Copper(I) Salt-Mediated Arylation of Phosphinyl-Stabilized Carbanions and Synthetic Application to Heterocyclic Compounds

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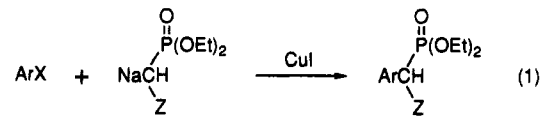
The copper-mediated reaction of phosphinyl-stabilized carbanions **2a–c** with aryl halides **1a–i** in DMF or HMPA produced (arylmethyl)phosphonates **3–11** in good yields. Similar treatment of *N*-(2-iodophenyl)- and *N*-(2-iodophenyl)-*N*-methyl-α-(diethoxyphosphinyl)acetamides (**12** and **14**) led to 2-[(diethoxyphosphinyl)methyl]benzoxazole (**13**) and 1-methyl-3-(diethoxyphosphinyl)oxindole (**15**) in 71 and 85% yields, respectively. 4-(Ethoxycarbonyl)-3,4-dihydroisoquinoline *N*-oxide (**33**) was synthesized by the reaction of ethyl α-(*o*-formylphenyl)acrylate (**31**), derived from **6** and paraformaldehyde, with hydroxylamine. The cycloaddition of **33** to olefins such as dimethyl maleate, methyl acrylate, and styrene was studied.

Although (arylmethyl)phosphonates containing an electron-withdrawing group such as an ester, sulfonyl, or cyano group on the α-carbon can be expected to be versatile intermediate reagents for organic synthesis, the number of studies on their synthesis and synthetic application have been, to our knowledge, limited.[1] This may be because the preparation of α-functionalized (arylmethyl)phosphonates is difficult and the functionality that can be tolerated on the aryl group is limited. We now report a new efficient synthesis of a variety of (arylmethyl)-phosphonates bearing electronegative substituents on the α-carbon and their synthetic application to heterocyclic compounds.

Results and Discussion

Synthesis of Diethyl α-Functionalized (Arylmethyl)phosphonates. As anticipated, ethyl α-(diethoxyphosphinyl)phenylacetate (**3a**) cannot be prepared by the reaction of iodobenzene (**1a**) with a triethyl phosphonoacetate carbanion (**2a**) upon simple heating (entry 1 in Table I). Since organocopper reagents are known to replace halogen with aliphatic or aromatic groups in aliphatic or aromatic halides,[2] the reaction of **1a** with the carbanion **2a** was carried out in the presence of a copper(I) salt to obtain the desired **3a** (eq 1). Treatment of the carbanion **2a** (2 equiv) with 1 equiv of iodobenzene (**1a**) in HMPA in the presence of copper(I) iodide (1 equiv) at 100 °C for 7 h led to **3a** in 69% yield (entry 4), while the same reaction upon using equimolar amounts of **2a**, CuI, and **1a** at 100 °C for 5 h, gave **3a** in 31% yield (entry 2).



1a–i **2a–c** **3–11**

1a : ArX=PhI
1b : ArX=PhBr
1c : ArX=*p*-IC$_6$H$_4$OMe
1d : ArX=*p*-IC$_6$H$_4$I
1e : ArX=*o*-IC$_6$H$_4$CHOCH$_2$CH$_2$O
1f : ArX=*p*-IC$_6$H$_4$CHOCH$_2$CH$_2$O
1g : ArX=*o*-IC$_6$H$_4$NO$_2$
1h : ArX=*p*-IC$_6$H$_4$NO$_2$
1i : ArX=*o*-IC$_6$H$_4$CH(OEt)$_2$

2a : Z=CO$_2$Et
2b : Z=SO$_2$Me
2c : Z=CN

3a : Ar=Ph; Z=CO$_2$Et
3b : Ar=Ph; Z=SO$_2$Me
3c : Ar=Ph; Z=CN
4 : Ar=*p*-MeOC$_6$H$_4$; Z=CO$_2$Et
5 : Ar=*p*-IC$_6$H$_4$; Z=CO$_2$Et
6 : Ar=*o*-OHCC$_6$H$_4$; Z=CO$_2$Et
7 : Ar=*p*-OHCC$_6$H$_4$; Z=CO$_2$Et
8 : Ar=*o*-NO$_2$C$_6$H$_4$; Z=CO$_2$Et
9 : Ar=*p*-NO$_2$C$_6$H$_4$; Z=CO$_2$Et
10 : Ar=*o*-OHCC$_6$H$_4$; Z=SO$_2$Me
11 : Ar=*o*-OHCC$_6$H$_4$; Z=CN

In order to optimize the yield of **3a**, the reaction conditions were systematically studied. The results are summarized in Table I.

The highest yield of **3a** was realized when 2 equiv of **2a** and CuI relative to **1a** were used (entry 8). The same reactions carried out in DMF, instead of HMPA, showed a similar trend in the yield of **3a** (entries 5, 7, and 9). Bromobenzene (**1b**) in a similar coupling reaction with **2a** provided a much lower yield of **3a** (27%) even with prolonged heating (entry 10). In the copper-mediated reaction with **1a**, diethyl[(methanesulfonyl)methyl]phosphonate and (cyanomethyl)phosphonate carbanions (**2b** and **2c**) as well as **2a** also gave the corresponding coupling products, **3b** and **3c**, in moderate yields (entries 11 and 12).

In order to explore the scope and limitations of this copper-mediated arylation of phosphinyl-stabilized carbanions, similar reactions of various iodobenzenes **1a–i** bearing electron-withdrawing or electron-donating substituents with the phosphinyl-stabilized carbanions **2a–c** were studied. The results are shown in Table II. The use of 4-iodoanisole (**1c**) (an electron-donating-group-substituted iodobenzene) necessitated a long heating period for the completion of the reaction (entry 13 in Table II). In contrast, the reaction of 1-iodo-2-nitrobenzene (**1g**) or 1-iodo-4-nitrobenzene (**1h**) which bears an electron-

• Abstract published in *Advance ACS Abstracts*, November 1, 1993.

(1) For the synthesis of ethyl α-(diethoxyphosphinyl)phenylacetate, see: (a) Blicke, F. F.; Raines, S. *J. Org. Chem.* **1964**, *29*, 2036. (b) Kreutzkamp, N.; Cordes, G. *Arch. Pharm.* **1962**, *295*, 276; *Chem. Abstr.* **1963**, *58*, 545c. (c) Berry, J. P.; Isbeli, A. F.; Hunt, G. E. *J. Org. Chem.* **1972**, *37*, 4396. (d) Jackson, J. A.; Hammound, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750. (e) Tammelin, L. E.; Fagerlind, L. *Acta. Chem. Scand.* **1960**, *14*, 1353. (f) Arbuzov, B. A.; Bogonostseva, N. P. *Sbornik Statei Obshchei Khim.* **1953**, 2, 1144; *Chem. Abstr.* **1955**, *49*, 4556. (g) Iliopulos, M. I. Z. *Naturforsch.* **1963**, *18b*(9), 767; *Chem. Abstr.* **1963**, *55*, 15307. (h) Lee, K.; Weimer, D. F. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1993**, *75*, 87. For the recent synthesis of β-keto phosphonates, see: (i) Aboujaoude, E. E.; Collignon, N.; Savignac, P. *J. Organomet. Chem.* **1984**, 264.

(2) For a review, see: Posner, G. H. *Org. React.* **1975**, *22*, 253. For acylation of copper salts of phosphonates, see: Coutrot, P.; Savignac, P.; Mathey, F. *Synthesis* **1978**, 36.

