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An Efficient and General Method for the Synthesis of 3-Phosphorylated 4-Aminoquinolines from β-Phosphine Oxide and Phosphonate Enamines.

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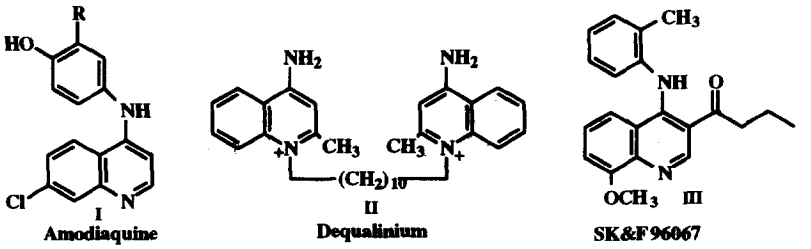
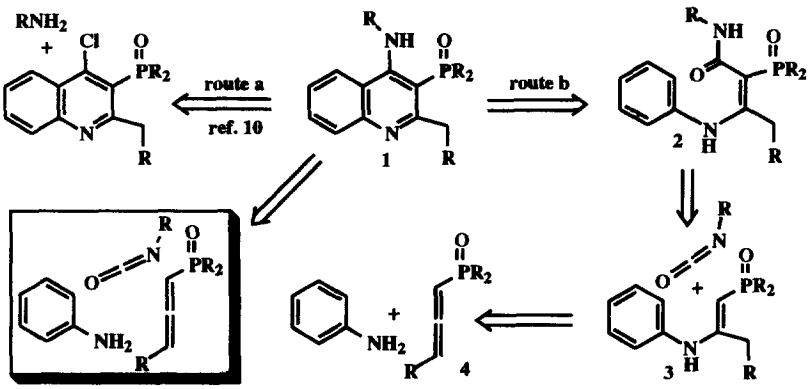
Abstract: An easy and efficient synthesis of 4-aminoquinolines substituted with a phosphine oxide **1**, phosphine sulphide **13** and phosphonate **11** group in the 3-position is described. The key step is a regioselective addition of lithiated β-enamino phosphine oxides **5** and phosphonate **6** to isocyanate and isothiocyanates to give functionalized amides **7**, **8** and thioamide **12**. Subsequent cyclization of these compounds with phosphorus oxychloride in the presence of triethylamine afforded the substituted 4-aminoquinolines **1**, **11** and **13**.

Quinoline ring systems represent an important class of compounds[1] and have attracted a great deal of attention in recent years because they constitute the backbone of a wide group of biologically active products such as alkaloids[1,2a] and azasteroids.[2b] Furthermore, the utility of 4-amino substituted quinolines has been recently demonstrated convincingly given that these compounds have interesting pharmacological properties and are widely used in medicinal chemistry. Amodiaquine **I** displays antimalarial activity,[3] while Dequalinium analogues **II** are potent and selective K^+ channel blockers.[4] 4-Arylaminoquinoline SK&F 96067 **III** has recently applied to the treatment of ulcers and related gastric disorders[5] (Scheme 1). Likewise, 4-aminoquinolines have been used as antiinflammatory[6a] and antihypertensive agents,[6b] as non-nucleoside HIV-1 inhibitors[7] and as reversible inhibitors of (H^+/K^+)-ATPase.[5,8] In these types of 4-aminoquinolines the presence of a carbonyl (see compound **III**, Scheme 1) or an ester group in the position 3 seems to play a key role in establishing the orientation of the arylamino group and therefore in the biological activity of these compounds.[5,8] With this in mind, we are interested in the design of new aminoquinoline derivatives substituted with a phosphine oxide, a phosphine sulphide or a phosphonate group in the 3 position of the heterocyclic system. These substitutents could regulate important biological functions and could increase the biological activity of these type of compounds, in a similar way to that reported for other pharmaceuticals.[9] Furthermore, we assume that, in 4-aminoquinolines, the phosphoryl group, a phosphorus isosteric analogue of the carbonyl group, might be responsible for fixing the conformation about the 4-arylamino moiety through a combination of *intra* molecular hydrogen-bonding and π-electron delocalization.



Scheme 1

While there are many approaches available for quinoline derivatives,[1a] synthetic routes to 4-aminoquinolines are relatively few and most of them involve nucleophilic displacement of the chlorine atom of 4-chloroquinoline.[1a,5,10] (Scheme 2, *route a*) Likewise, 4-aminoquinolines can alternatively be prepared by tandem reactions that involve simultaneously both the construction of the quinoline ring and the introduction of the amino group in the position 4 (see Scheme 2, *route b*) such as been reported when functionalized amines,[11a] imines,[11b,c] enamines[11d-h] and carbodiimides[11i,j] have been used.



Scheme 2

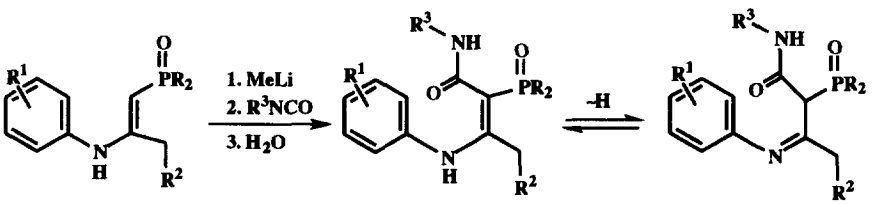
In connection with our interest in the synthesis of five[12] and six[13] membered phosphorylated nitrogen heterocycles we have used β-functionalized enamines derived from phosphazenes, phosphonium salts, phosphine oxides and phosphonates as synthetic intermediates in the synthesis of acyclic derivatives such as oximes[14a] allylamines,[14b] hydrazones,[14c] azadienes[14d] and aminodienes[14e] as well as phosphorus containing heterocycles.[15] In this context, we have recently described the synthesis of β-enamines derived from phosphine oxides and phosphonates and the use of these compounds as homologation reagents for the conversion of carbonyl derivatives into allylamines.[16] A recent publication,[17] reporting an excellent method for synthesis of aminoquinoline SK&F96067 (III, Scheme 1) has prompted us to report our own results concerning the preparation of 3-phosphorylated 4-aminoquinolines **1** from easily available starting material such as arylamines, isocyanates and phosphorylated allenes **4** (Scheme 2). Therefore, here we aim to extend the synthetic use of phosphorylated enamines **3** (R= Ph, OEt) in the preparation of substituted 4-aminoquinolines **1** containing phosphine oxide and phosphonate groups in the 3-position. Retrosynthetically,

we envisaged obtaining quinolines **1** by insertion of both a carbon atom and the amino group between the *ortho*-position of the aryl group and the enaminic carbon atom of functionalized compound **3** (Scheme 2). A tandem combination of isocyanates and phosphorus oxychloride was used and the key step in this synthetic methodology involved the regioselective reaction of metallated enamines **3** with isocyanates.

