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An Efficient One-Pot Synthesis of 3-(Aryl and Alkyl)methylene-*1H*-isoindolin-1-ones *via* Aryne Cyclization and Horner Reaction of *o*-(and *m*-) Halogeno-*N*-phosphorylmethylbenzamide Derivatives.

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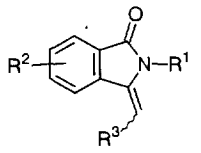
Abstract: A series of 3-(alkyl and aryl)methylene-2,3-dihydro-*1H*-isoindol-1-one derivatives was synthesized by a one-pot reaction sequence involving lithiation of 2- (or 3-)halogeno-*N*-phosphoryl-methylbenzamides, cyclization of the aryne intermediate, metal migration and Horner reaction of the resulting phosphorylated aminocarbanion with selected aromatic and aliphatic aldehydes.

INTRODUCTION

In recent years, members of the 3-(alkyl and aryl)methylene-2,3-dihydro-*1H*-isoindol-1-one (phthalimidine) class of compounds **1** have generated a certain interest in the scientific community as reflected by recent articles dealing with their synthesis and emphasizing their pharmaceutical and medicinal activities.[1] Thus the phenylethylidene derivatives **2** (AKS 186) and **3** have been recently reported to inhibit the thromboxane A2 analog (U-46619)-induced vasoconstriction[1a] whereas the 4-acetoxyphenylmethylene derivative **4** has been



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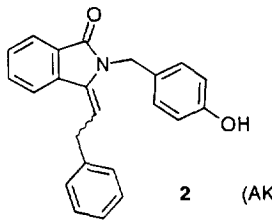

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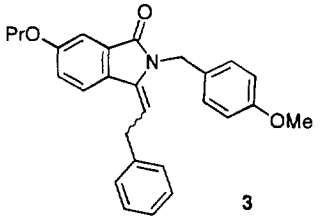

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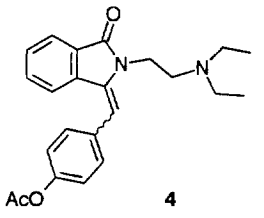

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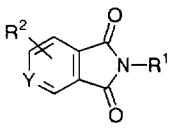
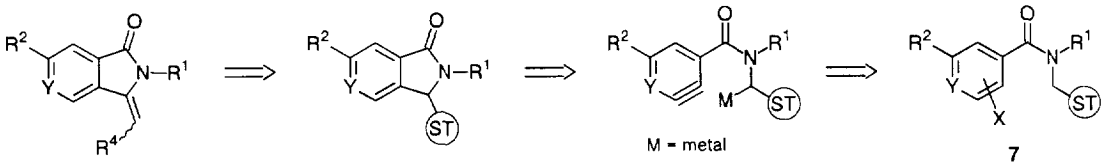
claimed to exhibit local anesthetic activity superior to that of procaine.[1c] Moreover they represent the core unit found in a number of isoindole derived alkaloid families.[2] Accordingly the synthesis of this heterobicyclic system has developed remarkably in recent years which is also obviously linked to the synthetic potential of compounds comprising the 3-methylenephthalimidine unit.[3] Indeed such highly conjugated models have been recently involved in the elaboration of sophisticated spiroheterocycles[4] and have been elegantly utilized by Castedo[5] for the construction of the aristolactam alkaloid framework. These compounds may be synthesized in a number of different ways but the most convenient route relies either upon the addition of appropriate Grignard reagents[1d,1g,6] to an *N*-substituted phthalimide **5** and subsequent dehydration of the resulting alcohol or directly by the reaction of **5** with a Wittig reagent.[7] However, these reactions generally require the use of a large excess of Grignard reagent for complete conversion[6e] and are often low yielding particularly with phenylethylmagnesium halides.[1b] Most of all, the regioselectivity of these reactions proved to be problematical for unsymmetrically substituted cyclic compounds **5** ($R^2 \neq H$) and for models **6** incorporating a pyridine unit. Indeed, the monosubstituted phthalimides give rise unavoidably to variable mixtures of regioisomers[1b] whereas, in agreement with theoretical expectations, the Grignard addition to pyrrolopyridinedione derivatives **6** is selectively directed to the carbonyl group attached to the 4-position of the pyridine ring.[8] Finally, these isoindolinone derivatives **1** are also accessible by different chemical processes which include the Parham-type cyclization of *N*-acyl-2-bromobenzamides,[9] the reaction of isocyanates with *ortho*-manganated aromatic ketones,[10] the base-induced cyclization of 2-phenylethynylbenzamide[11] and the treatment of the corresponding phthalides with primary amines.[12] However, these methods are rather restricted in scope and do not permit the introduction of a great diversity of aromatic and even less heteroaromatic units in the fused isoindolinones. Furthermore, few of them may solve the aforementioned problem of regioselectivity.