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Table I. Copper-Mediated Arylation of Phosphinyl-Stabilized Carbanions 2 with Halobenzenes 1

				reaction conditions[a]		
entry	PhX (1)	2 (Z)	solvent	molar ratio of 1/2/CuI	time, h	product (yield, %)[b]
1	PhI(1a)	2a (CO_2Et)	HMPA	1:2:0	16	3a (0)
2	1a	2a	HMPA	1:1:1	5	3a (31)
3	1a	2a	DMF	1:1:1	5	3a (56)
4	1a	2a	HMPA	1:2:1	7	3a (69)
5	1a	2a	DMF	1:2:1	5	3a (69)
6	1a	2a	HMPA	1:1:2	5	3a (67)
7	1a	2a	DMF	1:1:2	5	3a (74)
8	1a	2a	HMPA	1:2:2	5	3a (84)
9	1a	2a	DMF	1:2:2	6	3a (88)
10	PhBr (1b)	2a	HMPA	1:2:2	10	3a (27)
11	1a	2b (SO_2Me)	DMF	1:2:2	5	3b (58)
12	1a	2c (CN)	DMF	1:2:2	5	3c (50)

[a] All reactions were carried out at 100 °C. [b] Based on 1.

Table II. Copper-Mediated Arylation of Phosphinyl-Stabilized Carbanions 2 with Substituted Iodobenzenes 1

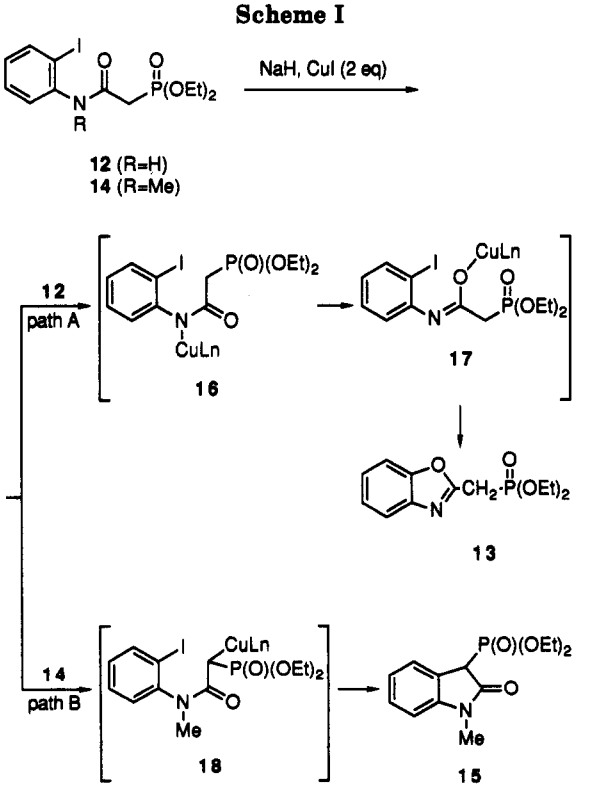
			reaction conditions[a]		
entry	ArX (1)	2 (Z)	temp, °C	time, h	product (yield, %)[b]
13	*p*-IC_6H_4OMe (1c)	2a (CO_2Et)	100	10	4 (81)
14	*p*-IC_6H_4I (1d)	2a	100	5	5 (75)
15	*o*-$IC_6H_4CHOCH_2CH_2O$ (1e)	2a	100	6	6 (75)
16	*p*-$IC_6H_4CHOCH_2CH_2O$ (1f)	2a	100	5	7 (68)
17	*o*-$IC_6H_4NO_2$ (1g)	2a	r.t.	5	8 (87)
18	*p*-$IC_6H_4NO_2$ (1h)	2a	r.t.	5	9 (87)
19	*o*-$IC_6H_4CH(OEt)_2$ (1i)	2b (SO_2Me)	100	5	10 (67)
20	1i	2c (CN)	100	5	11 (57)

[a] All reactions were carried out in DMF using 1 (10 mmol), 2 (20 mmol), and CuI (20 mmol). [b] Based on 1.

withdrawing group on the benzene, took place readily even at room temperature to produce the expected ethyl α-(diethoxyphosphinyl)-2-nitrophenyl-(8) or α-(diethoxyphosphinyl)-4-nitrophenylacetate (9) in 87% yield (entry 17 or 18). The copper-mediated reaction of *p*-diiodobenzene (1d) with the carbanion 2a (2 equiv) led only to a monocoupling product ethyl α-(diethoxyphosphinyl)-4-iodophenylacetate (5) (75% yield), but the desired para-disubstituted product, diethyl α,α′-bis(diethoxyphosphinyl)-*p*-phenylenediacetate, was not formed (entry 14). This fact suggests that the initially formed coupling compound 5 undergoes facile abstraction of the active α-methine proton, either by excess copper triethyl phosphonoacetate reagent or by 2a, which results in the generation of an unreactive α-phosphinyl-(4-iodophenyl)acetate carbanion. In the case of *o*- and *p*-formyliodobenzenes, protection of the formyl group with ethylene glycol, leading to *o*- and *p*-(1,3-dioxolan-2-yl)iodobenzenes (1e and 1f), the coupling reaction with 2a did occur to afford the corresponding ethyl α-(diethoxyphosphinyl)-2-formylphenyl- (6) and α-(diethoxyphosphinyl)-4-formylphenylacetate (7) in 75% and 68% yields, respectively (entries 15 and 16). Similar treatment of the carbanion 2b or 2c with 1-iodo-2-(diethoxymethyl)benzene (1i) led to the expected diethyl [α-(*o*-formylphenyl)-α-(methanesulfonyl)methyl]phosphonate (10) or diethyl[α-cyano-α-(*o*-formylphenyl)methyl]phosphonate (11) in 67 or 57% yield (entries 19 and 20).

We further attempted to apply this method to an intramolecular coupling. Thus, *N*-(2-iodophenyl)-α-(diethoxyphosphinyl)acetamide (12), prepared by the condensation of 2-iodoaniline with (diethoxyphosphinyl)acetic acid, was treated with sodium hydride in DMF at 100 °C for 5 h in the presence of copper(I) iodide to give, unexpectedly, only 2-[(diethoxyphosphinyl)methyl]benzoxazole (13) in 71% yield (Scheme I). The structural assignment of 13 was made on the basis of its IR and ^1H and ^{13}C NMR spectral data (see Experimental Section) as well as its chemical reactivity mentioned below. The structure of 13 was confirmed by comparison of its spectral data with those of an authentic sample prepared by the reaction of 2-(lithiomethyl)benzoxazole with diethyl chlorophosphate. As depicted in path A of Scheme I, the formation of 13 can be explained by the intramolecular *O*-arylation of the copper amide iminolate 17, which is the tautomer of the copper-metalated amide intermediate 16