RESULTS AND DISCUSSION

Reaction of metallated enamines derived from phosphine oxides **5** and phosphonates **6** with isocyanates.

Enamines **5** (R^2= H), easily prepared by simple addition of amines to phosphine oxide allenes,[16] were treated with methyllithium in tetrahydrofuran followed by addition of isocyanates (*TLC* control) and aqueous work-up giving polyfunctionalized phosphine oxides **7** in high yield (table 1, entries 1-7). Compounds **7** were characterized on the basis of their spectroscopic data, which indicate that they are isolated as the enamino tautomer **7**. Thus, the ^{31}P-*NMR* spectrum of **7a** showed absorption at δ_P= 36.8 ppm and in the ^1H-*NMR* spectrum of this derivative **7a** the methyl group gave a singlet at δ_H= 1.48, and the enamine and imide protons resonates at δ_H= 11.68 and 13.72 ppm, while the ^{13}C-*NMR* spectrum showed absorptions at δ_C= 83.3 ($^1J_{PC}$= 115.8 Hz) for the carbon bonded to phosphorus as well a doublet at 22.0 ppm ($^3J_{PC}$= 6.0 Hz) assignable to the methyl group of the *E*-isomer.[14b,c,16]



5 R= C_6H_5
6 R= OC_2H_5

7 R= C_6H_5
8 R= OC_2H_5

7' R= C_6H_5
8' R= OC_2H_5

Scheme 3

The substitution in the starting enamine **5** seems to play an important role in this process since when enamines **5** are substituted by an alkyl group (R^2= CH_3) a mixture of *Z* and *E* enamines **7** (table 1, entries 8,9) was obtained, whereas when enamines **5** are substituted by an aryl group (R^2= *p*-CH_3-C_6H_4) a mixture of not only *Z*- and *E*-enamines **7j** but also the β-iminophosphine oxide **7'j** was obtained (table 1, entry 10), although for our subsequent purposes the separation of the enamines and imines is not necessary. In ^1H-*NMR* the imine **7'j**, for example, showed clearly different absorptions related to the enamine tautomer **7j**, namely a doublet at δ_H= 4.73 ppm ($^1J_{PC}$= 15.4 Hz) for the methine protons, and in the ^{13}C-*NMR* spectrum the methine carbon showed an absorption at δ_C= 56.4 ppm ($^1J_{PC}$= 51.1 Hz), while in the ^{13}C-*NMR* spectrum of **7j** the absorption of the carbon bonded to phosphorus was shifted to lower field (δ_C= 85.4 and 95.9 ppm for *E*- and *Z*-isomers) relative to those of the imine compound **7'j**. Furthermore, in this case the ^{31}P-*NMR* spectrum of the mixture **7j/7'j** showed three different absorptions at δ_P= 35.6, 35.0 and 31.5 ppm in an approximate isomer ratio 33/33/34 as evidenced by the relative peak areas for each compound, in

which the high-field chemical shift corresponds to the imine compound **7'j**. Similarly, the enamine derived from phosphonate ester **6** reacted with phenylisocyanate and gave β-functionalized phosphonate **8** in very high yield (table 1, entry 11).

Table 1. Functionalized phosphine oxides **7/7'** and phosphonate **8** obtained.

Entry	Compound	R^1	R^2	R^3	Yield (%)[a]	Ratio(7:7')[b]	m.p. (°C)
1	**7a**	H	H	Ph	76	100 : 0	124-126
2	**7b**	*p*-Me	H	Ph	72	100 : 0	85-87
3	**7c**	*p*-MeO	H	Ph	83	100 : 0	77-80
4	**7d**	*o*-MeO	H	*o*-MePh	77	100 : 0	85-87
5	**7e**	3,4-$(Me)_2$	H	Ph	74	100 : 0	86-88
6	**7f**	*o*-Br	H	Ph	71	100 : 0	85-88
7	**7g**	*m*-Cl	H	Ph	76	100 : 0	82-84
8	**7h**	H	Me	Ph	81	100[c] : 0	130-132
9	**7i**	*p*-Me	Me	Ph	78	100[d] : 0	168-170
10	**7j**	*p*-Me	*p*-MePh	Ph	72	66[e] : 34	137-140
11	**8**	H	H	H	74	100 : 0	85-86

[a]Yield of isolated product **7/7'** and **8** based on **5**, **6**. [b]Enamino/imino and *Z/E* ratio determinated by ^{31}P-*NMR*. [c]*Z/E* ratio (33/67). [d]*Z/E* ratio (32/68). [e]*Z/E* ratio (33/33).

Preparation of substituted 4-aminoquinolines from phosphine oxide **7** and phosphonate derivatives **8**.

