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New Methods and Reagents in Organic Synthesis. 34.[1] Diphenyl Phosphorazidate (DPPA) as a 1,3-Dipole. A Simple, Efficient Conversion of Akyl Phenyl Ketones to 2-Phenylalkanoic Acids[2]

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Propiophenone (**11**) was conveniently converted to its enamines **12a—c** using boron trifluoride etherate as a catalyst. Reaction of diphenyl phosphorazidate (DPPA) with the enamines **12a—c** efficiently afforded the *N*-phosphorylated amidines **14a—c** by the 1,3-dipolar cycloaddition of DPPA to the enamine double bond, followed by the evolution of nitrogen from the intermediate triazoline **13**, and 1,2-migration of the phenyl group. 1,3-Dipolar elimination products **15a—c** were also formed, though in very low yields. Some chemical properties of the *N*-phosphorylated amidine **14a**, as well as the 1,3-dipolar character of DPPA, were investigated. By the same reaction sequences (enamine formation followed by the 1,3-dipolar cycloaddition of DPPA), some alkyl phenyl ketones **29a—c** were conveniently converted to the *N*-phosphorylated amidines **31a**, **31b**, and **27** *via* the enamines **30a—c**. However, in the case of acetophenone and its derivatives **33a—c**, these reaction sequences proceeded sluggishly. Alkaline hydrolysis of the *N*-phosphorylated amidines **14a**, **31a**, **31b**, and **27** with potassium hydroxide afforded 2-phenylalkanoic acids **25** and **32a—c**, respectively, in excellent yields. The overall three-step process of successive treatment of alkyl phenyl ketones (alkyl≒methyl) with pyrrolidine, DPPA, and potassium hydroxide may provide a new general method for the efficient conversion of alkyl aryl ketones to 2-arylalkanoic acids.

Keywords——enamine; diphenyl phosphorazidate; boron trifluoride etherate; 1,3-dipolar cycloaddition; 1,2-migration; *N*-phosphorylated amidine; alkaline hydrolysis; alkyl aryl ketone; 2-arylalkanoic acid

We have already demonstrated[4] that diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[5] acts as a 1,3-dipole towards enamines of cyclic ketones. Thus, pyrrolidine enamines **2** from various cyclic ketones **1** react smoothly with DPPA to give the ring-contracted *N*-phosphorylated amidines **4** *via* the 1,3-dipolar cycloadducts **3**, as shown in Chart 1. Hydrolysis of **4** affords the ring-contracted carboxylic acids **5**.

Our attention was next directed to the application of this reaction sequence to enamines of alkyl aryl ketones. The overall process is depicted in Chart 2. The enamines **7** derived from alkyl aryl ketones **6** should react with DPPA to give the 1,3-dipolar cycloadducts **8a**. The triazoline rings of **8a** should be cleaved to give betaines **8b**. Evolution of nitrogen from **8b** followed by 1,2-aryl migration should give the *N*-phosphorylated amidines **9**, which should then undergo hydrolysis to give 2-arylalkanoic acids **10**.

As a preliminary investigation, we chose propiophenone (**11**), which was easily converted to the pyrrolidine enamine **12a** by treatment with pyrrolidine in refluxing benzene in the presence of catalytic amounts of boron trifluoride etherate. Addition of DPPA to the enamine **12a** in tetrahydrofuran or ethyl acetate afforded the desired amidine **14a** in about 80% yield *via* the 1,3-dipolar cycloadduct **13a** (path a in Chart 3). Another amidine **15a** was