Scheme I



Scheme II

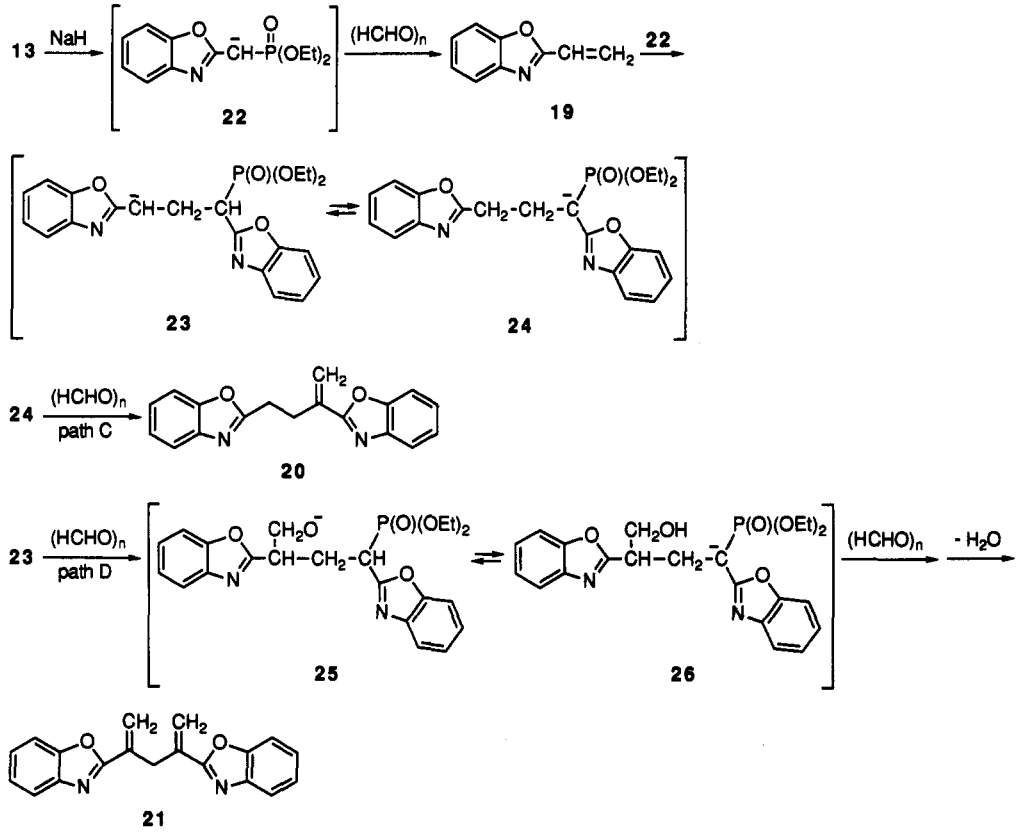


Table III. The Wittig-Horner Reaction of the Phosphonate Carbanion 22 with Paraformaldehyde

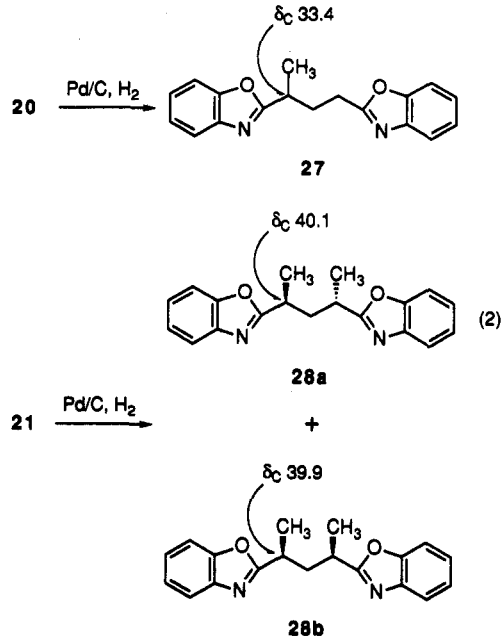
entry	reaction conditions: molar ratio of 13/NaH/aldehyde	temp, °C	time, h	products, yield (%): 19	20	21
1	1:1:2	rt	3	38	10	10
2	1:1:2	0	1.5	20	12	5
3	1:2:4	rt	8	48	7	11

prepared from the initially generated amide anion and copper(I) iodide.

In contrast to **12**, treatment of *N*-(2-iodophenyl)-*N*-methyl-α-(diethoxyphosphinyl)acetamide (**14**), which contains no NH proton, under similar conditions led to 1-methyl-3-(diethoxyphosphinyl)oxindole (**15**) in 85% yield, and the corresponding intramolecular *O*-arylation reaction of the copper enaminolate was not observed. As depicted by path B in Scheme I, the formation of **15** is readily rationalized by way of the intramolecular *C*-arylation of the organocopper intermediate **18**, similar to the intermolecular copper-mediated reaction of aryl iodides with the phosphinyl-stabilized carbanions. Thus, it became evident that this copper-mediated coupling can lead to intermolecular or intramolecular arylation of phosphinyl-stabilized carbanions.

Synthetic Application of (Arylmethyl)phosphonates to Heterocyclic Compounds. The α-arylated methyl phosphates obtained above, such as 2-[(diethoxyphosphinyl)methyl]benzoxazole (**13**), can be interesting intermediate reagents for organic synthesis.

Thus, treatment of the 2-[(diethoxyphosphinyl)methyl]-benzoxazole carbanion, generated in situ from **13** and sodium hydride, with paraformaldehyde under various conditions led to a mixture of 2-vinylbenzoxazole (**19**) (20–48% yields) and two unexpected dimeric products **20** (7–12% yields) and **21** (5–11% yields) (Table III) (Scheme II).[3] For structural identification of the products **20** and **21**, hydrogenation of compound **20** over Pd/C was carried out resulting in compound **27** in 85% yield, while similar treatment of compound **21** led to a 1:1 mixture of two isomeric hydrogenated products **28a** and **28b** in 96% yield (eq 2).



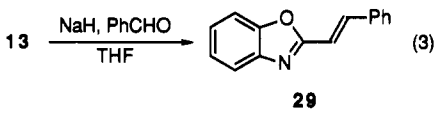
As outlined in Scheme II, the product **20** could result from a sequence of (i) the Michael addition[4] of the phosphonate carbanion **22** to the initially formed Wittig-Horner olefination product **19** resulting in the carbanion

(3) The Wittig-Horner reaction of **13** with formaldehyde (3 equiv) in CH_2Cl_2/H_2O (1:2) using tetrabutylammonium hydroxide at room temperature for 8 h similarly gave a mixture of **19** (14%), **20** (41%), and **21** (0.4%).

23, (ii) a [1,3]-proton shift to generate the phosphonate carbanion 24, and (iii) the Wittig–Horner reaction of 24 with a second molecule of paraformaldehyde (path C). On the other hand, the formation of the compound 21 can be accounted for by the reaction of carbanion 23 with excess paraformaldehyde to give the intermediate alcoholate anion 25, subsequent proton shift to generate the phosphonate carbanion 26, and then a Wittig–Horner reaction with paraformaldehyde followed by dehydration (path D).

To confirm the mechanism by which 20 is formed, the phosphonate carbanion 24, generated from the Michael addition of the phosphonate carbanion 22 to independently prepared 19, was trapped with paraformaldehyde (1 equiv) to give 20 as an isolable product in 40% yield. This result supports the proposed mechanism (path C) for the formation of 20.

In contrast, similar reaction of 13 with benzaldehyde gave only 2-styrylbenzoxazole (29) in 79% yield, but the dimeric product corresponding to compounds 20 and 21 was not formed. Compound 29 is apparently unable to undergo the addition of the phosphonate carbanion 22 due to steric hindrance at the α-styryl carbon (eq 3).



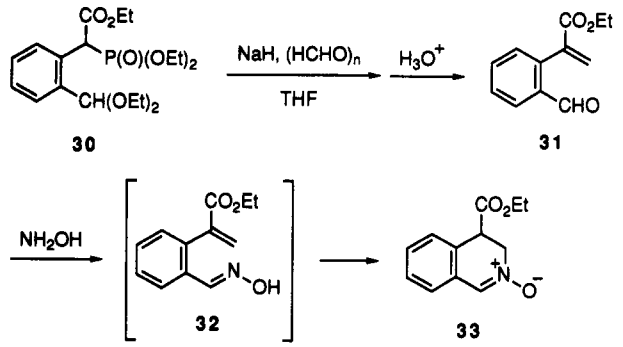
(3)

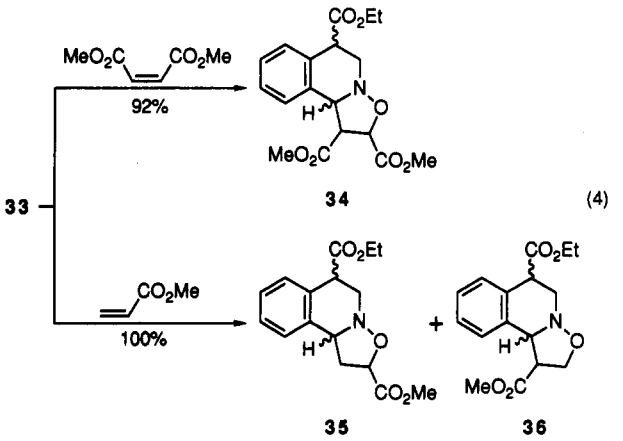
29

Furthermore, we have explored the synthetic utility of the α-arylated phosphonates. For instance, the Wittig–Horner reaction of the α-(diethoxyphosphinyl)-α-(*o*-formylphenyl)acetate carbanion with aldehydes such as paraformaldehyde and benzaldehyde failed to afford olefination products. However, use of the diethyl acetal 30, upon similar treatment with paraformaldehyde, resulted in the desired olefination product, which was isolated as ethyl α-(*o*-formylphenyl)-acrylate (31) in 95% yield after deprotection of the diethyl acetal group. Interestingly, the reaction of compound 31 with hydroxylamine produced a valuable intermediate reagent, 4-(ethoxycarbonyl)-3,4-dihydroisoquinoline *N*-oxide (33) (68% yield). The formation of 33 can be explained by the intramolecular Michael addition of an initially produced oxime 32 (Scheme III).[5]