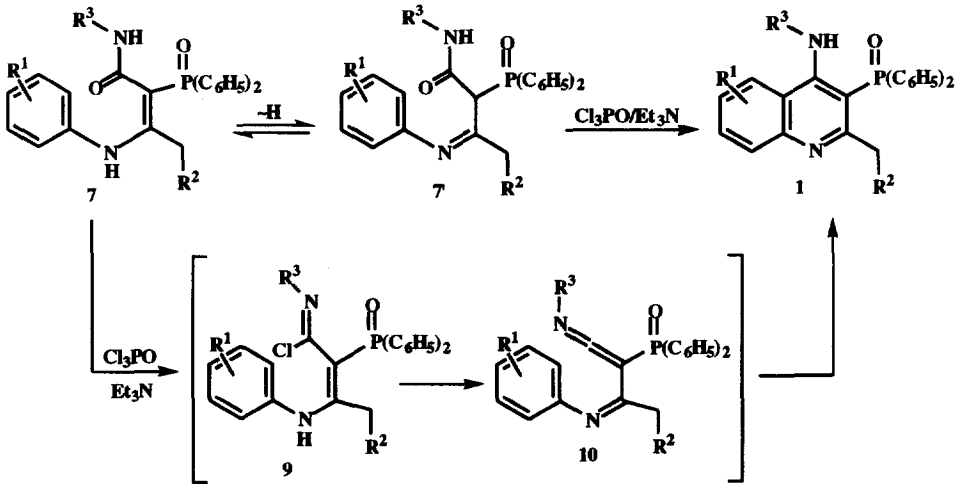
Treatment of functionalized enamines **7** with phosphorus oxychloride in the presence of triethylamine led to the formation of aminoquinolinylphosphine oxides **1** (Scheme 4) in excellent yield (table 2, entries 1-7). Spectroscopic data were in agreement with the assigned structure. Mass spectrometry of **1a** showed the molecular ion peak (*m/z* 434, 100 %), while the methyl group gave ^1H resonance at δ_H= 2.04 ppm. The formation of substituted quinolines **1** can be assumed to proceed *via* 6π-electrocyclization of conjugated imidoyl ketene imines **10** formed by the reaction of functionalized enamines **7** with phosphorus oxychloride in a similar way to that previously reported.[11b,17]

Formation of aminoquinolines were observed not only when enamines **7** were used, but also when a mixture of the *Z*- and *E*-enamines **7** and the imine-tautomers **7'** was used as starting material (Table 2, entries 8-10). The scope of this reaction was not limited to phosphine oxide derivatives **7**, since the enamine derived from phosphonate ester **8** also reacted with phosphorus oxychloride in the presence of triethylamine and gave in excellent yield the 4-aminoquinoline containing a phosphate group in 3 position **11** (Table 2, entry 11). From a preparative point of view it is noteworthy that the synthesis of phosphorylated 4-aminoquinolines **1** does not require the isolation and purification of functionalized phosphine oxides **7** and phosphonate **8** and they can be obtained in "one pot" reaction from the enamines derived from phosphine oxides **5** and phosphonate **6** when these compounds are directly metallated with methyllitium in *THF* with subsequent addition of isocyanates phosphorus oxychoride and aqueous work-up.

Table 2. 4–Aminoquinolines **1**, **11** and **13** obtained.

Entry	Compound	R^1	R^2	R^3	Yield (%)[a]	m.p. (°C)
1	**1a**	H	H	Ph	78(67)[b]	188-190
2	**1b**	6-Me	H	Ph	72(62)[b]	218-220
3	**1c**	6-MeO	H	Ph	71	191-192
4	**1d**	8-MeO	H	*o*-MePh	74	197-199
5	**1e**	6,7-$(Me)_2$	H	Ph	64	245-247
6	**1f**	8-Br	H	Ph	66	215-218
7	**1g**	7-Cl	H	Ph	69	207-208
8	**1h**	H	Me	Ph	76	169-171
9	**1i**	6-Me	Me	Ph	71	196-197
10	**1j**	6-Me	*p*-MePh	Ph	63	152-153
11	**11**	H	H	Ph	77[c](65)[d]	101-103
12	**13**	6-Me	H	Ph	72[e]	152-155

[a] Yield of isolated product **1** based on **7**. [b]Yield of isolated product **1** in "one pot" reaction from **5**. [c]Yield of isolated product **11** based on **8**. [d]Yield of isolated product **11** in "one pot" reaction from **6**. [e]Yield of isolated product **13** based on **12**.



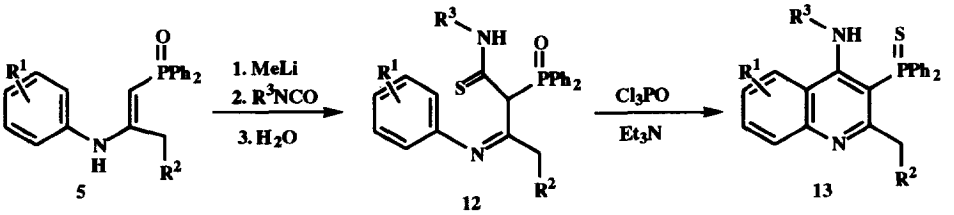
Scheme 4

Synthesis of 4-aminoquinolines derived from phosphine sulphides **13**.

This methodology used for the preparation of aminoquinolines **1** can also be applied to the synthesis of 4-aminoquinolines derived from phosphine sulphides **13** when isothiocyanates are used instead of isocyanates. Metallation of β-enamino phosphine oxides **5** with methyllitium in tetrahydrofuran followed by addition of isothiocyanates (*TLC* control) and aqueous work-up afforded the functionalized thioamide **12**.

Treatment of thioamides **12** with phosphorus oxychloride in the presense of triethylamine gave aminoquinolinyl phosphine sulphides **13** (Scheme 5). Formation of these compounds **13** could be explained

by a similar process to that mentioned in Scheme 4, although with a spontaneous exchange of oxygen for sulphur, with transformation of phosphine oxide into the phosphine sulphide group, caused by the reaction conditions.



Scheme 5

In conclusion, we describe an easy and efficient method for synthesis of 4-aminoquinolines substituted with a phosphine oxide **1**, a phosphonate **11** and a phosphine sulphide **13** group in 3-position from readily available starting materials such as arylamines, allenes and isocyanates or isothiocyanates (see Scheme 2) and under mild reaction conditions. 4-Aminoquinolines are useful compounds in medicinal chemistry since these products display a broad range of biological activities and have been widely used as pharmaceuticals.[3-8]

