = 7.0 Hz, 1H) [6.46 (d, J = 6.9 Hz, 1H)], 6.80−6.95 (m, 1H), 7.01−7.15 (m, 1H), 7.24−7.51 (m, 5H), 7.60−7.75 (m, 1H), 7.81−7.95 (m, 1H); ^{13}C NMR δ 20.2 (20.5), 27.3 (26.7), 29.3 (29.4), 54.9 (53.9), 61.9 (61.5), 77.4 (76.8), 118.3 (118.1), 126.6, 127.1, 127.3, 127.6, 127.7, 127.9, 128.6, 128.9, 134.7, 134.9, 144.3 (144.0), 170.6 (171.6), 176.1 (175.9).

General Procedure for the Reaction of 9 with Allylsilanes. To an ice-cold solution of **9** (0.7 mmol) in dry CH_2Cl_2 (10 mL) under N_2 was added an appropriate allylsilane (2.8 mmol) and the mixture stirred for 10 min. $BF_3{\cdot}Et_2O$ (4.2 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise, and the mixture was stirred at 0 °C for 24 h. Then 2 M NaOH (10 mL) was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. After removal of solvents in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (3:2) as eluent to give **18**.

5-Allyl-1-benzyl-pyrrolidin-2-one (18a): yellow oil; ^{1}H NMR δ 1.72−1.90 (m, 1H), 2.03−2.11 (m, 1H), 2.14−2.30 (m, 1H), 2.36−2.65 (m, 3H), 3.51−3.56 (m, 1H), 4.02 (d, J = 14.7 Hz, 1H), 5.02−5.17 (m, 3H), 5.60−5.73 (m, 1H), 7.20−7.48 (m, 5H); ^{13}C NMR δ 23.1, 30.0, 37.0, 44.1, 56.2, 118.7, 127.4, 127.8, 128.5, 132.4, 136.3, 175.4; HRMS calcd for $C_{14}H_{18}NO$ 216.1388 (M + 1), found 216.1390.

5-Allyl-1-phenethylpyrrolidin-2-one (18b): yellow oil; ^{1}H NMR δ 1.65−1.89 (m, 1H), 1.97−2.53 (m, 5H), 2.75−3.07 (m, 2H), 3.10−3.28 (m, 1H), 3.45−3.67 (m, 1H), 3.85−4.05 (m, 1H), 5.05−5.30 (m, 2H), 5.55−5.80 (m, 1H), 7.15−7.45 (m, 5H); ^{13}C NMR δ 23.4, 30.0, 33.7, 37.4, 41.9, 57.2, 118.7, 126.4, 128.4, 128.6, 132.7, 138.8, 175.0; HRMS calcd for $C_{15}H_{20}NO$ 230.1545 (M + 1), found 230.1546.

5-(2-Methyl-2-propenyl)-1-phenethylpyrrolidin-2-one (18c): yellow oil; ^{1}H NMR δ 1.66 (s, 3H), 1.83−2.10 (m, 2H), 2.25−2.61 (m, 4H), 2.75−3.00 (m, 2H), 3.12−3.30 (m, 1H), 3.45−3.60 (m, 1H), 3.87−4.05 (m, 1H), 4.71 (s, 1H), 4.83 (s, 1H), 7.10−7.50 (m, 5H); ^{13}C NMR δ 22.4, 23.8, 29.8, 33.9, 41.4, 42.1, 56.4, 113.6, 126.4, 128.5, 128.6, 138.7, 140.9, 175.4; HRMS calcd for $C_{16}H_{22}NO$ 244.1701 (M + 1), found 244.1688.

1-(4-Methoxybenzyl)-5-(2-methyl-2-propenyl)pyrrolidin-2-one (18d): yellow oil; ^{1}H NMR δ 1.64 (s, 3H), 1.70−1.80 (m, 1H), 1.91−2.10 (m, 2H), 2.30−2.60 (m, 3H), 3.50−3.60 (m, 1H), 3.80 (s, 3H), 3.94, 4.93 (AB, J = 14.7 Hz, 2H), 4.87 (d, J = 14.5 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 22.9, 24.1, 30.3, 41.7, 44.0, 55.5, 55.6, 113.9,

114.3, 114.4, 118.8, 127.3, 129.2, 129.7, 130.4, 141.7, 159.4, 175.3; HRMS calcd for $C_{16}H_{22}NO_2$ 260.1651 (M + 1), found 260.1659.