The functionalized dihydroisoquinoline *N*-oxide 33 is difficult to obtain from the usual oxidation[6] of the corresponding 2-hydroxy-1,2,3,4-tetrahydroisoquinoline, because the hydroxylamine is not easily prepared. This new method provides a ready synthesis of the functionalized dihydroisoquinoline *N*-oxide 33. Establishment of such a convenient route to nitrone 33 encouraged us to explore its function as a 1,3-dipolar reagent. Dihydroisoquinoline *N*-oxide 33 reacted smoothly with dimethyl maleate at room temperature, and the 1,3-dipolar cycloadduct 34 was isolated in 92% yield as a mixture of four stereoisomers, on the basis of its ^1H and ^{13}C NMR data (see Experimental Section). Unfortunately, attempts to separate the individual, pure isomers were unsuccessful. Cycloaddition of the nitrone 33 to the unsymmetrical 1,3-dipolarophile methyl acrylate similarly gave a 1:1 cycloaddition product. Although the product is assumed to

Scheme III





(4)

be a mixture of the 5-substituted isoxazolidine 35 and its regioisomer, 4-substituted derivative 36 each including its stereoisomers,[7] the regiochemistry and stereochemistry of each adduct has not been determined because they could be neither purified nor separated. In contrast, the cycloaddition reaction of the nitrone 33 with a nonactivated olefin, styrene, resulted in the formation of a quantitative yield of a 68:32 mixture of two stereoisomeric 5-phenylisoxazolidines 38a and 38b, with regiospecificity.[8] In the 2D NOESY spectrum of the cycloadducts 38a and 38b, cross peaks were observed between H^{2a} and H^{6a}, H^{5b} and H^{10b}, and H^{1a} and H^{5a} for 38a, while they were evident between H^{2b} and H^{5b}, H^{5a} and H^{10a}, and H^{1b} and H^{5b} for 38b. Our assignment of the stereochemistry of 38a and 38b is consistent with these spectroscopic observations. This result implies that the cycloaddition is controlled by LUMO (the nitrone 31)–HOMO (styrene interactions),[6b] and proceeds exclusively through the anti-exo 37a and the syn-exo-37b transition states to give 38a and 38b, respectively, and does not proceed via the endo mode 39. In this case, the endo transition state 39, which benefits

(4) Similar to the vinyloxazole 19, 2-alkenyloxazoles are well-known to undergo nucleophilic addition of organolithium reagents. Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* 1979, *44*, 2250.

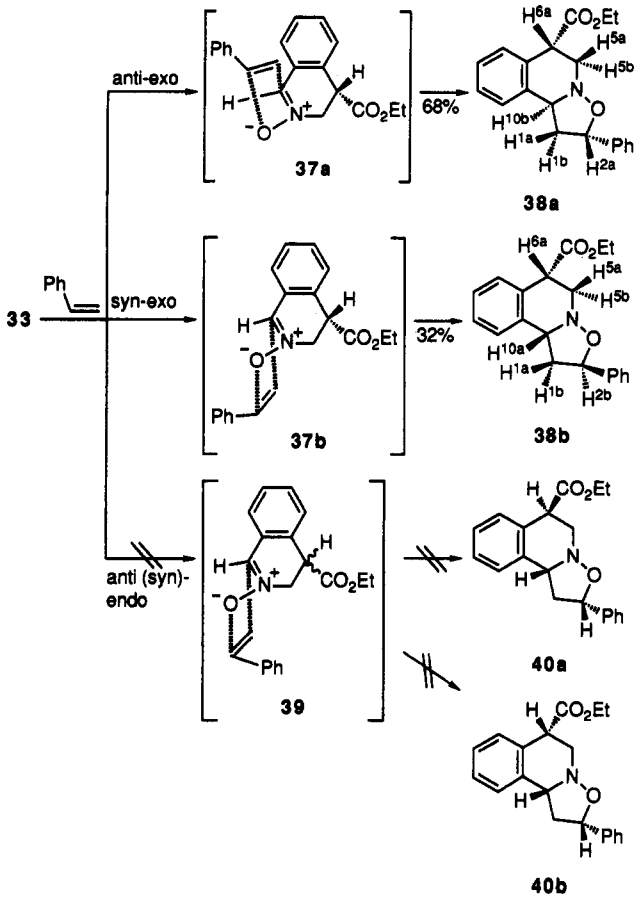
(5) For related generations of nitrones *via* an intermolecular Michael addition of oximes to electronegative olefins, see: (a) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* 1992, *48*, 6929. (b) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* 1992, *48*, 10399. (c) Armstrong, P.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* 1991, *47*, 4495. (d) Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* 1987, 1325. (e) Armstrong, P.; Grigg, R.; Surendrakumar, S.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* 1987, 1327.

(6) For reviews of nitrone synthesis, see: (a) Hamer, J.; Macaluso, A. *Chem. Rev.* 1964, *64*, 473. (b) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol 2, p 83.

(7) The presence of two regioisomers 35 and 36 is suggested by the ^{13}C NMR spectrum showing substituted C-5 of the isoxazolidine ring at δ 74.6–79.2 and δ 68.6–69.2, respectively. The addition of 3,4-dihydroisoquinoline *N*-oxide to methyl methacrylate is known to give two regioisomeric adducts.[5b]

(8) 3,4-Dihydroisoquinoline *N*-oxide has been previously reported to undergo a regiospecific addition to styrene to afford the 5-phenylisoxazolidine. Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* 1968, *101*, 2548.

Scheme IV



from a favorable secondary orbital interaction, is probably precluded due to steric interactions between the phenyl group in the approaching styrene and the ring methylene hydrogens of the nitrone **33**. Furthermore, the anti-syn ratio (i.e., ca 2.1) of the exo adducts **38** suggests that the anti transition state is more favorable than its syn counterpart due to its lesser steric interaction between styrene and the ester group of the nitrone **33** (Scheme IV).

In conclusion, we note the following results of this investigation: (1) a variety of (arylmethyl)phosphonates have been prepared; (2) (arylmethyl)phosphonates have been shown to be valuable reagents for the synthesis of heterocyclic compounds; (3) the synthesis and synthetic application of a new type of nitrone compound, 4-(ethoxycarbonyl)-3,4-dihydroisoquinoline *N*-oxide (**33**) are reported.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained on a JEOL JNM-FX-60 or a JEOL JNM-EX-270 spectrometer for solutions in $CDCl_3$, operating at 60 or 270 MHz for ^1H and at 15.04 or 67.89 MHz for ^{13}C, respectively, with Me_4Si as an internal standard. DEPT, NOESY, and 2D proton–proton and carbon–proton correlations were used when necessary to assign ^1H and ^{13}C NMR spectra. IR spectra were recorded with a Shimadzu IR-408 instrument. Mass spectra were taken with a JEOL DX-300 spectrometer. Melting points were measured in open capillary tubes and are uncorrected.

Synthesis of (Arylmethyl)phosphonates 3–11. General Procedure. To a suspension of sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol) in DMF or HMPA (4 mL) was added a solution of a diethyl methylphosphonate **2** (20 mmol) in DMF or HMPA (3 mL) at room temperature. After the solution was stirred at this temperature for 10 min, a halobenzene **1** (10 mmol) and copper(I) iodide (3.81 g, 20 mmol) were added in turn, and the mixture was stirred under the reaction conditions shown in Table I or II. The reaction was quenched by the addition of 10% aqueous HCl, filtered through a Celite pad, and extracted with AcOEt, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give (arylmethyl)phosphonates **3–11**. The reaction conditions and the yields of **3–11** are summarized in Tables I and II. The compounds **3-11** had the following physical properties.