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SPM-20 apparatus and are uncorrected. Analytical *TLC* was performed on 0.25mm silica gel plates (Merck). Visualization was accomplished by *UV* light and iodine. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: CH_2Cl_2 (P_2O_5); *n*-hexane and diethyl ether (sodium benzophenone ketyl); ethyl acetate (K_2CO_3). All solvents used in reactions were freshly distilled from appropriate drying agents before use: acetonitrile (P_2O_5); $CHCl_3$ (P_2O_5). All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was carried out on silica gel (Merck, 70-230 mesh). Mass spectra were obtained on a Hewlett Packard 5890 spectrometer. Infrared spectra were taken on a Nicolet IRFT Magna 550 spectrometer. *^{1}H-NMR* spectra were recorded on a Varian 300 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ solutions. *^{13}C-NMR* spectra were recorded at 75 MHz with chloroform (77.0 ppm) as an internal reference in $CDCl_3$ solutions. *^{31}P-NMR* spectra were recorded at 120 MHz with 85% phosphoric acid as an external reference. Elemental analyses were performed in a Perkin Elmer Model 240 instrument. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet) q (quadruplet) or m (multiplet). Coupling constants, *J*, are reported in hertz. Infrared spectra *(IR)* were obtained as neat liquids, or as solids in *KBr*. Peaks are reported in cm^{-1}. Mass spectra *(EI)* were obtained with a ionization voltage of 70 eV. Data are reported in the form m/z (intensity relative to base = 100). All reactions were performed in oven (125 °C) or flame-dried glassware under an inert atmosphere of dry N_2.

General procedure for the reaction of enamino carbanions derived from phosphine oxides 5 and phosphonate 6 with isocyanates or isothiocyanates. A dry flask, 100-mL, 2-necked, fitted with a dropping funnel, gas inlet, and magnetic stirrer, was charged with 5 mmol of β-enamino phosphine oxides **5** and phosphonates **6** and 20 mL of *THF*. The temperature was allowed to descend to 0 °C and a solution (5.5 mmol) of methyllithium in *THF* was then added. The mixture was allowed to stir for 1 h. A solution (5 mmol) of isocyanate or isothiocyanate in 10 mL of *THF* was added at this temperature. The mixture was stirred until *TLC* indicated the disappearance of the compound **5** or **6** (~ 16 h). The mixture was washed with water and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization from diethyl ether.

***E*-1-Phenylamide-2-(*N*-phenylamino)prop-1-enyldiphenylphosphine oxide (7a).** 1717 mg (76 %) of 7a as a white solid. Data for 7a: mp 124-126 °C; ^{1}*H-NMR* (300 MHz) 1.48 (s, 3H, CH_3), 6.93-7.83 (m, 20H, arom), 11.68 (s, 1H, NH), 13.72 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 22.0 (d, $^3J_{PC}$= 6.0 Hz, CH_3), 83.3 (d, $^1J_{PC}$= 115.8 Hz, C-P), 118.7-138.8 (C-arom), 165.3 (d, $^2J_{PC}$= 17.1 Hz), 170.2 (d, $^2J_{PC}$= 11.0 Hz); ^{31}*P-NMR* (120 MHz) 36.8; *IR* (*KBr*) 3254, 3053, 1602, 1548, 1490, 1132 cm^{-1}; *MS* (EI) 452 (M^+, 10). Anal. Calcd for $C_{28}H_{25}N_2O_2P$: C, 74.34; H, 5.53; N, 6.19. Found: C, 74.55; H, 5.38; N, 6.25.

***E*-1-Phenylamide-2-(*N*-*p*-tolylamino)prop-1-enyldiphenylphosphine oxide (7b).** 1678 mg (72 %) of 7b as a white solid. Data for 7b: mp 85-87 °C; ^{1}*H-NMR* (300 MHz) 1.52 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 6.93-7.87 (m, 19H, arom), 10.81 (s, 1H, NH), 12.95 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 20.9 (CH_3), 22.1 (d, $^3J_{PC}$= 6.2 Hz, CH_3), 83.3 (d, $^1J_{PC}$= 116.3 Hz, C-P), 120.9-139.0 (C-arom), 165.6 (d, $^2J_{PC}$= 16.9 Hz), 170.4 (d, $^2J_{PC}$= 11.1 Hz); ^{31}*P-NMR* (120 MHz) 37.5; *IR* (*KBr*) 3433, 3059, 1542, 1439, 1223 cm^{-1}; *MS* (EI) 466 (M^+, 4). Anal. Calcd for $C_{29}H_{27}N_2O_2P$: C, 74.68; H, 5.79; N, 6.01. Found: C, 74.75; H, 5.68; N, 6.17.

***E*-1-Phenylamide-2-(*N*-*p*-methoxyphenylamino)prop-1-enyldiphenylphosphine oxide (7c).** 2001 mg (83 %) of 7c as a white solid. Data for 7c: mp 78-80 °C; ^{1}*H-NMR* (300 MHz) 1.42 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 6.75-7.82 (m, 19H, arom), 11.57 (s, 1H, NH), 13.46 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 21.9 (d, $^3J_{PC}$= 6.0 Hz, CH_3), 55.3 (O-CH_3), 82.5 (d, $^1J_{PC}$= 116.7 Hz, C-P), 114.2-158.0 (C-arom), 166.1 (d, $^2J_{PC}$= 17.6 Hz), 170.3 (d, $^2J_{PC}$= 11.1 Hz); ^{31}*P-NMR* (120 MHz) 37.2; *IR* (*KBr*) 3191, 3054, 1540, 1510, 1247 cm^{-1}; *MS* (EI) 482 (M^+, 7). Anal. Calcd for $C_{29}H_{27}N_2O_3P$: C, 72.20; H, 5.60; N, 5.81. Found: C, 72.35; H, 5.69; N, 5.97.

***E*-1-*o*-Tolylamide-2-(*N*-*o*-methoxyphenylamino)prop-1-enyldiphenylphosphine oxide (7d).** 1909 mg (77 %) of 7d as a white solid. Data for 7d: mp 85-87 °C; ^{1}*H-NMR* (300 MHz) 1.42 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 6.75-7.82 (m, 18H, arom), 11.23 (s, 1H, NH), 13.45 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 17.2 (CH_3), 21.5 (d, $^3J_{PC}$= 6.1 Hz, CH_3), 55.2 (O-CH_3), 83.4 (d, $^1J_{PC}$= 116.6 Hz, C-P), 110.2-158.0 (C-arom), 166.5 (d, $^2J_{PC}$= 17.7 Hz), 170.4 (d, $^2J_{PC}$= 11.2 Hz); ^{31}*P-NMR* (120 MHz) 37.1; *IR* (*KBr*) 3189, 3050, 1533, 1521, 1235 cm^{-1}; *MS* (EI) 496 (M^+, 3). Anal. Calcd for $C_{30}H_{29}N_2O_3P$: C, 72.58; H, 5.85; N, 5.64. Found: C, 72.71; H, 5.73; N, 5.67.