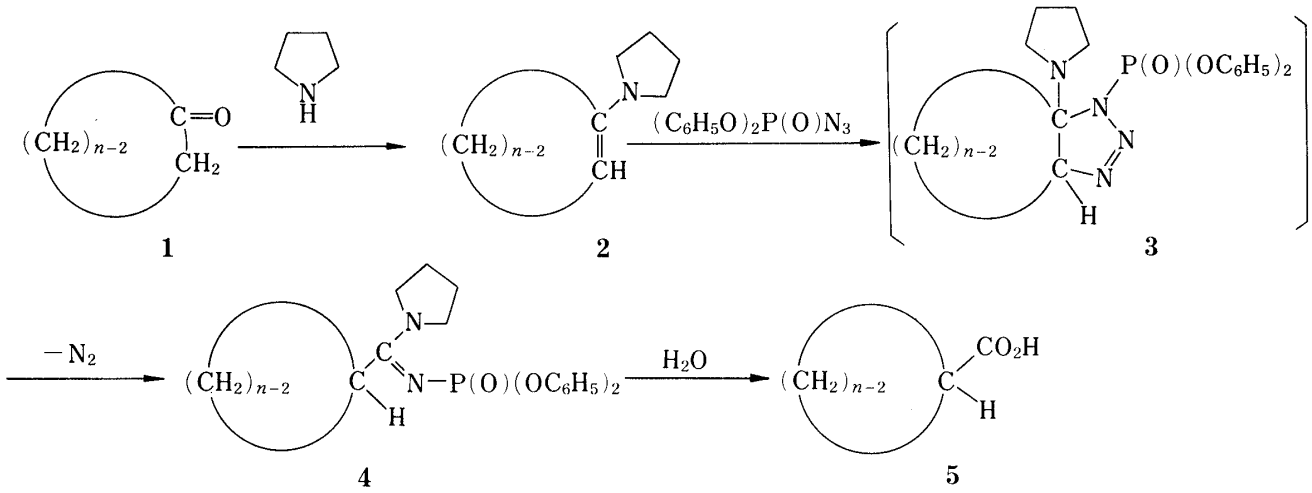


Chart 1

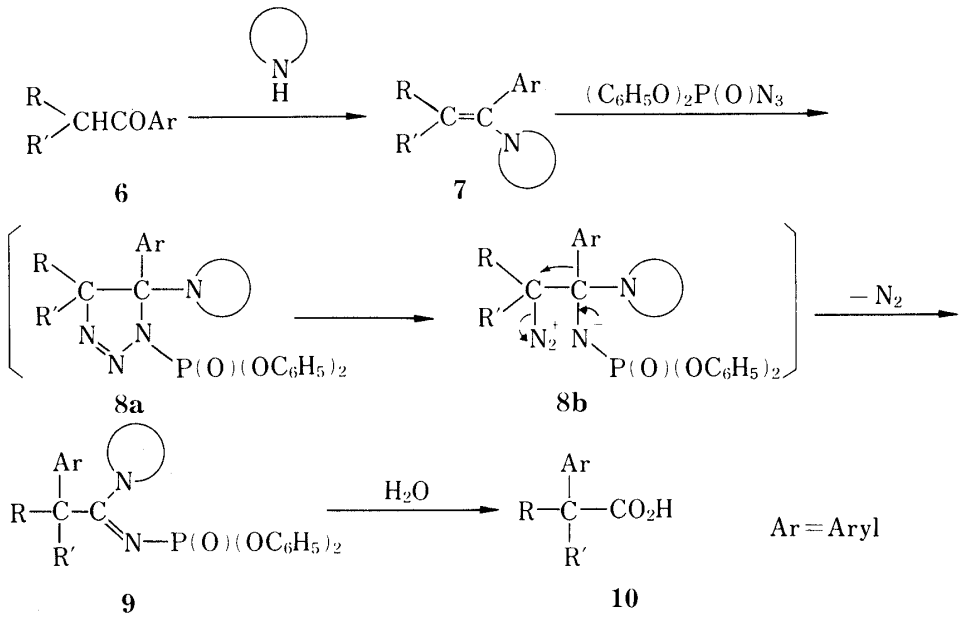


Chart 2

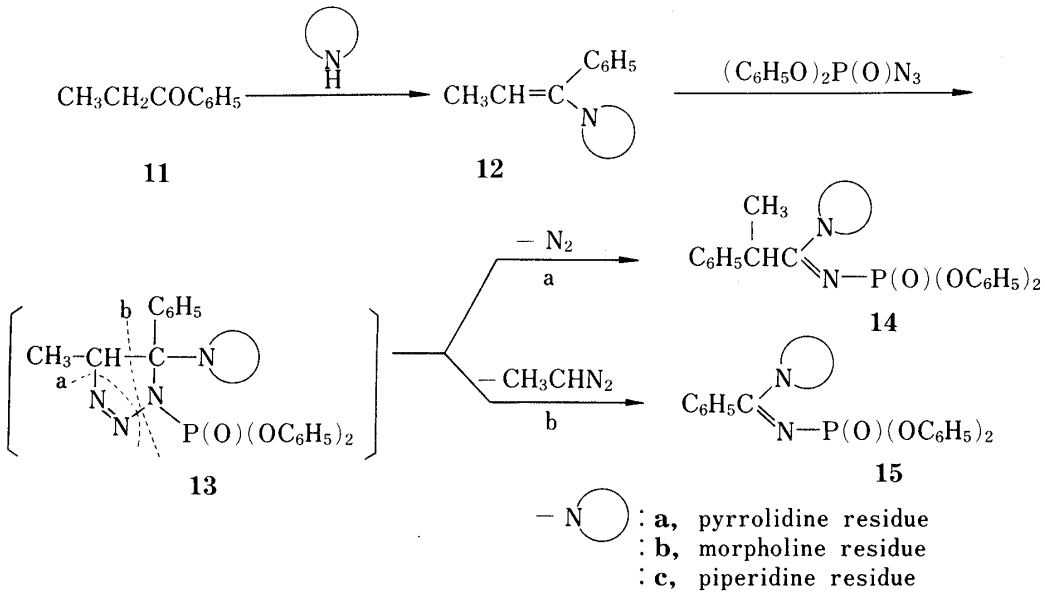


Chart 3

TABLE I. Conversion of Propiophenone (**11**) to Amidines **14** and **15**

Run	Amine	Enamine **12** Yield (%)	Solvent for amidine formation	Yield (%) of amidine	
				14	**15**
1	Pyrrolidine	79	Ethyl acetate	81	3.6
2	Pyrrolidine		Tetrahydrofuran	80	3.6
3	Pyrrolidine	[a]	Tetrahydrofuran	84[b]	3[b]
4	Morpholine	55	Ethyl acetate	63	7
5	Piperidine	62	Ethyl acetate	67	6.2

a) By the one-flask procedure. *b*) Based on **11**.

obtained in 3.6% yield. This by-product is presumably formed by the 1,3-dipolar elimination of **13a** (path b),[6] as shown in Chart 3.

When pyrrolidine was replaced with morpholine or piperidine, the yields of the enamine **12b** or **12c** and the *N*-phosphorylated amidine **14b** or **14c** decreased while the yield of the 1,3-dipolar elimination product **15b** or **15c** increased, as summarized in Table I. The most satisfactory result was obtained by the one-flask procedure in which the reaction of propiophenone (**11**) with pyrrolidine was carried out as usual, and the solvent was removed *in vacuo*. The residue was dissolved in tetrahydrofuran under an argon atmosphere and the reaction with DPPA was carried out in the same flask. By this one-flask procedure, the amidine **14a** was obtained in 84% yield based on **11**.

Interestingly, neither the methyl enol ether **16**, the enol acetate **17**,[7] nor the silyl enol ether **18**[8] underwent the 1,3-dipolar cycloaddition reaction with DPPA.[4] Furthermore, 1-phenyl-1-propene (**19**) and ethyl 2-cyano-3-hydroxy-3-phenylacrylate[9] (**20**) were also completely unreactive to DPPA. The starting materials were recovered in every case.

However, the lithium enolate **21a** of propiophenone, prepared from propiophenone (**11**) and lithium diisopropylamide in tetrahydrofuran, reacted with DPPA to give the enol phosphate **22** (a *cis*, *trans* mixture) and 4-methyl-5-phenyl-1*H*-1,2,3-triazole (**23**) in 56 and 25% yields, respectively, as shown in Chart 4. The latter compound may be formed by the 1,3-dipolar cycloaddition of DPPA to the enolate **21a**, followed by elimination of lithium diphenyl phosphate. Addition of hexamethylphosphoric triamide as a co-solvent did not change the reaction course. Replacement of the base with sodium hydride afforded the triazole **23** in 21% yield, with recovery of propiophenone.