Ethyl α-(diethoxyphosphinyl)phenylacetate (3a): from **1a** (2.04 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:4). **3a** (2.63 g, 8.76 mmol, 88%): oil; R_f 0.38 (Et_2O); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.40 (m, 9H, CH_3), 3.70–4.40 (m, 7H, OCH_2, CH), 7.20–7.50 (m, 5H, Ph).

Diethyl [α-phenyl-α-(methanesulfonyl)methyl]phosphonate (3b): from **1a** (2.04 g, 10 mmol) and **2b** (4.60 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:4). **3b** (1.77 g, 5.78 mmol, 58%): oil; R_f 0.28 (Et_2O); IR (neat) 1315, 1145 (SO_2Me) cm^{-1}; ^1H NMR δ 1.00–1.50 (m, 6H, CH_3), 3.06 (s, 3H, SO_2CH_3), 3.80–4.50 (m, 4H, OCH_2), 4.72 (d, $^2J_{P-H}$ = 20.8 Hz, 1H, CH), 7.30–7.80 (m, 5H, Ph); HRMS *m/z* calcd for $C_{12}H_{19}O_5PS$ 306.0690 (M^+), found 306.0647. Anal. Calcd for $C_{12}H_{19}O_5PS$: C, 47.05; H, 6.25. Found: C, 46.97; H, 6.28.

Diethyl [α-cyano-α-phenylmethyl]phosphonate (3c): from **1a** (2.04 g, 10 mmol) and **2c** (3.54 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:9). **3c** (1.26 g, 4.98 mmol, 50%): oil; R_f 0.44 (Et_2O); IR (neat) 2270 (CN) cm^{-1}; ^1H NMR δ 1.00–1.30 (m, 6H, CH_3), 3.60–4.50 (m, 5H, OCH_2, CH), 7.20–7.40 (m, 5H, Ph); HRMS *m/z* calcd for $C_{12}H_{16}NO_3P$ 253.0867 (M^+), found 253.0851. Anal. Calcd for $C_{12}H_{16}NO_3P$: C, 56.92; H, 6.37; N, 5.53. Found: C, 56.88; H, 6.36; N, 5.49.

Ethyl α-(diethoxyphosphinyl)-α-(4-methoxyphenyl)acetate (4): from **1c** (2.34 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:9). **4** (2.69 g, 8.14 mmol, 81%): oil; R_f 0.35 (Et_2O); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.40 (m, 9H, CH_3), 3.78 (s, 3H, OCH_3), 3.80–4.40 (m, 7H, OCH_2, CH), 6.70–7.60 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{15}H_{23}O_6P$ 330.1232 (M^+), found 330.1211. Anal. Calcd for $C_{15}H_{23}O_6P$: C, 54.54; H, 7.02. Found: C, 54.84; H, 7.16.

Ethyl α-(diethoxyphosphinyl)-α-(4-iodophenyl)acetate (5): from **1d** (3.30 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:9). **5** (3.20 g, 7.51 mmol, 75%): oil; R_f 0.42 (Et_2O); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR δ 0.90–1.40 (m, 9H, CH_3), 3.70–4.40 (m, 7H, OCH_2, CH), 7.00–7.80 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{14}H_{20}O_5PI$ 426.0094 (M^+), found 426.0053. Anal. Calcd for $C_{14}H_{20}O_5PI$: C, 39.46; H, 4.73. Found: C, 39.58; H, 4.87.

Ethyl α-(diethoxyphosphinyl)-α-(2-formylphenyl)acetate (6): from **1e** (2.76 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:2). **6** (2.46 g, 7.49 mmol, 75%): oil; R_f 0.20 (Et_2O); IR (neat) 1730, 1690 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.50 (m, 9H, CH_3), 3.80–4.40 (m, 6H, OCH_2), 6.16 (d, $^2J_{P-H}$ = 25.8 Hz, 1H, CH), 7.40–8.20 (m, 4H, Ar*H*), 10.11 (s, 1H, CHO); HRMS *m/z* calcd for $C_{15}H_{21}O_6P$ 328.1076 (M^+), found 328.1096. Anal. Calcd for $C_{15}H_{21}O_6P$: C, 54.88; H, 6.45. Found: C, 54.29; H, 6.60.

Ethyl α-(diethoxyphosphinyl)-α-(4-formylphenyl)acetate (7): from **1f** (2.76 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:2). **7** (2.23 g, 6.79 mmol, 68%): oil; R_f 0.19 (Et_2O); IR (neat) 1735, 1700 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.50 (m, 9H, CH_3), 3.80–4.60 (m, 7H, OCH_2, CH), 7.20–7.90 (m, 4H, Ar*H*), 10.01 (s, 1H, CHO); HRMS *m/z* calcd for $C_{15}H_{21}O_6P$ 328.1076 (M^+), found 328.1085. Anal. Calcd for $C_{15}H_{21}O_6P$: C, 54.88; H, 6.45. Found: C, 54.40; H, 6.73.

Ethyl α-(diethoxyphosphinyl)-α-(2-nitrophenyl)acetate (8): from **1g** (2.49 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:9). **8** (3.01 g, 8.72 mmol, 87%): **8**: oil; R_f 0.32 (Et_2O); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.50 (m, 9H, CH_3), 3.80–4.50 (m, 6H, OCH_2), 5.34 (d, $^2J_{P-H}$ = 25.6 Hz, 1H, CH), 7.30–8.20 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{14}H_{21}NO_7P$ (M^+ + 1) 346.1056, found 346.1062. Anal. Calcd for $C_{14}H_{20}NO_7P$: C, 48.70; H, 5.84; N, 4.06. Found: C, 48.49; H, 5.89; N, 3.98.

Ethyl α-(diethoxyphosphinyl)-α-(4-nitrophenyl)acetate (9): from **1h** (2.49 g, 10 mmol) and **2a** (4.48 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:9). **9** (3.00 g, 8.69 mmol, 87%): oil; R_f 0.29 (Et_2O); IR (neat) 1735 (C=O) cm^{-1}; ^1H NMR δ 0.90–1.30 (m, 9H, CH_3), 3.70–4.50 (m, 7H, OCH_2, CH), 7.40–8.20 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{14}H_{20}NO_7P$ 345.0976 (M^+), found 345.0958.

Anal. Calcd for $C_{14}H_{20}NO_7P$: C, 48.70; H, 5.84 N, 4.06. Found: C, 48.42; H, 5.92; N, 3.98.

Diethyl α-(2-formylphenyl)-α-(methanesulfonyl)methylphosphonate (10): from **1i** (3.06 g, 10 mmol) and **2b** (4.60 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:2). **10** (2.24 g, 6.70 mmol, 67%): oil; R_f 0.17 (Et_2O); IR (neat) 1310, 1140 (SO_2Me) cm^{-1}; ^1H NMR δ 1.00–1.50 (m, 6H, CH_3), 3.18 (s, 3H, SO_2CH_3), 3.90–4.50 (m, 4H, OCH_2), 7.04 (d, $^2J_{P-H}$ = 21.1 Hz, 1H, CH), 7.50–8.10 (m, 4H, Ar*H*), 10.04 (s, 1H, CHO); HRMS *m/z* calcd for $C_{13}H_{19}O_6PS$ 334.0640 (M^+), found 334.0650. Anal. Calcd for $C_{13}H_{19}O_6PS$: C, 46.70; H, 5.73. Found: C, 46.53; H, 5.88.