5 Y = CH
6 Y = N

RESULTS AND DISCUSSION

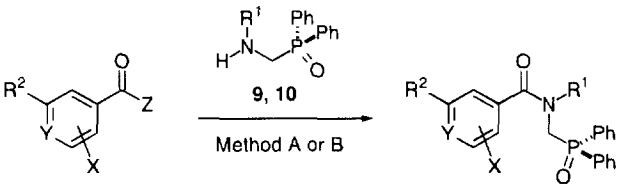
In this paper we wish to describe an alternative, more efficient, tactically and conceptually new approach to these highly conjugated systems that is based on the retrosynthetic analysis shown in Scheme 1. The key step is the intramolecular trapping of a benzyne intermediate with an adjacent side-chain carbon nucleophile. Since



Scheme 1

the pioneering work of Huisgen[13] and Bunnett[14] this concept has been successfully applied to the elaboration of a large variety of benzofused heterocyclic systems[15] as witnessed by the recent syntheses of diversely substituted benzoxazole,[16] benzothiazole[17] and indoline[18] derivatives. In the formation of these heterocycles the heteroatom

acts directly as the nucleophile. Alternatively a carbon nucleophile may be produced and the heteroatom not be directly involved in the ring closure but applications of this concept to the preparation of benzo five- and six-membered mononitrogen heterocycles[19] where the nitrogen is not attached to the benzene ring are extremely rare. This is undoubtedly due to the fact that generation of α-aminocarbanions is a prerequisite to the annelation process and, although several procedures have been recently developed to solve this problem,[20] the regioselective creation of carbanions adjacent to a nitrogen atom remains a challenging synthetic task. Usually the direct introduction of aryl groups at the α-position of substituted amines is achieved by reaction of Grignard,[21] organocopper[22] or cuprate reagents[23] with *N,O*- or *N,S*-acetals or by palladium promoted coupling of α-aminoalkyllithium reagents with electron rich aryl iodides.[24] Intramolecularly this operation may be carried out by reaction of α-aminoalkylcarbanions with epoxides[25] or by a tandem α-arylation-isomerization of cyclic enamides.[26] However, considerable limitations for all these processes abound. Critical to the success of our strategy was therefore the ability to identify an α-aminocarbanion stabilizing group ST (Scheme 1) that was sufficiently robust to survive the projected metallation addition steps and yet was labile enough to promote the formation of the fragile enamide function under mild conditions. This dual requirement prompted us to incorporate the diphenylphosphinyl group in the parent models. The remarkable nucleophilicity of phosphorylated α-aminocarbanions has been illustrated by the synthesis of *N*-alkylaminoalkylphosphane oxides[27,28] and their ylidic character has been cleverly used for enamine[29] and enamide syntheses.[30] On the other hand the choice of the diphenylphosphinyl group was dictated by the properties of diphenylphosphane oxides incontestably superior in many respects to phosphonium salts and phosphonates.[31]



8a-h **7a-h**

Scheme 2

Among the various routes[32] liable to give access to compounds of structure **7** (ST = $P(O)Ph_2$, X = 2- or 3-Cl, Br, F, Y = CH or N) the coupling reaction between an appropriate aromatic or heteroaromatic acylating partner **8** and a suitable *N*-alkyl-*N*-diphenylphosphinylmethylamine **9, 10** emerged as the most simple, general and tolerant of other functionalities (Scheme 2). Initially the phosphorylated secondary amines **9, 10** were prepared according to a procedure recently developed in our laboratory[28c,30b] and two different protocols depending on the availability of the acylating (hetero)aromatic reagents were adopted for the synthesis of the desired halogenated aromatic and heteroaromatic carboxamides **7a-h** (Scheme 2, Table 1). Thus compounds **7a,f,g** were easily obtained by coupling the 2- or 3-halogenobenzoic or pyridinecarboxylic acids **8a,f,g** with the phosphorylated amines **9, 10** under classical conditions (DCC, DMAP, CH_2Cl_2, Table 1, method A). Compounds **7b-e,h** were directly accessible from the more affordable aromatic carboxaldehydes **8b-e,h** by adapting a recently described procedure[33] for the conversion of aromatic aldehydes into tertiary carboxamides