***E*-1-Phenylamide-2-(*N*-3,4-dimethylphenylamino)prop-1-enyldiphenylphosphine oxide (7e).** 1678 mg (74 %) of 7e as a white solid. Data for 7e: mp 86-87 °C; ^{1}*H-NMR* (300 MHz) 1.46 (s, 3H, CH_3), 2.14 (s, 6H, CH_3), 6.76-7.80 (m, 18H, arom), 10.81 (s, 1H, NH), 12.95 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 19.2 (CH_3), 19.7 (CH_3), 22.0 (d, $^3J_{PC}$= 6.0 Hz, CH_3), 82.6 (d, $^1J_{PC}$= 116.8 Hz, C-P), 118.8-138.9 (C-arom), 165.6 (d, $^2J_{PC}$= 17.1 Hz), 170.4 (d, $^2J_{PC}$= 10.6 Hz); ^{31}*P-NMR* (120 MHz) 37.1; *IR* (*KBr*) 3052, 2952, 1542, 1441, 1320 cm^{-1}; *MS* (EI) 480 (M^+, 8). Anal. Calcd for $C_{30}H_{29}N_2O_2P$: C, 75.00; H, 6.04; N, 5.83. Found: C, 75.16; H, 6.08; N, 5.91.

***E*-1-Phenylamide-2-(*N*-*o*-bromophenylamino)prop-1-enyldiphenylphosphine oxide (7f).** 1885 mg (71 %) of 7f as a brown solid. Data for 7f: mp 86-88 °C; ^{1}*H-NMR* (300 MHz) 1.35 (s, 3H, CH_3), 6.92-8.25 (m, 19H, arom), 11.62 (s, 1H, NH), 13.60 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 22.0 (d, $^3J_{PC}$= 6.0 Hz, CH_3), 84.6 (d, $^1J_{PC}$= 118.8 Hz, C-P), 114.8-138.9 (C-arom), 165.0 (d, $^2J_{PC}$= 16.1 Hz), 170.4 (d, $^2J_{PC}$= 10.6 Hz); ^{31}*P-NMR* (120 MHz) 37.3; *IR* (*KBr*) 3352, 3056, 1542, 1441, 1220 cm^{-1}; *MS* (EI) 531 (M^+-Br, 14). Anal. Calcd for $C_{28}H_{24}N_2O_2PBr$: C, 63.27; H, 4.52; N, 5.27. Found: C, 63.16; H, 4.38; N, 5.37.

***E*-1-Phenylamide-2-(*N*-*m*-chlorophenylamino)prop-1-enyldiphenylphosphine oxide (7g).** 1847 mg (76 %) of 7g as a brown solid. Data for 7g: mp 82-84 °C; ^{1}*H-NMR* (300 MHz) 1.51 (s, 3H, CH_3), 6.62-7.83 (m, 19H, arom), 11.65 (s, 1H, NH), 13.79 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 21.9 (d, $^3J_{PC}$= 6.1 Hz, CH_3), 84.8 (d, $^1J_{PC}$= 119.0 Hz, C-P), 114.7-139.3 (C-arom), 164.8 (d, $^2J_{PC}$= 16.1 Hz), 170.0 (d, $^2J_{PC}$= 10.6 Hz); ^{31}*P-NMR* (120 MHz) 37.1; *IR* (*KBr*) 3341, 3066, 1595, 1555, 1441, 1220 cm^{-1}; *MS* (EI) 486 (M^+-Cl, 12). Anal. Calcd for $C_{28}H_{24}N_2O_2PCl$: C, 69.06; H, 4.93; N, 5.75. Found: C, 69.18; H, 4.78; N, 5.67.

***Z*- and *E*-1-Phenylamide-2-(*N*-phenylamino)but-1-enyldiphenylphosphine oxide (7h).** 1887 mg (81 %) of 7h as a white solid. Data for 7h: mp 130-132 °C; ^{1}*H-NMR* (300 MHz) 1.11 (m, 3H, *E*- and *Z*-CH_3), 2.16 (m, 2H, *E*- and *Z*-CH_2), 6.94-7.82 (m, 20H, arom), 11.66 (s, 1H, NH), 13.65 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 10.5 (CH_3), 25.1 (d, $^3J_{PC}$= 9.5 Hz, *Z*-CH_2), 26.2 (d, $^3J_{PC}$= 6.1 Hz, *E*-CH_2), 82.8 (d, $^1J_{PC}$= 116.3 Hz, *E*-C-P), 94.3 (d, $^1J_{PC}$= 102.1 Hz, *Z*-C-P), 118.3-139.6 (C-arom), 167.3 (d, $^2J_{PC}$= 17.0 Hz), 170.7 (d, $^2J_{PC}$= 12.7 Hz); ^{31}*P-NMR* (120 MHz) 35.1 and 36.6; *IR* (*KBr*) 3161, 1664, 1434, 1162 cm^{-1}; *MS* (EI) 466 (M^+, 4). Anal. Calcd for $C_{29}H_{27}N_2O_2P$: C, 74.68; H, 5.79; N, 6.01. Found: C, 74.82; H, 5.61; N, 5.88.

***Z*- and *E*-1-Phenylamide-2-(*N*-*p*-tolylamino)but-1-enyldiphenylphosphine oxide (7i).** 1872 mg (78 %) of 7i as a white solid. Data for 7i: mp 168-170 °C; ^{1}*H-NMR* (300 MHz) 1.07 (m, 3H, *E*- and *Z*-CH_3), 2.11 (m, 2H, *E*- and *Z*-CH_2), 2.24 (s, 3H, *E*- and *Z*-CH_3), 6.91-7.87 (m, 19H, arom), 11.69 (s, 1H, NH), 13.35 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 10.3 (CH_3), 20.9 (CH_3), 25.2 (d, $^3J_{PC}$= 9.7 Hz, *Z*-CH_2), 26.0 (d, $^3J_{PC}$= 6.0 Hz, *E*-CH_2), 82.3 (d, $^1J_{PC}$= 116.8 Hz, *E*-C-P), 94.7 (d, $^1J_{PC}$= 101.9 Hz, *Z*-C-P), 119.1-139.7 (C-arom), 169.3 (d, $^2J_{PC}$= 17.1 Hz), 171.2 (d, $^2J_{PC}$= 13.1 Hz); ^{31}*P-NMR* (120 MHz) 35.0 and 35.6; *IR* (*KBr*) 3161, 1664, 1434, 1162 cm^{-1}; *MS* (EI) 480 (M^+, 4). Anal. Calcd for $C_{30}H_{29}N_2O_2P$: C, 75.01; H, 6.04; N, 5.83. Found: C, 75.12; H, 6.11; N, 5.78.