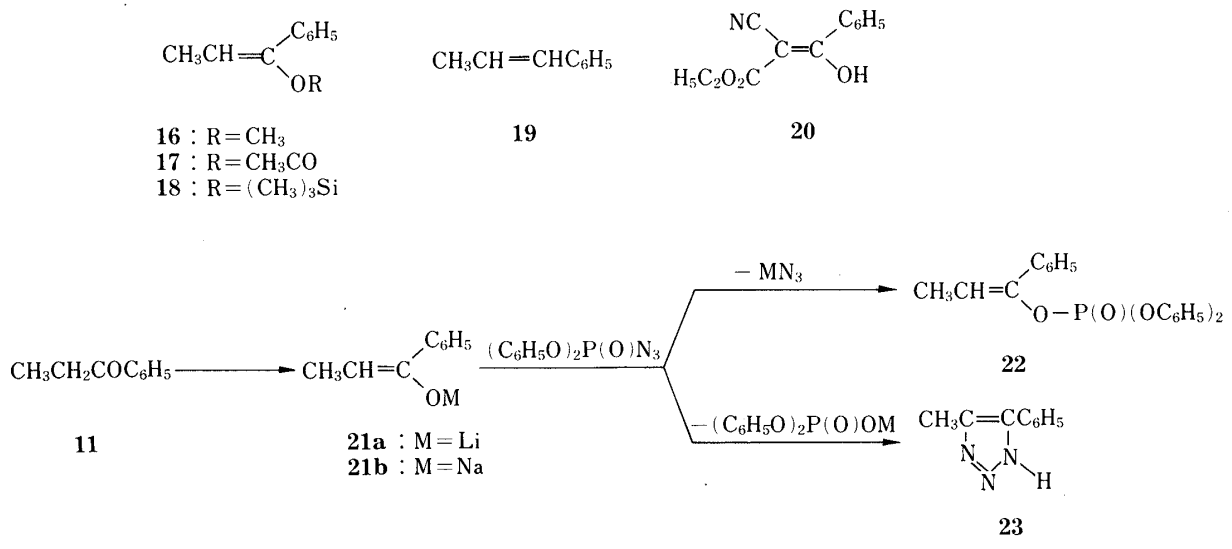


Chart 4

Next, some chemical properties of the *N*-phosphorylated amidine **14a** were investigated. When **14a** was treated with hot ethanolic potassium hydroxide, 1-(2-phenylpropionyl)-pyrrolidine (**24**) was obtained in 31% yield. The structure of **24** was confirmed by comparison with a sample prepared from 2-phenylpropionic acid (**25**) and pyrrolidine using diethyl phosphorocyanidate as a coupling reagent.[10] However, a change of the solvent for the alkaline hydrolysis from hot ethanol to hot ethylene glycol afforded 2-phenylpropionic acid in 91% yield, as shown in Chart 5. Reduction of the amidine **14a** with an excess of lithium aluminum hydride in refluxing tetrahydrofuran proceeded smoothly to give the pyrrolidinylamine **26** in 76% yield; this product was characterized as its methiodide.

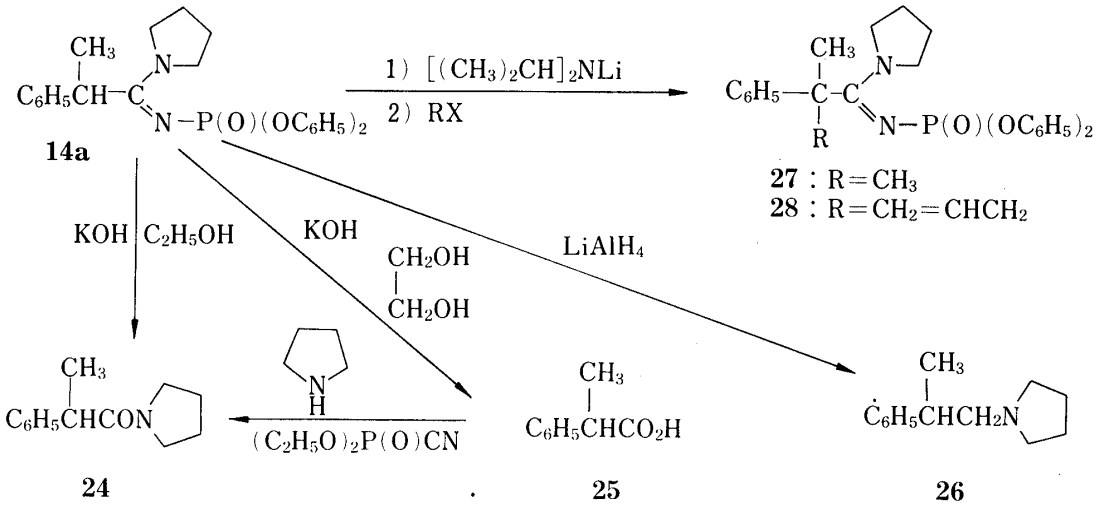
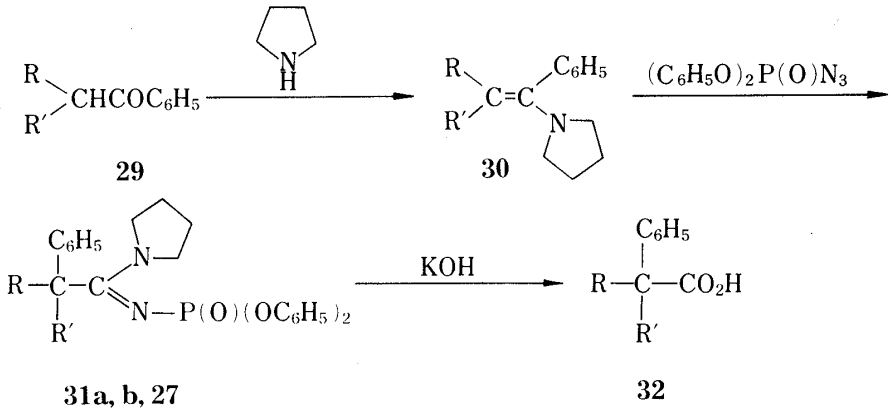


Chart 5

Since the carbon atom adjacent to the amidino group of the *N*-phosphorylated amidine **14a** was expected to be acidic, formation of the metallic salt followed by alkylation was attempted. Treatment of **14a** with lithium diisopropylamide followed by the addition of methyl iodide produced the methylated amidine **27** in 62% yield. Similar treatment of the lithiated amidine with allyl bromide yielded the allylated amidine **28** in 50% yield.

The above experiments demonstrated that a three-step conversion of propiophenone (**11**) to 2-phenylpropionic acid (**25**) could be achieved efficiently, and the method was applied to the conversion of the other alkyl phenyl ketones to 2-phenylalkanoic acids.[1] Butyrophenone (**29a**) and 4-pentenophenone (**29b**) were easily converted to the pyrrolidine enamines **30a** and **30b** with pyrrolidine in refluxing toluene in the presence of boron trifluoride etherate, as shown in Chart 6. The pyrrolidine enamine **30c** of isobutyrophenone (**29c**) was prepared according to the literature[11] using titanium tetrachloride, since the analogous conversion using boron trifluoride etherate proceeded sluggishly. The enamines **30a—c** were easily transformed to the corresponding *N*-phosphorylated amidines **31a**, **31b**, and **27** by the reaction with DPPA in tetrahydrofuran. The one-flask procedure as well as the use of an argon atmosphere afforded better results, as shown in Table II. Interestingly, the double bond of **30b** was completely inactive, demonstrating the functional specificity of the DPPA method.[12] Hydrolysis of the *N*-phosphorylated amidines **31a**, **31b**, and **27** was accomplished with potassium hydroxide in refluxing ethylene glycol to give 2-phenylalkanoic acids **32** in 91—100% yields.