5-Allyl-1-(4-methoxyphenethyl)-pyrrolidin-2-one (18e): yellow oil; ^{1}H NMR δ 1.61−1.78 (m, 1H), 1.95−2.10 (m, 1H), 2.10−2.25 (m, 1H), 2.25−2.47 (m, 3H), 2.65−2.90 (m, 2H), 3.00−3.20 (m, 1H), 3.45−3.55 (m, 1H), 3.77 (s, 3H), 3.75−4.00 (m, 1H), 5.05−5.20 (m, 2H), 5.60−5.77 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H); ^{13}C NMR 23.2, 29.9, 32.6, 37.3, 41.9, 55.0, 57.0, 113.7, 118.5, 129.4, 130.6, 132.6, 158.0, 174.7; HRMS calcd for $C_{16}H_{22}NO_2$ 260.1651 (M + 1), found 260.1676.

1-(4-Methoxyphenethyl)-5-(2-methyl-2-propenyl)pyrrolidin-2-one (18f): yellow oil; ^{1}H NMR δ 1.68 (s, 3H), 1.68−1.80 (m, 1H), 1.90−2.10 (m, 2H), 2.20−2.50 (m, 3H), 2.70−2.90 (m, 2H), 3.00−3.20 (m, 1H), 3.40−3.60 (m, 1H), 3.70 (s, 3H), 3.80−4.00 (m, 1H), 4.73 (d, J = 8.5 Hz, 1H), 4.85 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 22.4, 23.8, 29.7, 33.0, 41.5, 42.0, 56.0, 56.1, 113.4, 113.7, 113.9, 129.5, 129.6, 141.1, 158.1, 174.7; HRMS calcd for $C_{17}H_{24}NO_2$ 274.1807 (M + 1), found 274.1802.

Methyl (2*S*)-2-(2-allyl-5-oxo-1-pyrrolidinyl)-3-phenylpropanoate (18g): yellow oil; ^{1}H NMR δ 1.50−1.90 (m, 2H), 2.00−2.60 (m, 4H), 2.70−2.90 (m, 1H), 3.30−3.50 (m, 2H), 3.76 (s, 3H), 4.05−4.20 (m, 1H), 5.00−5.20 (m, 2H), 5.40−5.80 (m, 1H), 7.10−7.50 (m, 5H); ^{13}C NMR δ 23.7, 29.5, 34.8, 37.8, 37.9, 52.4, 57.7, 59.6, 118.3, 126.7, 128.4, 129.1, 133.2, 170.3, 174.9; HRMS calcd for $C_{17}H_{22}NO_3$ 288.1600 (M + 1), found 288.1588.

General Procedure for the Reaction of 9 with Organozinc Reagents. To an ice-cold solution of Grignard reagent (8.0 mmol) in dry THF (10 mL) under N_2, was added $ZnCl_2$ (8.5 mmol) and the solution allowed to warm to room temperature over 0.5 h. A solution of **9b** or **9e** (2.7 mmol) in dry THF (10 mL) was then added, and the reaction mixture was refluxed for 48 h. After cooling, CH_2Cl_2 (20 mL) and 2 M NaOH (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. After removal of solvents in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (3:2) as eluent to give **19a**−**g**.

1-Benzyl-5-(1-propynyl)pyrrolidin-2-one (19a): yellow oil; ^{1}H NMR δ 1.84 (s, 3H), 2.00−2.18 (m, 1H), 2.20−2.33 (m, 1H), 2.35−2.50 (m, 1H), 2.50−2.71 (m, 1H), 4.00−4.09 (m, 2H), 5.04 (d, J = 14.6 Hz, 1H), 7.26−7.31 (m, 5H); ^{13}C NMR δ 26.2, 30.0, 44.3, 48.6, 81.6, 127.4, 128.4, 128.5, 136.4, 174.0; HRMS calcd for $C_{14}H_{16}NO$ 214.1232 (M + 1), found 214.1215.

1-(4-Methoxyphenethyl)-5-(1-propynyl)pyrrolidin-2-one (19b): yellow oil; ^{1}H NMR δ 1.83 (s, 3H), 1.90−2.10 (m, 1H), 2.15−2.30 (m, 1H), 2.30−2.40 (m, 1H), 2.40−2.55 (m, 1H), 2.70−2.90 (m, 2H), 3.20−3.35 (m, 1H), 3.77 (s, 3H), 3.80−3.90 (m, 1H), 4.05−4.15 (m, 1H), 6.82 (d, J = 7.7 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H); ^{13}C NMR δ 3.5, 26.8, 30.1, 32.8, 42.5, 49.9, 55.3, 76.9, 81.3, 114.0, 129.7, 130.9, 158.2, 174.2; HRMS calcd for $C_{16}H_{20}NO_2$ 258.1494 (M + 1), found 258.1490.