***Z*- and *E*-1-Phenylamide-2-(*N*-*p*-tolylamino)-3-*p*-tolylprop-1-enyldiphenylphosphine oxide (7j) and 1-Phenylamide-2-(*N*-*p*-tolylimino)-3-p-tolylpropyldiphenylphosphine oxide (7'j).** 2001 mg (72 %) of 7j/7'j as a white solid. Data for 7j/7'j: mp

138-139 °C; ^{1}*H-NMR* (300 MHz) **7j**: 2.10 (s, 3H, *E*- and *Z*-CH_3), 2.15 (s, 3H, *E*- and *Z*-CH_3), 3.38 (s, 2H, *E*- and *Z*-CH_2), 6.17-7.93 (m, 23H, arom), 11.59 (s, 1H, NH), 13.21 (s, 1H, NH). **7'j**: 2.18 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 4.73 (d, $^2J_{PH}$= 15.4 Hz, CH-P), 6.17-7.93 (m, 23H, arom), 10.27 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) **7j**: 20.7 (CH_3), 20.8 (CH_3), 35.8 (d, $^3J_{PC}$= 9.0 Hz, Z-CH_2), 37.6 (d, $^3J_{PC}$= 6.0 Hz, *E*-CH_2), 85.4 (d, $^1J_{PC}$= 115.2 Hz, *E*-C-P), 95.9 (d, $^1J_{PC}$= 102.2 Hz, Z-C-P), 119.1-138.7 (C-arom), 165.7 (d, $^2J_{PC}$= 13.1 Hz), 166.7 (d, $^2J_{PC}$= 7.0 Hz), 167.1 (d, $^2J_{PC}$= 17.1 Hz), 170.4 (d, $^2J_{PC}$= 11.5 Hz). **7'j**: 20.7 (CH_3), 20.8 (CH_3), 56.4 (d, $^1J_{PC}$= 51.1 Hz, C-P), 119.1-138.7 (C-arom), 162.5 (d, $^2J_{PC}$= 2.5 Hz), 162.8 (d, $^2J_{PC}$= 2.0 Hz); ^{31}*P-NMR* (120 MHz) **7j**: 35.0 and 35.6. **7'j**: 31.5; *IR* (*KBr*) 3161, 1664, 1434, 1162 cm^{-1}; *MS* (EI) 480 (M^+, 4). Anal. Calcd for $C_{30}H_{29}N_2O_2P$: C, 75.01; H, 6.04; N, 5.83. Found: C, 75.12; H, 6.11; N, 5.78.

***E*-1-Phenylamide-2-(*N*-phenylamino)prop-1-enyldiethylphosphonate (8).** 861 mg (74 %) of **8** as a white solid. Data for **8**: mp 85-86 °C; ^{1}*H-NMR* (300 MHz) 1.28 (t, 6H, $^3J_{HH}$= 7.0 Hz,CH_3), 2.18 (s, 3H, CH_3), 4.09 (m, 4H, CH_2), 6.94-7.53 (m, 10H, arom), 11.38 (s, 1H, NH), 12.65 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 16.0 and 16.2 (CH_3), 19.2 (d, $^3J_{PC}$= 3.1 Hz, CH_3), 81.7 (d, $^1J_{PC}$= 196.4 Hz, C-P), 119.1-138.9 (C-arom), 168.8 (d, $^2J_{PC}$= 16.1 Hz), 169.5 (d, $^2J_{PC}$= 19.7 Hz); ^{31}*P-NMR* (120 MHz) 27.3; *IR* (*KBr*) 3200, 2986, 1542, 1333 cm^{-1}; *MS* (EI) 388 (M^+, 10). Anal. Calcd for $C_{20}H_{25}N_2O_4P$: C, 61.86; H, 6.43; N, 7.22. Found: C, 61.98; H, 6.38; N, 7.25.

1-Phenylthioamide-2-(*N*-p-tolylimino)propyldiphenylphosphine oxide (12). 1996 mg (83 %) of **12** as a yellow solid. Data for **12**: mp 145-146 °C; ^{1}*H-NMR* (300 MHz) 1.78 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 5.30 (d, $^2J_{PH}$= 9.1 Hz, CH-P), 6.36-7.94 (m, 19H, arom), 10.51 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 20.8 (CH_3), 22.5 (CH_3), 68.2 (d, $^1J_{PC}$= 47.3 Hz, C-P), 119.3-138.9 (C-arom), 165.5 (C=N), 189.1 (C=S); ^{31}*P-NMR* (120 MHz) 30.3; *IR* (*KBr*) 3174, 3005, 1592, 1513, 1373, 1149 cm^{-1}; *MS* (EI) 482 (M^+, 17). Anal. Calcd for $C_{29}H_{27}N_2OSP$: C, 72.21; H, 5.60; N, 5.81. Found: C, 72.45; H, 5.48; N,5.75.

General procedure for the preparation of the phosphorylated quinolines 1, 11 and 13. A dry flask, 100-mL, 2-necked, fitted with a dropping funnel, gas inlet, and magnetic stirrer, was charged with (3 mmol) of amide **7**, **8** or thioamide **12**, 0.55 mL (4 mmol) of triethylamine and 15 mL of *THF*. A solution 0.30 mL (3.2 mmol) of phosphorus oxychloride and 10 mL of *THF* was added over 10 min. The mixture was stirred and refluxed until *TLC* indicated the disappearance of the compound **7**, **8** or **12** (~2 days). The mixture was diluted with 30 mL water and extracted with CH_2Cl_2 (3 x 15). The CH_2Cl_2 layers were washed with water. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash-chromatography on silica gel (hexane/diethyl ether, 1/1). Quinolines can also be obtained in "one pot" reaction: 4 mmol of **5** in 20 mL of *THF* was metallated with methyl lithium at 0 °C. The mixture was allowed to stir for 1 h. A solution 4 mmol of isocyanate in 10 mL of *THF* was added at this temperature. The mixture was stirred for 24 h, and a solution of 0.39 mL (4.2 mmol) of phosphorus oxychloride and 10 mL of *THF* was added. The quinoline was purified as described above.