Finally, some experiments on the 1,3-dipolar cycloaddition of DPPA to enamines of acetophenone and its derivatives **33a—c** were carried out. The enamines were so labile that the one-flask procedure was employed under an argon atmosphere. Acetophenone (**33a**) afforded the expected *N*-phosphorylated amidine **34a** in only 5% yield. Though the methoxy derivative



a : R = CH_3CH_2, R′ = H
b : R = CH_2=$CHCH_2$, R′ = H
c : R = R′ = CH_3

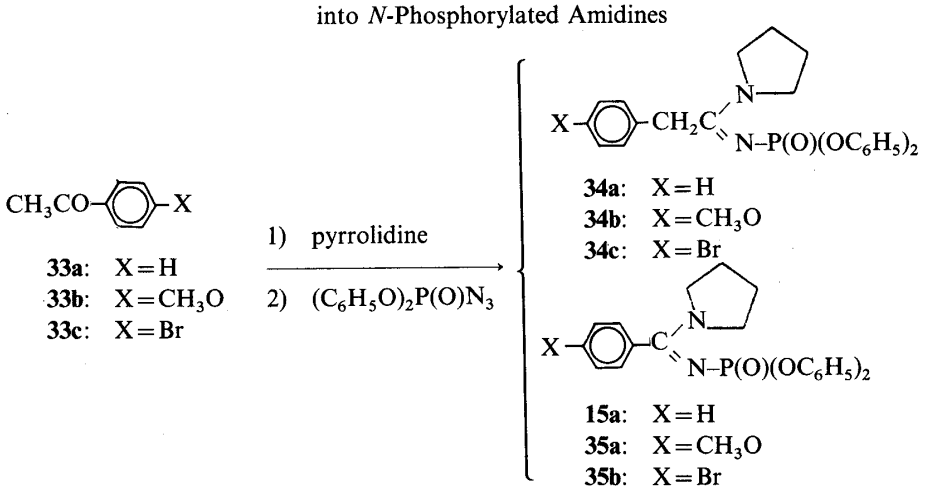
Chart 6

TABLE II. Conversion of Alkyl Phenyl Ketones **29** to 2-Phenylalkanoic Acids **32**

Run	R	R′	Yield (%)		
			Enamine **30**	Amidine **31a, b, 27**	Acid **32**
1	CH_3CH_2	H	77	74	91
2	CH_3CH_2	H		82[a]	
3	CH_3CH_2	H	[b]	81[a,c]	
4	CH_2=$CHCH_2$	H	79	80[d]	91
5	CH_3	CH_3	[e]	70	Quant.

a) Under argon. *b*) By the one-flask procedure.
c) Based on **28**. *d*) **15** (6.4%). *e*) Ref. 11.

TABLE III. Conversion of Acetophenone and Its Derivatives (**33**) into *N*-Phosphorylated Amidines



Run	X	Yield (%)[a] of amidine	
		34a—c	**15a, 35a, b**
1	H	5	17
2	CH_3	15	25
3	Br	—	26

a) Based on **33**.

33b gave the amidine **34b** in 15% yield, the bromo derivative **33c** did not yield any of the desired *N*-phosphorylated amidine **34c**. In all cases, the main products were found to be the 1,3-dipolar elimination products **15a**, **35a**, and **35b**, as shown in Table III, though the yields were not satisfactory.

The present investigation has clearly shown that a facile conversion of alkyl aryl ketones (alkyl ≠ methyl) to 2-arylalkanoic acids may be conveniently achieved by successive treatments with pyrrolidine, DPPA, and potassium hydroxide. One of the remarkable features of the method is that all the transformations can be carried out in multigram quantities using a single reaction vessel. Application of the method to an efficient synthesis of medicinally important 2-arylpropionic acids will be reported in our forthcoming paper.[13]

Experimental

Melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-1 or DS-402G spectrophotometer (potassium bromide discs for crystals and films for oils). Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-PS-100 or Hitachi R-24 spectrometer with tetramethylsilane as an internal standard using carbon tetrachloride or deuteriochloroform.

1-(1-Phenyl-1-propenyl)pyrrolidine (12a)——A mixture of propiophenone (**11**) (9.38 g, 70 mmol), pyrrolidine (14.93 g, 70 × 3 mmol), and boron trifluoride etherate (0.99 g, 70 × 0.1 mmol) in benzene (50 ml) was refluxed for 67 h using a Cope water separator and molecular sieve 4A as the dehydrating agent. After removal of the solvent *in vacuo*, the residue was distilled at 101 °C (3 mmHg) (lit.[14] bp 139.5—140 °C (13 mmHg)) to give **12a** (10.33 g, 79%) as a pale yellow oil. IR ν_{max} cm^{-1}: 1640. NMR δ: 1.41 (3H, d, J=7 Hz), 1.65—1.87 (4H, m), 2.77 (4H, m), 4.28 (1H, q, J= 7 Hz), 7.16 (5H, s).

1-(1-Phenyl-1-propenyl)morpholine (12b)——A mixture of propiophenone (**11**) (5.36 g, 40 mmol), morpholine (10.45 g, 40 × 3 mmol), and boron trifluoride etherate (0.28 g, 40 × 0.05 mmol) in toluene (30 ml) was refluxed for 67 h and worked up as described for the preparation of **12a** to give **12b** (4.46 g, 55%) as a colorless oil, bp 103 °C (3 mmHg) (lit.[14] bp 160—160.5 °C (14 mmHg)). IR ν_{max} cm^{-1}: 1645. NMR δ: 1.15 (3H, d, J=7 Hz), 2.55—2.72 (4H, m), 3.51—3.66 (4H, m), 4.60 (1H, q, J=7 Hz), 7.23 (5H, s).

1-(1-Phenyl-1-propenyl)piperidine (12c)——A mixture of propiophenone (**11**) (2.68 g, 20 mmol), piperidine (5.3 g, 20 × 3 mmol), and boron trifluoride etherate (0.14 g, 20 × 0.05 mmol) in toluene (30 ml) was refluxed for 48 h and worked up as described for the preparation of **12a** to give **12c** (2.50 g, 62%) as a colorless oil, bp 99.5—100 °C (3 mmHg) (lit.[14] 139—139.5 °C (10 mmHg)). IR ν_{max} cm^{-1}: 1630. NMR δ: 1.49 and 1.60 (9H, m) 2.64 (4H, m), 4.56 (1H, q, J=7 Hz), 7.24 (5H, s).