Diethyl [α-cyano-α-(2-formylphenyl)methyl]phosphonate (11): from **1i** (3.06 g, 10 mmol) and **2c** (3.54 g, 20 mmol); eluent AcOEt/$CHCl_3$ (1:1). **11** (1.60 g, 5.69 mmol, 57%): oil; R_f 0.31 (Et_2O); (neat) 2230 (CN) cm^{-1}; ^1H NMR δ 1.10–1.50 (m, 6H, CH_3), 3.80–4.50 (m, 4H, OCH_2), 6.37 (d, $^2J_{P-H}$ = 27.1 Hz, 1H, CH), 7.30–8.00 (m, 4H, Ar*H*), 10.05 (s, 1H, CHO); HRMS *m/z* calcd for $C_{13}H_{16}NO_4P$ 281.0816 (M^+), found 281.0810. Anal. Calcd for $C_{13}H_{16}NO_4P$: C, 55.52; H, 5.73; N, 4.98. Found: C, 55.32; H, 5.93; N, 4.90.

Preparation of *N*-(2-Iodophenyl)-α-(diethoxyphosphinyl)acetamide (12). 1-Methyl-2-chloropyridinium iodide[9] (1.53 g, 6 mmol), 2-iodoaniline (0.44 g, 2 mmol), (diethoxyphosphinyl)-acetic acid (0.59 g, 3 mmol), and triethylamine (1.4 mL, 10 mmol) in CH_2Cl_2 (9 mL) was mixed at 0 °C. After the mixture was stirred at room temperature for 8 h, the reaction was quenched by the addition of 10% aqueous HCl. The organic layer was washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel [elution with AcOEt/$CHCl_3$ (1:4)] to give **12** (0.69 g, 1.74 mmol, 87%) as a colorless crystal. **12**: mp 79.5–80.0 °C; IR (KBr) 1680 (C=O) cm^{-1}; ^1H NMR δ 1.36 (t, *J* = 7.2 Hz, 6H, CH_3), 3.09 (d, $^2J_{P-H}$ = 20.9 Hz, 2H, CH_2), 3.90–4.40 (m, 4H, OCH_2), 6.70–8.50 (m, 5H, NH and Ar*H*); HRMS *m/z* calcd for $C_{12}H_{17}NO_4PI$ 396.9942 (M^+), found 396.9968. Anal. Calcd for $C_{12}H_{17}NO_4PI$: C, 36.29; H, 4.31; N, 3.53. Found: C, 36.29; H, 4.37; N, 3.36.

Copper-Mediated Reaction of a *N*-(2-Iodophenyl)-α-(diethoxyphosphinyl)acetamide Carbanion. To a solution of the carbanion, generated *in situ* from **12** (7.94 g, 20 mmol) and sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol) in DMF (45 mL) at room temperature with 10 min stirring, was added copper(I) iodide (7.62 g, 40 mmol). After the mixture was stirred at 100 °C for 5 h, the reaction mixture was quenched by the addition of 10% aqueous HCl, filtered through celite pad, extracted with $CHCl_3$, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel (elution with AcOEt) to give 2-[(diethoxyphosphinyl)methyl]benzoxazole **13** (3.80 g, 14.11 mmol, 71%) as a colorless oil. **13**: R_f 0.30 (AcOEt); IR (neat) 1610 (C=N) cm^{-1}; ^1H NMR δ 1.33 (t, *J* = 7.2 Hz, 6H, CH_3), 3.48 (d, $^2J_{P-H}$ = 21.8 Hz, 2H, CH_2P), 3.90–4.50 (m, 4H, OCH_2), 7.20–7.80 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{12}H_{16}NO_4P$ 269.0816 (M^+), found 269.0801. Anal. Calcd for $C_{12}H_{16}NO_4P$: C, 53.53; H, 5.99; N, 5.20. Found: C, 53.13; H, 6.14; N, 5.15.

Preparation of Authentic 2-[(Diethoxyphosphinyl)methyl]benzoxazole (13). To a solution of LDA (2 mmol), generated *in situ* from diisopropylamine (0.28 mL, 2 mmol) and BuLi (1.5 M in hexane, 1.28 mL, 2 mmol) in THF (5 mL) at −75 °C for 10 min, was added a solution of 2-methylbenzoxazole (0.133 g, 1 mmol) in THF (5 mL) at this temperature. After being stirred at this temperature for 15 min, diethyl chlorophosphate (0.173 g, 1 mmol) was added to the solution and the reaction mixture was stirred for 1 h at this temperature. The reaction was quenched by the addition of 10% aqueous HCl and extracted with $CHCl_3$, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on preparative TLC (silica gel, elution with AcOEt) to give 2-[(diethoxyphosphinyl)methyl]benzoxazole (0.218 g, 0.81 mmol, 81%), whose physical properties were completely consistent with those of **13** obtained in the above experiment.

Preparation of *N*-(2-Iodophenyl)-*N*-methyl-α-(diethoxyphosphinyl)acetamide (14). This compound was prepared in a similar manner described above for **12** using *N*-methyl-2-iodoaniline (0.46 g, 2 mmol) and (diethoxyphosphinyl)acetic acid (0.59 g, 3 mmol). After similar workup, the residue give **14** (0.70 g, 1.70 mmol, 85%) as a colorless oil. **14**: R_f 0.30 (AcOEt); IR (neat) 1650 (C=O) cm^{-1}; ^1H NMR δ 1.10–1.50 (m, 6H, CH_3), 2.71 (d, $^2J_{P-H}$ = 21.1 Hz, 2H, CH_2), 3.20 (d, J_{P-H} = 1.2 Hz, 3H, NCH_3), 3.80–4.50 (m, 4H, OCH_2), 6.90–8.10 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{13}H_{19}NO_4PI$ 411.0098 (M^+), found 411.0075. Anal. Calcd for $C_{13}H_{19}NO_4PI$: C, 37.97; H, 4.66; N, 3.41. Found: C, 37.77; H, 4.76; N, 3.26.

Copper-Mediated Reaction of a *N*-(2-Iodophenyl)-*N*-(diethoxyphosphinyl)acetamide Carbanion. The reaction was carried out as described above using **14** (8.22 g, 20 mmol), sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol), and copper(I) iodide (7.62 g, 40 mmol). After similar workup, the residue was chromatographed on silica gel (elution with AcOEt) to give 1-methyl-3-(diethoxyphosphinyl)oxindole (**15**) (4.83 g, 17.05 mmol, 85%) as a colorless crystal. **15**: mp 122.5–123.0 °C; IR (KBr), 1700 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.60 (m, 6H, CH_3), 3.22 (s, 3H, NCH_3), 3.80–4.50 (m, 5H, CH, OCH_2), 6.70–7.50 (m, 4H, Ar*H*); HRMS *m/z* calcd for $C_{13}H_{16}NO_4P$ 283.0929 (M^+), found 283.0958. Anal. Calcd for $C_{13}H_{16}NO_4P$: C, 55.12; H, 6.41; N, 4.94. Found: C, 55.11; H, 6.30; N, 4.93.

Reaction of 2-[(Diethoxyphosphinyl)methyl]benzoxazole (13) with Paraformaldehyde. General Procedure. To a solution of a carbanion **22**, generated *in situ* from **13** (1.786 g, 6.63 mmol) and sodium hydride (60% dispersion in mineral oil, 0.265 g, 6.63 mmol) in THF (15 mL) at room temperature with 10 min stirring, was added paraformaldehyde (0.40 g, 13.26 mmol). After the mixture was stirred for 3 h at room temperature, the reaction mixture was quenched by the addition of 10% aqueous HCl and extracted with AcOEt, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on preparative TLC [silica gel, elution with AcOEt–hexane (1:9)] to give **19** (0.364 g, 2.51 mmol, 38%), **20** (0.092 g, 0.32 mmol, 10%), and **21** (0.105 g, 0.35 mmol, 10%). The results in the reactions of **13** with paraformaldehyde under various conditions are summarized in Table III. The compounds **19–21** had the following properties.