3-Diphenylphosphoryl-2-methyl-4-phenylaminoquinoline (1a). 1015 mg (78 %) of **1a** as a yellow solid. Data for **1a**: mp 188-190 °C; ^{1}*H-NMR* (300 MHz) 2.04 (s, 3H, CH_3), 7.04-7.80 (m, 19H, arom), 10.96 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 28.4 (CH_3), 106.7 (d, $^1J_{PC}$= 98.2 Hz, C-P), 119.9-158.4 (C-arom); ^{31}*P-NMR* (120 MHz) 38.7; *IR* (*KBr*) 3200, 3059, 1568, 1400, 1118 cm^{-1}; *MS* (EI) 434 (M^+, 100). Anal. Calcd for $C_{28}H_{23}N_2OP$: C, 77.42; H, 5.30; N, 6.45. Found: C, 77.61; H, 5.53; N, 6.55.

3-Diphenylphosphoryl-2,6-dimethyl-4-phenylaminoquinoline (1b). 968 mg (72 %) of **1b** as a yellow solid. Data for **1b**: mp 218-220 °C; ^{1}*H-NMR* (300 MHz) 2.02 (s, 3H, CH_3-C=N), 2.18 (s, 3H, CH_3), 6.70-7.73 (m, 18H, arom), 10.84 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 21.9 (CH_3), 28.2 (CH_3), 107.0 (d, $^1J_{PC}$= 99.1 Hz, C-P), 120.1-157.7 (C-arom); ^{31}*P-NMR* (120 MHz) 38.2; *IR* (*KBr*) 3261, 3059, 1609, 1575, 1179 cm^{-1}; *MS* (EI) 448 (M^+, 88). Anal. Calcd for $C_{29}H_{25}N_2OP$: C, 77.68; H, 5.58; N, 6.25. Found: C, 77.51; H, 5.69; N, 6.51.

3-Diphenylphosphoryl-2-methyl-6-methoxy-4-phenylaminoquinoline (1c). 988 mg (71 %) of **1c** as a yellow solid. Data for **1c**: mp 191-192 °C; ^{1}*H-NMR* (300 MHz) 2.01 (s, 3H, CH_3-C=N), 3.33 (s, 3H, CH_3-O), 6.72-7.73 (m, 18H, arom), 10.82 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 28.0 (CH_3), 54.8 (CH_3-O), 107.3 (d, $^1J_{PC}$= 98.2 Hz, C-P), 104.7-156.9 (C-arom); ^{31}*P-NMR* (120 MHz) 38.6; *IR* (*KBr*) 3113, 3027, 1568, 1491, 1238 cm^{-1}; *MS* (EI) 464 (M^+, 88). Anal. Calcd for $C_{29}H_{25}N_2O_2P$: C, 75.01; H, 5.39; N, 6.03. Found: C, 75.23; H, 5.54; N, 6.11.

3-Diphenylphosphoryl-2-methyl-8-methoxy-4-*o*-tolylaminoquinoline (1d). 1061 mg (74 %) of **1d** as a yellow solid. Data for **1d**: mp 197-199 °C; ^{1}*H-NMR* (300 MHz) 2.02 (s, 3H, CH_3-C=N), 2.16 (s, 3H, CH_3), 3.37 (s, 3H, CH_3-O), 6.69-7.63 (m, 17H, arom), 10.67 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 25.4 (CH_3), 28.0 (CH_3), 54.6 (CH_3-O), 106.9 (d, $^1J_{PC}$= 98.0 Hz, C-P), 104.3-157.5 (C-arom); ^{31}*P-NMR* (120 MHz) 38.5; *IR* (*KBr*) 3121, 3019, 1561, 1482, 1223 cm^{-1}; *MS* (EI) 478 (M^+, 88). Anal. Calcd for $C_{30}H_{27}N_2O_2P$: C, 75.31; H, 5.65; N, 5.86. Found: C, 75.43; H, 5.52; N, 5.91.

3-Diphenylphosphoryl-2,6,7-trimethyl-4-phenylaminoquinoline (1e). 887 mg (64 %) of **1e** as a yellow solid. Data for **1e**: mp 245-247 °C; ^{1}*H-NMR* (300 MHz) 2.04 (s, 3H, CH_3-C=N), 2.11 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.74-7.75 (m, 17H, arom), 10.84 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 19.9 (CH_3), 20.2 (CH_3), 28.2 (CH_3), 106.1 (d, $^1J_{PC}$= 99.7 Hz, C-P), 118.3-157.4 (C-arom); ^{31}*P-NMR* (120 MHz) 38.4; *IR* (*KBr*) 3269, 2978, 1712, 1594, 1430, 1115 cm^{-1}; *MS* (EI) 462 (M^+, 95). Anal. Calcd for $C_{30}H_{27}N_2OP$: C, 77.92; H, 5.84; N, 6.06. Found: C, 77.71; H, 5.72; N, 6.14.

8-bromo-3-Diphenylphosphoryl-2-methyl-4-phenylaminoquinoline (1f). 1016 mg (66 %) of **1f** as a yellow solid. Data for **1f**: mp 215-218 °C; ^{1}*H-NMR* (300 MHz) 2.09 (s, 3H, CH_3), 6.71-7.90 (m, 18H, arom), 11.03 (s, 1H, NH); ^{13}*C-NMR* (75

MHz) 27.6 (CH_3), 107.4 (d, $^1J_{PC}$= 98.6 Hz, C-P), 117.2-152.2 (C-arom); ^{31}*P-NMR* (120 MHz) 38.8; *IR* (*KBr*) 3341, 3294, 1649, 1552, 1238 cm^{-1}; *MS* (EI) 513 (M^+, 98). Anal. Calcd for $C_{28}H_{22}N_2OPBr$: C, 65.50; H, 4.29; N, 5.46. Found: C, 65.61; H, 4.33; N, 5.35.