1-(4-Methoxyphenethyl)-5-vinyl-pyrrolidin-2-one (19c): colorless crystalline; mp 63−64 °C (from $CHCl_3$/hexane); ^{1}H NMR δ 1.60−1.80 (m, 1H), 2.10−2.20 (m, 1H), 2.20−2.50 (m, 2H), 2.60−2.90 (m, 2H), 3.00−3.20 (m, 1H), 3.78 (s, 3H), 3.70−3.90 (m, 2H), 5.16 (d, J = 17.0 Hz, 1H), 5.19 (d, J = 8.4 Hz, 1H), 5.50−5.70 (m, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 25.5, 30.0, 32.7, 42.2, 55.1, 61.7, 113.7, 117.9, 129.7, 131.0, 137.8, 158.1, 174.8. Anal. Calcd for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.82.

1-(4-Methoxyphenethyl)-5-(1-propenyl)pyrrolidin-2-one (19d): yellow oil; ^{1}H NMR δ 1.50−1.90 (m, 4H), 2.00−2.20 (m, 1H), 2.20−2.50 (m, 2H), 2.60−2.85 (m, 2H), 3.00−3.20 (m, 1H), 3.60−3.80 (m, 1H), 3.77 (s, 3H), 4.20−4.40 (m, 1H), 5.10−5.30 (m, 1H), 5.50−5.80 (m, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 12.8, 25.6, 30.3, 32.8, 42.4, 54.8, 55.1, 113.7, 128.0, 129.5, 130.1, 130.9, 158.0, 174.7; HRMS calcd for $C_{16}H_{22}NO_2$ 260.1651 (M + 1), found 260.1643.

5-Benzyl-1-(4-methoxyphenethyl)pyrrolidin-2-one (19e): yellow oil; ^{1}H NMR δ 1.60−1.75 (m, 1H), 1.80−1.90 (m, 1H), 1.90−2.10 (m, 1H), 2.10−2.20 (m, 1H), 2.40−2.60 (m, 1H), 2.70−3.00 (m, 2H), 3.00−3.30 (m, 1H), 3.50−3.65 (m, 1H), 3.76 (s, 3H), 3.85−4.00 (m, 1H), 4.30−4.50 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.02−7.20 (m, 3H), 7.20−7.40 (m, 4H); ^{13}C NMR δ 23.6, 24.6, 28.6, 29.6, 32.9, 33.0, 39.2, 42.0, 42.1, 55.0, 58.8, 68.1, 89.0, 113.7, 126.5, 127.5, 127.7, 128.4, 129.0, 129.4, 129.5, 130.7, 130.8, 136.8, 158.0, 174.8; HRMS calcd for $C_{20}H_{24}NO_2$ 310.1807 (M + 1), found 310.1806.

5-Cyclopentyl-1-(4-methoxyphenethyl)pyrrolidin-2-one (19f): yellow oil; ^{1}H NMR δ 1.40−1.80 (m, 8H), 1.80−2.00 (m, 1H), 2.00−2.40 (m, 2H), 2.40−2.60 (m, 1H), 2.70−2.90 (m, 2H), 3.10−3.35 (m, 1H), 3.60−3.80 (m, 1H), 3.78 (s, 3H), 3.80−3.90 (m, 1H), 4.64 (d, J = 5.9 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 23.1, 25.9, 28.7, 32.3, 33.1, 33.2, 42.1, 55.1, 78.6, 88.5, 113.8, 129.5, 131.0, 158.1, 174.6; HRMS calcd for $C_{18}H_{26}NO_2$ 288.1964, found 288.1961.

1-(4-Methoxyphenethyl)-5-pentylpyrrolidin-2-one (19g): colorless oil; ^{1}H NMR δ 0.90 (br s, 3H), 1.22−1.38 (m, 4H), 1.50−1.63 (m, 2H), 1.90−2.00 (m, 2H), 2.20−2.40 (m, 1H), 2.40−2.60 (m, 1H), 2.70−2.90 (m, 2H), 3.20−3.40 (m, 3H), 3.60−3.80 (m, 1H), 3.85 (s, 3H), 4.67−4.69 (m, 1H), 6.83 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H); ^{13}C NMR δ 13.9, 22.3, 24.6, 28.3, 28.9, 29.3, 33.1, 42.1, 55.1, 65.9, 89.5, 113.8, 129.5, 131.0, 158.1, 174.8; HRMS calcd for $C_{18}H_{28}NO_2$ 290.2120 (M + 1), found 290.2101.