1-(1-Phenyl-1-butenyl)pyrrolidine (30a)——A mixture of butyrophenone (**29a**) (4.44 g, 30 mmol), pyrrolidine (6.40 g, 30 × 3 mmol), and boron trifluoride etherate (0.43 g, 30 × 0.1 mmol) in toluene (50 ml) was refluxed for 47 h and worked up as described for the preparation of **12a** to give **30a** (4.66 g, 77%) as a pale yellow oil, bp 106—108 °C (4 mmHg). IR ν_{max} cm^{-1}: 1640. NMR δ: 0.88 (3H, t, J=7 Hz), 1.78 (6H, m), 2.81 (4H, m), 4.23 (1H, t, J=7 Hz), 7.19 (5H s).

1-(1-Phenyl-1,4-pentadienyl)pyrrolidine (30b)——A mixture of 4-pentenophenone (**29b**) (1.60 g, 10 mmol), pyrrolidine (2.13 g, 10 × 3 mmol), and boron trifluoride etherate (0.14 g, 10 × 0.1 mmol) in toluene (50 ml) was refluxed for 46 h and worked up as described for the preparation of **12a** to give **30b** (1.68 g, 79%) as a pale yellow viscous oil, bp 80—84 °C (0.15 mmHg). IR ν_{max} cm^{-1}: 1635, 1620. NMR δ: 1.8 (4H, m), 2.53 and 2.8 (6H, m), 4.20 (1H, t, J= 8 Hz), 4.69—4.99 (2H, m), 5.39—6.02 (1H, m), 7.19 (5H, s).

1-(2-Methyl-1-phenyl-1-propenyl)pyrrolidine (30c)——Prepared according to the literature[11] using titanium tetrachloride; a colorless oil, bp 88—90 °C (2 mmHg) (lit.[11] 86 °C (1 mmHg)). IR ν_{max} cm^{-1}: 1645. NMR δ: 1.69 (m) and 1.82 (s) (10H), 2.76 (4H, m), 7.0 (5H, m).

Diphenyl *N*-[2-Phenyl-1-(1-pyrrolidinyl)propylidene]phosphoramidate (14a)——(a) In Ethyl Acetate: DPPA (1.65 g, 5.4 × 1.1 mmol) was added to the enamine **12a** (1.01 g, 5.4 mmol) in ethyl acetate (15 ml). The mixture was stirred at room temperature for 1 h and at 40 °C for 1 h, then refluxed for 2 h. A mixture of ethyl acetate and benzene (1 : 1, 100 ml) was added, and the mixture was successively washed with 30 ml each of 5% aqueous citric acid, water, saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, then dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*, and the residue was separated by silica gel column chromatography with ethyl acetate–benzene (1 : 5) to give **14a** (1.91 g, 81%) in the first eluate fraction. Recrystallization from ethyl acetate–hexane gave colorless needles, mp 74—76 °C. IR ν_{max} cm^{-1}: 1557, 1276, 1209, 1165. NMR δ: 1.47 (3H, d, J=7 Hz), 1.61 (4H, m), 2.13—3.41 (4H, m), 4.79 (1H, q, J=7 Hz), 7.11 (15H, m). *Anal.* Calcd for $C_{25}H_{27}N_2O_3P$: C, 69.11; H, 6.26; N, 6.45. Found C, 68.72; H, 6.53; N, 6.47.

The amidine **15a** (0.08 g, 3.6%) was obtained in the second eluate fraction. Recrystallization from diethyl ether–

petroleum benzin afforded colorless crystals, mp 101—102.5 °C. IR ν_{max} cm^{-1}: 1550, 1474, 1263, 1256, 1210. NMR δ: 1.79 (4H, m), 3.15—3.54 (4H, m), 6.79 and 7.28 (15H, m). *Anal.* Calcd for $C_{23}H_{23}N_2O_3P$: C, 67.97; H, 5.70; N, 6.89. Found: C, 67.78; H, 5.72; N, 7.00.

(b) In Tetrahydrofuran: A mixture of the enamine **12a** (3.05 g, 16.3 mmol) and DPPA (4.95 g, 16.3 × 1.1 mmol) in tetrahydrofuran (45 ml) was stirred and worked up as described in (a) to give **14a** (5.68 g, 80%) and **15a** (0.24 g, 3.6%).

(c) By The One-Flask Procedure: A mixture of propiophenone (**11**) (0.67 g, 5 mmol), pyrrolidine (1.07 g, 5 × 3 mmol), and boron trifluoride etherate (0.07 g, 5 × 0.1 mmol) in toluene (30 ml) was refluxed for 40 h using a Cope water separator and molecular sieve 4A as the dehydrating agent. After removal of the solvent *in vacuo*, the residue was dissolved in tetrahydrofuran (15 ml) under argon and DPPA (1.65 g, 5 × 1.2 mmol) was added. The mixture was stirred at room temperature for 24 h and worked up as described in (a) to give **14a** (1.83 g, 84%) and **15a** (0.06 g, 3%).

Diphenyl *N*-[2-Phenyl-1-(4-morpholinyl)propylidene]phosphoramidate (14b)——A mixture of the enamine **12b** (1.10 g, 5.4 mmol) and DPPA (1.65 g, 5.4 × 1.1 mmol) in ethyl acetate (15 ml) was stirred at room temperature for 1 h, at 55 °C for 15 min, then at reflux for 3 h. The mixture was worked up as described in (a) for the preparation of **14a**. The concentrated residue was separated by silica gel column chromatography with ethyl acetate–benzene (1 : 4) to give **14b** (1.54 g, 63%) in the first eluate fraction. Recrystallization from ethyl acetate–hexane gave colorless prisms, mp 71—73.5 °C. IR ν_{max} cm^{-1}: 1565, 1276, 1207, 1165. NMR δ: 1.52 (3H, d, J=7 Hz), 3.21 (8H, m), 5.21 (1H, q, J=7 Hz), 7.15 (15H, m). *Anal.* Calcd for $C_{25}H_{27}N_2O_4P$: C, 66.65; H, 6.04; N, 6.22. Found: C, 66.79; H, 6.12; N, 6.30.

The amidine **15b** (0.16 g, 7%) was obtained from the second eluate fraction as a brown viscous oil. NMR δ: 3.04—3.58 (8H, m), 6.88 (m) and 7.15 (s) (15H).