(NBS, AIBN, CCl_4, Et_3N, Table 1, method B). The latter protocol delivered the phosphorylated amides with excellent yields (Table 1) and thus enriches the repertoire of synthetic methods available for the preparation of *N*-acylaminomethylphosphane oxide derivatives.

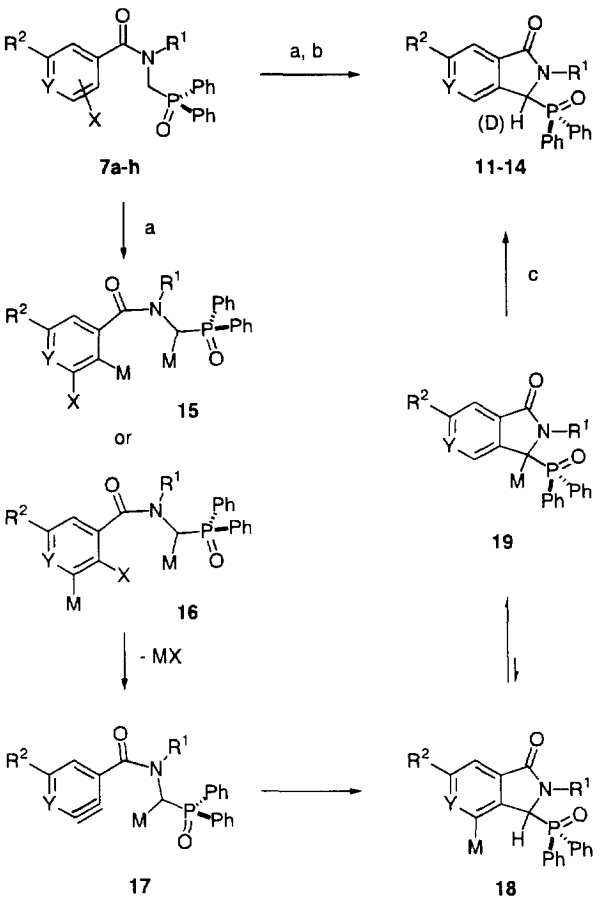
Table 1. Halogenated Aromatic and Heteroaromatic Carboxamides 7a-h Prepared

7, 8	R^1	R^2	Y	X	Z	method[a]	yield %
a	4-$MeOC_6H_4CH_2$	H	CH	3-F	OH	A	85
b	4-$MeOC_6H_4CH_2$	H	CH	2-Cl	H	B	80
c	4-$MeOC_6H_4CH_2$	H	CH	2-Br	H	B	78
d	4-$MeOC_6H_4CH_2$	O-CH_2-O-CH		5-Br	H	B	75
e	Me	OPr	CH	2-Br	H	B	81
f	4-$MeOC_6H_4CH_2$	H	N	3-Cl	OH	A	78
g	Me	H	CH	2-Br	OH	A	84
h	4-$MeOC_6H_4CH_2$	OPr	CH	2-Br	H	B	82

[a] Method A: from carboxylic acid and phoshorylated amine, DCC, DMAP, CH_2Cl_2;
Method B: from carboxaldehyde and phosphorylated amine, NBS, AIBN, CCl_4, Et_3N.