7-chloro-3-Diphenylphosphoryl-2-methyl-4-phenylaminoquinoline (1g). 969 mg (69 %) of **1g** as a yellow solid. Data for **1g**: mp 207-208 °C; ^{1}*H-NMR* (300 MHz) 2.11 (s, 3H, CH_3), 6.77-7.94 (m, 18H, arom), 10.95 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 26.6 (CH_3), 106.5 (d, $^1J_{PC}$= 99.1 Hz, C-P), 116.5-152.9 (C-arom); ^{31}*P-NMR* (120 MHz) 39.1; *IR* (*KBr*) 3365, 3094, 1633, 1542, 1211 cm^{-1}; Anal. Calcd for $C_{28}H_{22}N_2OPCl$: C, 71.79; H, 4.70; N, 5.98. Found: C, 71.90; H, 4.63; N, 5.85.

3-Diphenylphosphoryl-2-ethyl-4-phenylaminoquinoline (1h). 1021 mg (76 %) of **1h** as a yellow solid. Data for **1h**: mp 169-171 °C; ^{1}*H-NMR* (300 MHz) 0.58 (t, 3H, $^3J_{HH}$= 7.2 Hz, CH_3), 2.40 (q, 2H, $^3J_{HH}$= 7.2 Hz, CH_2), 6.75-7.98 (m, 19H, arom), 11.05 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 12.8 (CH_3), 32.9 (CH_2), 105.7 (d, $^1J_{PC}$= 99.7 Hz, C-P), 119.0-163.2 (C-arom); ^{31}*P-NMR* (120 MHz) 39.7; *IR* (*KBr*) 3335, 3056, 1602, 1568, 1407, 1125 cm^{-1}; *MS* (EI) 448 (M^+, 97). Anal. Calcd for $C_{29}H_{25}N_2OP$: C, 77.68; H, 5.58; N, 6.25. Found: C, 77.78; H, 5.73; N, 6.20.

3-Diphenylphosphoryl-2-ethyl-6-methyl-4-phenylaminoquinoline (1i). 984 mg (71 %) of **1i** as a yellow solid. Data for **1i**: mp 196-197 °C; ^{1}*H-NMR* (300 MHz) 0.57 (t, 3H, $^3J_{HH}$= 7.3 Hz, CH_3), 2.19 (s, 3H, CH_3), 2.38 (q, 2H, $^3J_{HH}$= 7.3 Hz, CH_2), 6.72-7.75 (m, 18H, arom), 11.00 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 12.9 (CH_3), 21.6 (CH_3), 32.8 (CH_2), 106.0 (d, $^1J_{PC}$= 99.2 Hz, C-P), 119.8-162.2 (C-arom); ^{31}*P-NMR* (120 MHz) 38.7; *IR* (*KBr*) 3046, 2989, 1593, 1414, 1114 cm^{-1}; *MS* (EI) 462 (M^+, 100). Anal. Calcd for $C_{30}H_{27}N_2OP$: C, 77.92; H, 5.84; N, 6.06. Found: C, 77.75; H, 5.76; N, 6.21.

3-Diphenylphosphoryl-2-(*p*-tolylmethyl)-6-methyl-4-phenylaminoquinoline (1j). 1017 mg (63 %) of **1j** as a yellow solid. Data for **1j**: mp 152-153 °C; ^{1}*H-NMR* (300 MHz) 2.26 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 6.48-7.86 (m, 22H, arom), 10.76 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 20.8 (CH_3), 21.6 (CH_3), 43.8 (CH_2), 108.8 (d, $^1J_{PC}$= 97.7 Hz, C-P), 108.0-158.8 (C-arom); ^{31}*P-NMR* (120 MHz) 37.6; *IR* (*KBr*) 3205, 3063, 1693, 1487, 1412 cm^{-1}; *MS* (EI) 538 (M^+, 100). Anal. Calcd for $C_{36}H_{31}N_2OP$: C, 80.30; H, 5.76; N, 5.20. Found: C, 80.15; H, 5.66; N, 5.31.

3-Diethylphosphonate-2-methyl-4-phenylaminoquinoline (1l). 855 mg (77 %) of **1l** as a yellow solid. Data for **1l**: mp 101-103 °C; ^{1}*H-NMR* (300 MHz) 1.27 (t, 6H, $^3J_{HH}$= 6.9 Hz, CH_3), 2.78 (s, 3H, CH_3), 3.97-4.10 (m, 4H, CH_2), 6.82-7.83 (m, 9H, arom), 10.39 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 16.1 (CH_3), 26.3 (CH_3), 62.3 (CH_2), 103.9 (d, $^1J_{PC}$= 178.8 Hz, C-P), 119.4-160.1 (C-arom); ^{31}*P-NMR* (120 MHz) 22.4; *IR* (*KBr*) 3241, 2985, 1602, 1488, 1407, 1031 cm^{-1}; *MS* (EI) 370 (M^+, 100). Anal. Calcd for $C_{20}H_{23}N_2O_3P$: C, 64.86; H, 6.21; N, 7.57. Found: C, 64.78; H, 6.13; N, 7.70.

3-Diphenylthiophosphoryl-2,6-dimethyl-4-phenylaminoquinoline (1m). 1002 mg (72 %) of **1m** as a yellow solid. Data for **1m**: mp 152-155 °C; ^{1}*H-NMR* (300 MHz) 2.05 (s, 3H, CH_3-C=N), 2.19 (s, 3H, CH_3), 6.28-7.87 (m, 18H, arom), 8.44 (s, 1H, NH); ^{13}*C-NMR* (75 MHz) 21.5 (CH_3), 27.8 (CH_3), 107.0 (d, $^1J_{PC}$= 99.1 Hz, C-P), 116.8-158.4 (C-arom); ^{31}*P-NMR* (120 MHz) 35.9; *IR* (*KBr*) 3194, 3052, 1715, 1501, 1441, 1098 cm^{-1}; *MS* (EI) 464 (M^+, 100). Anal. Calcd for $C_{29}H_{25}N_2SP$: C, 75.00; H, 5.38; N, 6.03. Found: C, 75.11; H, 5.59; N, 5.91.

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