Diphenyl *N*-[2-Phenyl-1-(1-piperidinyl)propylidene]phosphoramidate (14c)——A mixture of the enamine **12c** (1.09 g, 5.4 mmol) and DPPA (1.65 g, 5.4 × 1.1 mmol) in ethyl acetate (15 ml) was stirred at room temperature for 1.25 h, at 50 °C for 0.5 h, at 80 °C for 0.5 h, then at reflux for 3 h. The mixture was worked up as described in (a) for the preparation of **14a**. The concentrated residue was separated by silica gel column chromatography with ethyl acetate–benzene (1 : 4) to give **14c** (1.61 g, 66%) in the first eluate fraction. Recrystallization from ethyl acetate–hexane gave colorless pillars, mp 67—69 °C. IR ν_{max} cm^{-1}: 1562, 1495, 1259, 1214, 1203. NMR δ: 1.32 (m) and 1.49 (d, J=7 Hz), 3.23 (4H, m), 5.15 (1H, q, J=7 Hz), 7.11 (15H, m). *Anal.* Calcd for $C_{26}H_{29}N_2O_3P$: C, 69.63; H, 6.52; N, 6.25. Found: C, 69.66; H, 6.66; N, 6.61.

The amidine **15c** (0.14 g, 7%) was obtained from the second eluate fraction as a colorles viscous oil. NMR δ: 1.52 (6H, m), 3.05 and 3.66 (4H, m), 6.90 (m) and 7.16 (s) (15H).

1-Methoxy-1-phenylpropene (16)——Propiophenone (**11**) (4.20 g, 30 mmol) was added to a suspension of potassium hydride (24.04% in oil, 7.5 ml, 30 × 1.5 mmol) in hexamethylphosphortriamide (30 ml) under argon, and the mixture was stirred until evolution of hydrogen gas ceased. Dimethyl sulfate (3.1 ml) was added, then the mixture was quenched with water and extracted with benzene. The extracts were washed with water and saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was distilled at 96—98 °C (25 mmHg) (lit.[15] bp 96—98 °C (19 mmHg)) to give **16** (2.65 g, 60%) as a colorless oil. IR ν_{max} cm^{-1}: 1660, 1490, 1450, 1315, 980. NMR δ: 1.11 (d, J=7 Hz) and 1.78 (d, J=7 Hz) (3H), 3.17 (s) and 3.41 (s) (3H), 5.26 (1H, q, J=7 Hz), 7.2 (5H, m).[16]

Attempted Reaction of DPPA with Styrene Derivatives 16—20——Carried out as described for the reaction of DPPA with the enamine **12a**, but the starting materials were recovered.

Reaction of Lithium Enolate 21a with DPPA——Propiophenone (**11**) (536 mg, 4 mmol) in tetrahydrofuran (2 ml) was added to lithium diisopropylamide[17] (4 × 1.1 mmol) in tetrahydrofuran (4 ml) at −70 °C under argon with stirring. After 20 min, DPPA (1.32 g, 4 × 1.2 mmol) in tetrahydrofuran (2 ml) was added and the mixture was stirred at −70 °C for 3 h, at 0 °C for 2 h, then at room temperature for 14 h. The mixture was quenched with 5% aqueous citric acid (16 ml), and extracted with ethyl acetate–benzene (1 : 1, 80 ml). The extracts were washed successively with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, and dried over magnesium sulfate. The residue obtained by concentration was separated by silica gel column chromatography with ethyl acetate–hexane (1 : 4). The first eluate fraction afforded the enol phosphate **22** (825 mg, 56%) as a colorless oil, bp 182—184 °C (0.13 mmHg). NMR δ: 1.76 (3H, dd), 5.63 (1H, qq), 7.11 (15H, m). MS *m/e*: 366 (M^+).

The second eluate fraction afforded 4-methyl-5-phenyl-1*H*-1,2,3-triazole (**23**) (159 mg, 25%) as colorless crystals, mp 167—169 °C (chloroform–hexane) (lit.[18] mp 160—162 °C). MS *m/e*: 159 (M^+).

Reaction of Sodium Enolate 21b with DPPA——Propiophenone (**11**) (269 mg, 2 mmol) in benzene (2 ml) was added to sodium hydride (53 mg, 2 × 1.1 mmol) in benzene (2 ml) under argon. The mixture was refluxed for 2 h, then cooled with ice-water, and DPPA (660 mg, 2 × 1.2 mmol) in benzene (2 ml) was added. The mixture was stirred with ice-cooling for 1.5 h, at room temperature for 0.5 h, then at reflux for 2.5 h. Work-up as described in the case of the lithium enolate **21a** afforded propiophenone (**11**) (138 mg, 51%), the enol phosphate **22** containing unknown impurities (57 mg), and 4-methyl-5-phenyl-1,2,3-triazole (**23**) (68 mg, 21%).

1-(2-Phenylpropionyl)pyrrolidine (24)——A mixture of the amidine **14a** (434 mg, 1 mmol) and potassium hydroxide (85% purity, 0.99 g, 1 × 15 mmol) in ethanol (1 ml) was refluxed for 24 h. After removal of the ethanol *in*

vacuo, water (20 ml) was added and the mixture was extracted with diethyl ether (40 ml). The extracts were washed with water and saturated aqueous sodium chloride, and dried over sodium sulfate. The mixture was concentrated, and the residue was purified by silica gel preparative thin layer chromatography with ethyl acetate–hexane (1 : 1) to give **24** (74 mg, 31%) as a colorless oil, bp 128—129 °C (3 mmHg), which was identical with a sample prepared from 2-phenylpropionic acid (**25**) and pyrrolidine using diethyl phosphorocyanidate.[10] IR ν_{max} cm^{-1}: 1638, 1451, 1426. NMR δ: 1.37 (3H, d, J=7 Hz), 1.8 (4H, m), 3.2 (m) and 3.57 (q, J=7 Hz) (5H), 7.12 (5H, s).

2-Phenylpropionic Acid (25)——A mixture of the amidine **14a** (1.30 g, 3 mmol) and potassium hydroxide (85% purity, 2.94 g, 3 × 15 mmol) in ethylene glycol (40 ml) was refluxed for 12 h. After dilution of the reaction mixture with water (300 ml), carbon dioxide gas was introduced until the pH of the solution reached 9. The mixture was washed with diethyl ether (50 ml × 6), and the aqueous layer was acidified with hydrochloric acid, then extracted with diethyl ether (50 ml × 6) and ethyl acetate (50 ml × 2). The organic extracts were washed with water and saturated aqueous sodium chloride, and dried over magnesium sulfate. The mixture was concentrated *in vacuo* to give **25** (408 mg, 91%) as a colorless oil, bp 103—105 °C (3 mmHg) (lit.[19] bp 153—155 °C (20 mmHg)). IR ν_{max} cm^{-1}: 3200—2600, 1705, 1457, 1419, 1233. NMR δ: 1.43 (3H, d, J=7 Hz), 3.62 (1H, q, J=7 Hz), 7.18 (5H, s), 10.78 (1H, s).