To freshly cleaned and dried Zn powder (1.56 g, 23.9 mmol) in THF (20 mL) was added diethyl 2-bromomalonate (0.75 g, 3.1 mmol) and the mixture allowed to reflux at 80 °C for 1 h. A solution of **9e** (0.35 g, 1.04 mmol) in THF (20 mL) was then added dropwise over a period of 10 min. The solution was allowed to reflux for 48 h, cooled, and quenched by 2 M NaOH (20 mL). The mixture was extracted with three portions of CH_2Cl_2 and dried over Na_2SO_4. After removal of solvents in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (3:1) as eluent to give **19h**.

Diethyl 2-(5-oxo-1-phenethyl-2-pyrrolidinyl)malonate (19h): yellow oil; ^{1}H NMR δ 1.20−1.39 (m, 6H), 2.10−2.48 (m, 4H), 2.70−2.86 (m, 1H), 2.86−3.12 (m, 2H), 3.68 (d, J = 5.2 Hz, 1H), 3.90−4.05 (m, 1H), 4.10−4.30 (m, 5H), 7.10−7.40 (m, 5H); ^{13}C NMR δ 13.9, 21.5, 29.4, 33.3, 42.2, 53.5, 56.8, 61.7, 61.8, 126.4, 128.4, 128.6, 138.4, 166.9, 167.0, 175.1. Anal. Calcd for $C_{19}H_{25}NO_5$: N, 4.03. Found: N, 4.50.

General Procedure for the Reaction of 9 with Phosphorus Compounds. To a solution of **9** (1.3 mmol) in dry CH_2Cl_2 (20 mL) under N_2 at 0 °C was added triethyl phosphite (0.36 mL, 2.1 mmol) and $ZnBr_2$ (0.30 g, 1.3 mmol). The reaction mixture was stirred at 0 °C for 20 h and then quenched with 2 M NaOH (10 mL). The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (4:1) as eluent to afford **20**.

Diethyl 1-(2-hydroxyethyl)-5-oxo-2-pyrrolidinylphosphonate (20a): yellow oil; ^{1}H NMR δ 1.30−1.50 (m, 6H), 2.05 (s, 2H), 2.20−2.45 (m, 2H), 2.45−2.60 (m, 1H), 3.40−3.60 (m, 1H), 4.00−4.30 (m, 7H), 4.30−4.50 (m, 1H); ^{13}C NMR δ 16.3 (J = 5.4 Hz), 20.4 (J = 32.3 Hz), 29.3, 40.9, 52.9, 55.1, 60.9, 62.3 (J = 7.1 Hz), 62.9 (J = 7.0 Hz), 170.6, 175.4 (J = 3.3 Hz); HRMS calcd for $C_{10}H_{21}NO_5P$ 266.1157 (M + 1), found 266.1162.

Diethyl 1-(4-methoxybenzyl)-5-oxo-2-pyrrolidinylphosphonate (20b): yellow oil; ^{1}H NMR δ 1.35 (t, J = 8.1 Hz, 6H), 2.00−2.50 (m, 3H), 2.55−2.70 (m, 1H), 3.63 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 4.10−4.30 (m, 5H), 5.17 (d, J = 14.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 16.2 (J = 5.5 Hz), 16.3 (J = 5.3 Hz), 29.5, 44.4, 51.2, 53.4, 55.0, 55.3, 62.2 (J = 7.3 Hz), 62.9 (J = 7.1 Hz), 113.8, 127.7, 129.5, 158.9, 174.9 (J = 2.9 Hz); HRMS calcd for $C_{16}H_{25}NO_5P$ 342.1470 (M + 1), found 342.1470.