2-Vinylbenzoxazole (19): R_f 0.44 ($CHCl_3$); IR (neat) 1600 (C=N) cm^{-1}; ^1H NMR δ 5.83 (dd, *J* = 1.2, 11.1 Hz, 1H, vinyl H), 6.45 (dd, *J* = 1.2, 17.7 Hz, 1H, vinyl H), 6.74 (dd, *J* = 11.1, 17.7 Hz, 1H, vinyl H), 7.20–7.80 (m, 4H, Ar*H*); ^{13}C NMR δ 110.4, 120.1, 123.9, 124.5, 125.3, 125.4, 141.8, 150.3, 162.0; HRMS *m/z* calcd for C_9H_7NO 145.0527 (M^+), found 145.0511. Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.21; H, 4.99; N, 9.59.

2,2′-(2,4-But-1-enediyl)bibenzoxazole (20): mp 97.5–98.0 °C; IR (KBr) 1605 (C=N) cm^{-1}; ^1H NMR δ 3.30–3.50 (m, 4H, CH_2CH_2), 5.60 (d, *J* = 0.6 Hz, 1H, vinyl H), 6.30 (s, 1H, vinyl H), 7.10–7.80 (m, 8H, Ar*H*); ^{13}C NMR δ 27.9, 30.1, 110.4, 119.6, 120.2, 122.0, 124.1, 124.4, 124.5, 125.4, 134.4, 141.2, 141.8, 150.4, 150.7, 162.4, 165.9; HRMS *m/z* calcd for $C_{18}H_{14}N_2O_2$ 290.1056 (M^+), found 290.1063. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.57; H, 4.85; N, 9.59.

2,2′-(2,4-Penta-1,4-dienediyl)bibenzoxazole (21): mp 110.5–111.0 °C; IR (KBr) 1600 (C=N) cm^{-1}; ^1H NMR δ 4.05 (s, 2H, CH_2), 5.73 (d, *J* = 0.9 Hz, 2H, vinyl H), 6.43 (d, *J* = 0.6 Hz, 2H, vinyl H), 7.10–7.90 (m, 8H, Ar*H*); ^{13}C NMR δ 35.0, 110.5, 120.4, 123.1, 124.4, 125.5, 133.3, 142.0, 150.6, 162.9; HRMS *m/z* calcd for $C_{19}H_{14}N_2O_2$ 302.1056 (M^+), found 302.1068. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.68; H, 4.71; N, 9.25.

Hydrogenation of 20. Hydrogenation of **20** (0.210 g, 0.72 mmol) was accomplished under an atmosphere of H_2 at room temperature for 3 h in AcOEt (5 mL) over palladium on activated carbon (10%, 0.200 g). After evaporation of the solvent, the residue was chromatographed on preparative TLC [silica gel, elution with AcOEt–hexane (1:4)] to give 2,2′-(2,4-butanediyl)-bibenzoxazole (**27**) (0.178 g, 0.61 mmol, 85%) as a colorless oil. **27**: R_f 0.12 (AcOEt–hexane (1:4)); IR (neat) 1610 (C=N) cm^{-1}; ^1H NMR δ 1.51 (d, *J* = 6.9 Hz, 3H, CH_3), 2.00–3.70 (m, 5H, $CHCH_2CH_2$), 7.10–7.80 (m, 8H, Ar*H*); ^{13}C NMR δ 18.2, 26.1, 31.4, 33.4, 110.0, 110.1, 119.3, 119.5, 123.8, 124.3, 141.1, 141.2, 150.5, 165.9, 169.1; HRMS *m/z* calcd for $C_{18}H_{16}N_2O_2$ 292.1211 (M^+), found 292.1186. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.02; H, 5.55; N, 9.44.

Hydrogenation of 21. The reaction was similarly carried out as described above using **21** (0.096 g, 0.32 mmol) and palladium

(9) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163.

on activated carbon (10%, 0.200 g). After similar workup, the residue was chromatographed on preparative TLC [silica gel, elution with AcOEt–hexane (1:4)] to give 2,2′-[(2*S**,4*S**)-2,4-pentanediyl]bibenzoxazole (**28a**) (0.046 g, 0.15 mmol, 47%) as a colorless crystal and 2,2′-[(2*R**,4*S**)-2,4-pentanediyl]bibenzoxazole (**28b**) (0.048 g, 0.16 mmol, 49%) as a colorless oil. The compounds **28a** and **28b** had the following properties.

28a: mp 107.5–108.5 °C; IR (KBr) 1610 (C=N) cm^{-1}; ^1H NMR δ 1.46 (d, J = 7.0 Hz, 6H, CH_3), 2.36 (ddd, J = 7.0, 7.0, 7.2 Hz, 2H, CHCH_2CH), 3.26 (ddq, J = 7.0, 7.0, 7.0 Hz, 2H, CH), 7.10–7.80 (m, 8H, ArH); ^{13}C NMR δ 19.1, 32.5, 40.1, 110.4, 119.8, 124.1, 124.5, 141.5, 150.8, 169.8; HRMS m/z calcd for $C_{19}H_{18}N_2O_2$ 306.1368 (M^+), found 306.1350. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.19; H, 5.89; N, 8.92.

28b: R_f 0.16 (AcOEt–hexane (1:4)); IR (neat) 1610 (C=N) cm^{-1}; ^1H NMR δ 1.50 (d, J = 6.7 Hz, 6H, CH_3), 1.80–2.36 (m, 1H, one proton of CH_2), 2.36–2.56 (m, 1H, one proton of CH_2), 3.00–3.56 (m, 2H, methine H), 7.00–7.80 (m, 8H, ArH); ^{13}C NMR δ 18.8, 32.3, 39.9, 110.3, 119.6, 124.0, 124.5, 141.1, 150.6, 169.5; HRMS m/z calcd for $C_{19}H_{18}N_2O_2$ 306.1368 (M^+), found 306.1417. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.31; H, 6.20; N, 8.98.

Synthesis of 2-Styrylbenzoxazole (29). To a solution of the carbanion **22** (2 mmol) in THF (15 mL) was added benzaldehyde (0.21 mL, 2 mmol). The mixture was stirred for 8 h at room temperature. After similar workup, the residue was chromatographed on preparative TLC (silica gel, elution with $CHCl_3$) to give **29** (0.35 g, 1.59 mmol, 79%) as a colorless crystal. **29**: mp 80.5–81.0 °C (lit.[10] mp 82.5 °C); IR (KBr) 1580 (C=N) cm^{-1}; ^1H NMR δ 7.04 (d, J = 16.3 Hz, 1H, olefinic H), 7.20–7.90 (m, 11H, ArH), 7.81 (d, J = 16.3 Hz, 1H, olefinic H).

Synthesis of Ethyl α-[2-(diethoxymethyl)phenyl]-α-(diethoxyphosphinyl)acetate (30). A mixture of **6** (2.78 g, 8.47 mmol) and ethyl orthoformate (1.51 g, 10.16 mmol) in ethanol (1 mL) containing a catalytic amount of concd HCl was heated at reflux for 10 min. Then the mixture was cooled to room temperature and neutralized with a few drops of alcoholic potassium hydroxide. After similar workup, the residue was distilled to give **30** (2.56 g, 6.36 mmol, 75%). **30**: bp 160 °C (0.8 mmHg); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR δ 1.00–1.50 (m, 15H, CH_3), 3.40–4.40 (m, 10H, OCH_2), 5.22 (d, $^2J_{P-H}$ = 24.8 Hz, 1H, CH), 5.61 (s, 1H, EtOCHOEt), 7.20–8.00 (m, 4H, ArH); MS m/z 373 ($M^+ - C_2H_5$). Anal. Calcd for $C_{19}H_{31}O_7P$: C, 56.71; H, 7.76. Found: C, 56.69; H, 7.71.