1-(2-Phenylpropyl)pyrrolidine (26)——The amidine **14a** (868 mg, 2 mmol) in tetrahydrofuran (5 ml) was added to a stirred suspension of lithium aluminum hydride (760 mg, 2 × 10 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at reflux for 3 h, then diethyl ether saturated with water was added. The white precipitate was filtered off, and the filtrate was washed successively with 10% aqueous sodium hydroxide, water, and saturated aqueous sodium chloride, then dried over potassium carbonate. The solvent was removed *in vacuo* to give **26** (289 mg, 76%) as a pale yellow oil. NMR δ: 1.31 (3H, d, J=7 Hz), 1.65 (4H, m), 2.42—3.01 (7H, m), 7.07 (5H, s). The amine **26** was converted to the methiodide with methyl iodide as usual; pale brown needles, mp 147.5—149.5 °C. *Anal.* Calcd for $C_{14}H_{22}IN$: C, 50.76; H, 6.69; N, 4.23. Found: C, 50.96; H, 6.79; N, 4.31.

Diphenyl *N*-[2-Methyl-2-phenyl-1-(1-pyrrolidinyl)propylidene]phosphoramidate (27)——(i) From **14a**. The amidine **14a** (869 mg, 2 mmol) was added to lithium diisopropylamide[17] (2 × 1.5 mmol) in tetrahydrofuran (8 ml) at −78 °C under argon with stirring. After 5 min, methyl iodide (0.5 ml, 2 × 4 mmol) was added and the mixture was stirred at −50 °C for 4 h. The mixture was quenched with 5% aqueous citric acid (10 ml), and extracted with ethyl acetate–benzene (1 : 1, 110 ml). The extract was successively washed with saturated aqueous sodium bicarbonate (10 ml), water (10 ml), and saturated aqueous sodium chloride (10 ml), then dried over magnesium sulfate. The residue obtained by concentration was purified by silica gel column chromatography with ethyl acetate–hexane (2 : 1) to give **27** (553 mg, 62%) as a pale yellow viscous oil.

(ii) From **30c**. A mixture of the enamine **30c** (0.81 g, 4 mmol) and DPPA (1.32 g, 4 × 1.2 mmol) in tetrahydrofuran (12 ml) was stirred under argon and worked up as described for the preparation of **14a**. Purification of the crude product by silica gel column chromatography with ethyl acetate–benzene (1 : 3) afforded **27** (1.87 g, 70%) as a pale yellow viscous oil, which solidified on standing. Recrystallization from ethyl acetate–hexane gave colorless needles, mp 87—88.5 °C. IR ν_{max} cm^{-1}: 1574, 1493, 1255, 1224, 1204, 930. NMR δ: 1.40 (s) and 1.51 (m) (10H), 2.6 and 3.7 (4H, m), 7.11 (15H, m). *Anal.* Calcd for $C_{26}H_{29}N_2O_3P$: C, 69.63; H, 6.52; N, 6.25. Found: C, 69.56; H, 6.57; N, 6.31.

Diphenyl *N*-[2-Methyl-2-phenyl-1-(1-pyrrolidinyl)-4-pentenylidene]phosphoramidate (28)——The amidine **14a** (869 mg, 2 mmol) in tetrahydrofuran (6 ml) was added to lithium diisopropylamide[17] (2 × 1.5 mmol) in tetrahydrofuran (6 ml) at −78 °C under argon with stirring. After 5 min, hexamethylphosphortriamide (0.5 ml) was added and the mixture was stirred for 10 min. Allyl bromide (1.6 ml, 2 × 10 mmol) was added and the mixture was stirred at −20 °C for 1.5 h, then quenched with 5% citric acid (10 ml) and worked up as described for the preparation of **27** from **14a**. Purification by silica gel column chromatography with ethyl acetate–hexane (5 : 2) afforded **28** (487 mg, 50%) as a colorless oil, which solidified on standing. Recrystallization from ethyl acetate–hexane gave colorless needles, mp 104—104.5 °C. IR ν_{max} cm^{-1}: 1548, 1484, 1273, 1249, 1211, 1198, 927, 887. NMR δ: 1.36 (s) and 1.6 (br m) (7H), 2.51 (d), 2.65 (br m), and 3.95 (br m) (6H), 4.15—5.41 (3H, m), 7.2 (15H, m). *Anal.* Calcd for $C_{28}H_{31}N_2O_3P$: C, 70.87; H, 6.58; N, 5.90. Found: C, 70.81; H, 6.31; N, 5.87.

Diphenyl *N*-[2-Phenyl-1-(1-pyrrolidinyl)butylidene]phosphoramidate (31a)——(i) Without Argon: A mixture of the enamine **30a** (1.01 g, 5 mmol) and DPPA (1.65 g, 5 × 1.2 mmol) in tetrahydrofuran (15 ml) was stirred and worked up as described for the preparation of **14a**. Purification of the crude product was done by a silica gel column chromatography with ethyl acetate–benzene (1 : 4) to give **31a** (1.67 g, 74%) as a pale yellow viscous oil, which solidified on standing. Recrystallization from ethyl acetate–hexane afforded colorless pillars, mp 83—85 °C. IR ν_{max} cm^{-1}: 1571, 1491, 1260, 1235, 1216, 1204, 1163. NMR δ: 0.94 (3H, t, J=7 Hz), 1.67 and 1.97 (6H, m), 3.05—3.72 (4H, br m), 4.43 (1H, t, J=7 Hz), 7.17 (15H, m). *Anal.* Calcd for $C_{26}H_{29}N_2O_3P$: C, 69.63; H, 6.52; N, 6.25. Found: C, 69.80; H, 6.49; N, 6.25.

(ii) With Argon: The reaction was carried out as described in (i) using argon to give **31a** (1.84 g, 82%).

(iii) By One-Flask Procedure: A mixture of butyrophenone (**29**) (0.74 g, 5 mmol), pyrrolidine (1.07 g, 5 × 3 mmol), and boron trifluoride etherate (0.07 g, 5 × 0.1 mmol) in benzene (50 ml) was refluxed for 68 h using a Cope water separator and molecular sieve 4A as the dehydrating agent. After removal of the solvent *in vacuo*, the residue was treated with DPPA (1.65 g, 5 × 1.2 mmol) in tetrahydrofuran (15 ml) under argon as described in (i) to give **31a** (1.81 g, 81%, based on **29**).