Diethyl 1-(3,4-dimethoxybenzyl)-5-oxo-2-pyrrolidinylphosphonate (20c): yellow oil; ^{1}H NMR δ 1.36 (t, J = 6.9 Hz, 6H), 2.00−2.50 (m, 3H), 2.55−2.77 (m, 1H), 3.68 (d, J = 9.4 Hz, 1H), 3.86 (s, 6H), 4.10−4.30 (m, 5H), 5.16 (d, J = 14.7 Hz, 1H), 6.80−6.88 (m, 3H); ^{13}C NMR δ 16.2 (J = 5.5 Hz), 16.3 (J = 5.2 Hz), 20.1, 29.7, 44.9, 51.3, 53.5, 55.7 (J = 8.2 Hz),

62.5 (J = 7.3 Hz), 63.1 (J = 7.2 Hz), 110.8 (J = 38.7 Hz), 120.7, 128.0, 148.5 (J = 38.7 Hz), 175.1 (J = 2.9 Hz); HRMS calcd for $C_{17}H_{27}NO_6P$ 372.1576 (M + 1), found 372.1597.

Diethyl 1-(4-methoxyphenethyl)-5-oxo-2-pyrrolidinylphosphonate (20d): yellow oil; ^{1}H NMR δ 1.33 (t, J = 6.9 Hz, 6H), 2.00−2.35 (m, 3H), 2.40−2.60 (m, 1H), 2.70−2.85 (m, 1H), 2.85−3.00 (m, 1H), 3.35−3.50 (m, 1H), 3.50−3.60 (m, 1H), 3.80 (s, 3H), 4.00−4.10 (m, 1H), 4.10−4.25 (m, 4H), 6.82 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 16.3 (J = 5.6 Hz), 16.4 (J = 5.2 Hz), 20.3, 29.5, 32.3, 43.5, 53.2, 55.0, 55.3, 62.0 (J = 7.0 Hz), 62.7 (J = 7.3 Hz), 113.7, 129.5, 130.4, 158.0, 174.9 (J = 3.0 Hz); HRMS calcd for $C_{17}H_{27}NO_5P$ 356.1627 (M + 1), found 356.1627.

Diethyl 1-[(1*S*)-2-hydroxy-1-phenylethyl]-5-oxo-2-pyrrolidinylphosphonate (20e): yellow oil; ^{1}H NMR δ 1.30−1.40 (m, 6H), 2.00−2.40 (m, 2H), 2.43−2.65 (m, 1H), 2.70−3.10 (m, 2H), 3.40−3.60 (m, 3H), 4.00−4.30 (m, 4H), 7.20−7.45 (m, 5H); ^{13}C NMR δ 16.2 (J = 5.2 Hz), 16.3 (J = 5.1 Hz), 20.2, 29.5, 33.1, 43.3, 50.1, 53.1, 55.3, 62.1 (J = 7.3 Hz), 62.8 (J = 7.0 Hz), 126.3, 128.3, 128.5, 138.4 (J = 4.1 Hz), 175.0 (J = 3.1 Hz). Anal. Calcd for $C_{16}H_{24}NO_5P$: C, 56.30, H, 7.09, N, 4.10. Found: C, 55.83, H, 7.28, N, 4.49.

Methyl (2*S*)-2-[2-(diethoxyphosphoryl)-5-oxo-1-pyrrolidinyl]-3-phenylpropanoate (20f): yellow oil; ^{1}H NMR δ 1.20−1.50 (m, 6H), 1.70−2.30 (m, 2H), 2.45−2.60 (m, 1H), 3.25−3.40 (m, 1H), 3.60−3.70 (m, 1H), 3.73 (s, 3H), 3.95−4.30 (m, 6H), 4.90−5.10 (m, 1H), 7.10−7.30 (m, 5H); ^{13}C NMR δ 16.2 (J = 6.6 Hz), 16.4 (J = 5.6 Hz), 20.6 (J = 2.6 Hz), 24.8 (J = 5.3 Hz), 29.5 (J = 12.5 Hz), 33.8, 34.6, 52.2, 52.6, 54.8, 55.0, 56.3, 57.2, 59.1, 62.0 (J = 7.1 Hz), 62.8 (J = 4.8 Hz), 63.1 (J = 4.6 Hz), 68.2, 70.4, 126.4, 126.8, 128.3, 128.5, 128.6, 129.0, 137.1, 137.8, 169.6, 170.3, 174.8, 176.7 (J = 5.0 Hz); HRMS calcd for $C_{18}H_{27}NO_6P$ 384.1576 (M + 1), found 384.1574.

Supporting Information Available: ^{1}H, ^{13}C NMR spectra and CHN analyses or HRMS for compounds **9a**,**c**−**g**,**k**, **10a**,**c**−**g**,**k**, and **11a**−**c**,**h**,**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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