Synthesis of Ethyl α-(2-Formylphenyl)acrylate (31). To a solution of the carbanion, generated *in situ* from **30** (4.02 g, 10 mmol) and sodium hydride (60% dispersion in mineral oil, 0.40 g, 10 mmol) in THF (35 mL) at room temperature with 10 min of stirring, was added paraformaldehyde (0.60 g, 20 mmol). After the mixture was stirred for 3 h at room temperature, the reaction mixture was quenched by the addition of 10% aqueous HCl and extracted with AcOEt, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel [elution with AcOEt–hexane (1:9)] to give **31** (1.95 g, 9.55 mmol, 95%) as a colorless oil. **31**: R_f 0.37 ($CHCl_3$); IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.1 Hz, 3H, CH_3), 4.21 (q, J = 7.1 Hz, 2H, OCH_2), 5.78 (d, J = 1.3 Hz, 1H, vinyl H), 6.56 (d, J = 1.5 Hz, 1H, vinyl H), 7.20–8.00 (m, 4H, ArH), 10.00 (s, 1H, CHO); HRMS m/z calcd for $C_{12}H_{12}O_3$ 204.0787 (M^+), found 204.0810. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.27; H, 6.02.

Reaction of 31 with Hydroxylamine. A solution of **31** (0.204 g, 1 mmol), hydroxylamine hydrochloride (0.083 g, 1.2 mmol), and triethylamine (0.18 mL, 1.3 mmol) in THF (6 mL) was stirred at room temperature for 8 h. After being quenched by the addition of 10% aqueous HCl, the mixture was extracted with $CHCl_3$. After usual workup, the residue was chromatographed on preparative TLC (silica gel, elution with AcOEt) to give 4-(ethoxycarbonyl)-3,4-dihydroisoquinoline *N*-oxide (**33**) (0.15 g, 0.68 mmol, 68%) as a colorless crystal. **33**: mp 105.0–105.5 °C; IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.2 Hz, 3H, CH_3), 3.90–4.44 (m, 5H, $CHCH_2$ and OCH_2), 7.00–7.40 (m, 4H, ArH), 7.72 (s, 1H, CH=N); ^{13}C NMR δ 13.8, 43.7, 58.8, 61.7, 125.4, 126.8, 128.0, 128.5, 129.2, 132.8, 169.6; HRMS m/z calcd for $C_{12}H_{13}NO_3$ 219.0895 (M^+), found 219.0861. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.74; H, 5.87; N, 6.33.

General Procedure for the 1,3-Dipolar Cycloaddition Reaction of 33 with Dipolarophiles. A mixture of **33** (0.110 g, 0.5 mmol) and a dipolarophile (0.75 mmol) in CH_2Cl_2 (5 mL) was stirred for 10 h at room temperature. After evaporation of the solvent, the residue was chromatographed on preparative TLC (silica gel) to give the 1,3-dipolar cycloadducts.

1,2-Bis(methoxycarbonyl)-6-(ethoxycarbonyl)-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline (34): from dimethyl maleate (0.108 g, 0.75 mmol); eluent AcOEt–hexane (1:4); **34** (0.167 g, 0.46 mmol, 92%): IR (KBr) 1720 cm^{-1}; ^1H NMR (for a stereoisomeric mixture) δ 1.10–1.40 (m, 3H, CH_3), 3.20–5.10 (m, 14H, CH, CH_2, CH_3), 7.10–7.30 (m, 4H, ArH); ^{13}C NMR (for a stereoisomeric mixture) δ 14.1, 42.5, 42.8, 43.8, 51.0, 51.4, 51.6, 52.3, 52.5, 57.0, 57.8, 61.1, 61.3, 64.4, 64.6, 65.3, 75.0, 76.9, 77.3, 79.1, 126.8, 127.4, 127.6, 127.9, 128.7, 130.8, 130.9, 132.1, 133.3, 169.3, 169.9, 170.3, 170.2, 171.7, 172.0, 172.2; HRMS m/z calcd for $C_{18}H_{21}O_7N$ 363.1317 (M^+), found 363.1291. Anal. Calcd for $C_{18}H_{21}O_7N$: C, 59.50; H, 5.83; N, 3.85. Found (for a stereoisomeric mixture): C, 59.59; H, 5.83; N, 3.78.

Cycloaddition Reaction Product of 33 with Methyl Acrylate: from methyl acrylate (0.065 g, 0.75 mmol); eluent AcOEt–hexane (1:4); adduct (0.153 g, 0.50 mmol, 100%); IR (neat) 1720 cm^{-1}; ^1H NMR (for a mixture) δ 1.10–1.50 (m, 3H, CH_3), 2.50–5.00 (m, 12H, CH, CH_2, and CH_3), 7.10–7.40 (m, 4H, ArH); ^{13}C NMR (for a mixture) δ 13.7, 14.2, 40.0, 40.5, 42.4, 42.7, 43.3, 44.2, 44.6, 48.4, 50.4, 51.1, 52.0, 52.5, 53.3, 55.4, 60.9, 61.1, 61.3, 65.3, 65.5, 68.6, 68.8, 69.2, 74.6, 79.2, 126.4, 126.7, 126.9, 127.3, 127.5, 127.8, 128.2, 128.4, 129.3, 130.4, 131.1, 131.3, 134.1, 134.3, 134.5, 171.3, 171.6, 171.8, 172.0, 172.3; HRMS m/z calcd for $C_{16}H_{19}O_5N$ 305.1264 (M^+), found 305.1297. Anal. Calcd for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found (for a mixture): C, 62.80; H, 6.24; N, 4.56.

(2*S,6*R**,10b*S**)-6-(Ethoxycarbonyl)-2-phenyl-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline (38a) and (2*R**,6*R**,10b*R**)-6-(Ethoxycarbonyl)-2-phenyl-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline (38b)**: from styrene (0.78 g, 0.75 mmol); eluent AcOEt–hexane (1:4); **38a** (0.110 g, 0.34 mmol, 68%) and **38b** (0.052 g, 0.16 mmol, 32%).

38a: R_f 0.24 (AcOEt–hexane (1:4)); ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3H, CH_3), 2.69 (ddd, J = 6.0, 7.8, 12.4 Hz, 1H, H^{1b}), 2.75 (ddd, J = 8.1, 8.1, 12.4 Hz, 1H, H^{1a}), 3.50 (dd, J = 4.1, 11.1 Hz, 1H, H^{5a}), 3.75 (dd, J = 4.9, 11.1 Hz, 1H, H^{5b}), 3.99 (t, J = 4.4 Hz, 1H, H^{6a}), 4.17–4.28 (m, 2H, OCH_2CH_3), 4.83 (t, J = 7.7 Hz, 1H, H^{10b}), 5.26 (dd, J = 6.2, 8.2 Hz, 1H, H^{2a}), 7.10–7.50 (m, 9H, ArH); ^{13}C NMR δ 14.1, 43.7, 45.3, 50.6, 61.3, 62.5, 79.0, 126.2, 126.8, 127.2, 127.6, 127.7, 128.5, 129.1, 130.6, 135.6, 141.5, 172.2.

38b: R_f 0.20 (AcOEt–hexane (1:4)); ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3H, CH_3), 2.72 (ddd, J = 7.0, 7.0, 12.4 Hz, 1H, H^{1a}), 2.84 (ddd, J = 6.3, 7.9, 12.4 Hz, 1H, H^{1b}), 3.51 (dd, J = 4.6, 11.5 Hz, 1H, H^{5a}), 3.85 (dd, J = 7.0, 11.5 Hz, 1H, H^{5b}), 3.91 (dd, J = 4.6, 7.0 Hz, 1H, H^{6a}), 4.20–4.30 (m, 2H, OCH_2CH_3), 4.79 (t, J = 6.7 Hz, 1H, H^{10a}), 5.15 (t, J = 7.4 Hz, 1H, H^{2b}), 7.10–7.50 (m, 9H, ArH); ^{13}C NMR δ 14.2, 43.2, 45.7, 51.3, 61.1, 62.7, 78.6, 126.2, 127.0, 127.1, 127.7, 128.5, 131.1, 135.4, 141.4, 172.4; HRMS m/z calcd for $C_{20}H_{21}O_3N$ 323.1522 (M^+), found 323.1532. Anal. Calcd for $C_{20}H_{21}O_3N$: C, 74.28; H, 6.55; N, 4.33. Found (for stereoisomeric isomers): C, 73.99; H, 6.70; N, 4.28.

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