Diphenyl *N*-[2-Phenyl-1-(1-pyrrolidinyl)-4-pentenylidene]phosphoramidate (31b)——A mixture of the enamine **30b** (1.07 g, 5 mmol) and DPPA (1.65 g, 5 × 1.2 mmol) in tetrahydrofuran (15 ml) was stirred under argon and worked up as described for the preparation of **14a**. Purification of the crude product by silica gel column chromatography with ethyl acetate–hexane (2 : 1) gave **31b** (1.84 g, 80%) as a pale yellow viscous oil. IR ν_{max} cm^{-1}: 1585, 1565, 1489, 1242, 1228, 1200. NMR δ: 1.6 (4H, br m), 3.58 (2H, dd), 3.1 and 3.5 (4H, br m), 4.44 (1H, t, J=8 Hz), 4.72—5.02 (2H, m), 5.4—6.02 (1H, m), 7.8 (15H, m). *Anal.* Calcd for $C_{27}H_{29}N_2O_3P$: C, 70.42; H, 6.35; N, 6.08. Found: C, 70.36; H, 6.38; N, 6.14.

2-Phenylbutyric Acid (32a)——A mixture of the amidine **31a** (448 mg, 1 mmol) and potassium hydroxide (85% purity, 1.00 g, 1 × 15 mmol) in ethylene glycol (20 ml) was refluxed for 6 h. After dilution of the mixture with water (200 ml), carbon dioxide gas was introduced until the pH of the solution reached 9. The mixture was washed with diethyl ether (50 ml × 5), and the aqueous layer was acidified with hydrochloric acid, then extracted with ethyl acetate (50 ml × 4). The organic extracts were washed with water and saturated aqueous sodium chloride, and dried over magnesium sulfate. The mixture was concentrated *in vacuo* to give **32a** (150 mg, 91%) as a colorless viscous oil (lit.[20] bp 134—136 °C (6 mmHg)). IR ν_{max} cm^{-1}: 3400—2600, 1710. NMR δ: 0.83 (3H, t, J=7 Hz), 1.93 (2H, m), 3.38 (1H, t, J=8 Hz), 7.17 (5H, s), 11.96 (1H, br s).

2-Phenyl-4-pentenoic Acid (32b)——A mixture of the amidine **31b** (468 mg, 1 mmol) and potassium hydroxide (85% purity, 1.00 g, 1 × 15 mmol) in ethylene glycol (20 ml) was refluxed and worked up as described for the preparation of **32a** to give **32b** (164 mg, 91%) as a colorless viscous oil.[21] IR ν_{max} cm^{-1}: 3400—2600, 1710. NMR δ: 2.60 (2H, m), 3.56 (1H, t, J=8 Hz), 4.81—5.11 (2H, m), 5.35—6.01 (1H, m), 7.20 (5H, s), 10.13 (1H, br s).

2-Methyl-2-phenylpropionic Acid (32c)——A mixture of the amidine **27** (448 mg, 1 mmol) and potassium hydroxide (85% purity, 1.00 g, 1 × 15 mmol) in ethylene glycol (20 ml) was refluxed and worked up as described for the preparation of **32a** to give **32c** (164 mg, 100%) as colorless needles, mp 75—77.5 °C (lit.[22] mp 80—81 °C). IR ν_{max} cm^{-1}: 3200—2600, 1695. NMR δ: 1.57 (6H, s), 7.2 (5H, m), 12.8 (1H, s).

Formation of Pyrrolidine Enamine of Acetophenone (33a) and Its Reaction with DPPA——A mixture of acetophenone (**33a**) (0.60 g, 5 mmol), pyrrolidine (1.07 g, 5 × 3 mmol), and boron trifluoride etherate (0.07 g, 5 × 0.1 mmol) in toluene (30 ml) was refluxed for 18 h using a Cope water separator and molecular sieve 4A as the dehydrating agent. After removal of the solvent *in vacuo*, the residue was dissolved in tetrahydrofuran (15 ml) and DPPA (1.65 g, 5 × 1.2 mmol) was added under argon. The mixture was stirred at room temperature for 24 h, and worked up as described for the preparation of **14a**. The crude product was separated by silica gel column chromatography with ethyl acetate–hexane to give the amidine **34a** (101 mg, 5%) in the first eluate fraction. A yellow viscous oil. IR ν_{max} cm^{-1}: 1567, 1486, 1246, 1220, 1198. NMR δ: 1.65 (4H, br m), 3.15—3.4 (4H, br m), 4.14 (2H, s), 7.05 (15H, s).

The amidine **15a** (344 mg, 17%) was obtained in the second eluate fraction.

Formation of Pyrrolidine Enamine of 4-Methoxyacetophenone (33b) and Its Reaction with DPPA——Carried out using 4-methoxyacetophenone (**33b**) (751 mg, 5 mmol) in the same way as described in the case of acetophenone (**33a**). The amidine **34b** (0.33 g, 15%) was obtained as a brown viscous oil. IR ν_{max} cm^{-1}: 1562, 1484, 1239, 1196. NMR δ: 1.70 (4H, br m), 3.23, 3.40 (br), and 3.69 (s) (7H), 4.10 (2H, s), 6.63—7.17 (14H).

The amidine **35a** (0.54 g, 25%) was obtained as colorless pillars (ethyl acetate–hexane), mp 124.5—126 °C. IR ν_{max} cm^{-1}: 1612, 1585, 1491, 1244, 1223, 1201, 905, 768. NMR δ: 1.85 (4H, m), 3.27 (m), 3.55 (m), 3.75 (s) (7H), 6.8—7.4 (14H, m). *Anal.* Calcd for $C_{24}H_{25}N_2O_4P$: C, 66.04; H, 5.77; N, 6.42. Found: C, 66.27; H, 6.07; N, 6.44.

Formation of Pyrrolidine Enamine of 4-Bromoacetophenone (33c) and Its Reaction with DPPA——Carried out using 4-bromoacetophenone (**33c**) (1.00 g, 5 mmol) in the same way as described in the case of acetophenone (**33a**). The amidine **35b** (0.63 g, 26%) was obtained as colorless needles (ethyl acetate–hexane), mp 102—104 °C. IR ν_{max} cm^{-1}: 1566, 1482, 1273, 1194, 932, 882. NMR δ: 1.75 (4H, br m), 3.02 and 3.46 (4H, br m), 6.94—7.39 (14H, m). *Anal.* Calcd for $C_{23}H_{22}BrN_2O_3P$: C, 56.92; H, 4.57; N, 5.77. Found: C, 56.81; H, 4.58; N, 5.76.

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