To test the synthetic approach depicted in Scheme 1 we then examined the chemical behavior under basic conditions of a series of phosphorylated 2- and 3-halophenyl and pyridyl carboxamide derivatives varying the aromatic, nitrogen and halogen substituents and using different bases (Scheme 3, Table 2). We first screened different base-solvent combinations with 3-fluoro derivative **7a** (entries 1-2) which was *a priori* the best suited for this study. Indeed the cooperative effects of the powerful 1,3-interrelated fluoro[34] and carboxamido[35] *ortho*-directing metallation groups should direct the lithiation at their common *ortho* "in between" site, initiating the expected reaction sequence depicted in scheme 3. Treatment of **7a** by making use of lithium diisopropylamide (LDA) as the base in THF (2.2 equiv., -78 °C to rt, 2 h) afforded the desired phosphorylated isoindolinone **11** but this was accompanied with the dehalogenated parent amide and some other minor unidentified products. Since this could be attributable to the difficulty of halide expulsion[36] from the transient dimetallated species **15** (Scheme 3), we managed to preclude this side reaction and increased the yield of phosphorylated isoindolinone by simply using the scarcely employed bulkier base potassium *bis*(trimethylsilyl)amide[36] (KHMDS, entry 2). We also proceeded to examine the effects of halogen atoms at different positions of the aromatic nucleus and found, firstly, that under the same conditions, no significant difference was observed in the reaction behavior between *o*-chloro and *m*-fluoro compounds (**7b** *vs* **7a**, entries 2, 3). On the other hand, a somewhat higher yield of the same product was obtained from the corresponding *o*-bromo derivative **7c** (entry 4). In fact the efficiency of the annelation process parallels the ease of halide expulsion, which ranks as Br>Cl>F.[36] For these reasons and because of easier accessibility, the bromo derivatives **7c-e** were used and subjected to KHMDS (THF / toluene, -78 °C). Warming to room temperature gave, in a consistently clean reaction, the phosphorylated isoindolinones **11-13** with yields in the range 69-94 %. Although the reaction proceeded satisfactorily with mono and unsubstituted phosphorylated 2- and 3-halophenylcarboxamides it was most efficient with models incorporating

methylenedioxy substituent **7d** (entry 5) and this small drop in yield is undoubtedly due to facile *ortho*-lithiation, [35] faster elimination of KBr[37] and easier benzyne formation. Finally it is also worth mentioning that for the



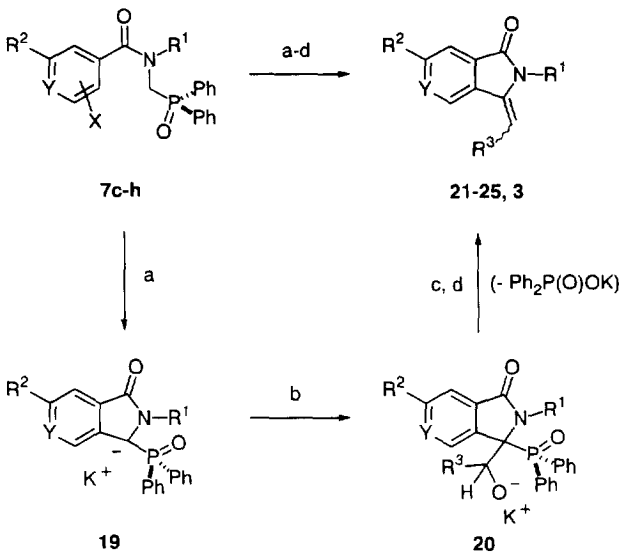
Scheme 3: (a) base R^4M (2.2 equiv.), THF, -78 °C to rt, 2 h; (b) H_3O^+; (c). H_2O or D_2O.

Table 2. Phosphorylated Isoindolinones 11-14 Prepared

entry	amide	R^1	R^2	Y	X	base/solvent	isoindolinone	yield %
1	**7a**	4-$MeOC_6H_4CH_2$	H	CH	3-F	LDA/hexanes/THF	**11**	68
2	**7a**	4-$MeOC_6H_4CH_2$	H	CH	3-F	KHMDS/toluene/THF	**11**	79
3	**7b**	4-$MeOC_6H_4CH_2$	H	H	2-Cl	KHMDS/toluene/THF	**11**	81
4	**7c**	4-$MeOC_6H_4CH_2$	H	CH	2-Br	KHMDS/toluene/THF	**11**	88
5	**7d**	4-$MeOC_6H_4CH_2$	O-CH_2-O-CH		5-Br	KHMDS/toluene/THF	**12**	94
6	**7e**	Me	OPr	CH	2-Br	KHMDS/toluene/THF	**13**	89
7	**7f**	4-$MeOC_6H_4CH_2$	H	N	3-Cl	KHMDS/toluene/THF	**14**	69

3-chloropyridyl derivative **7f** metallation occurs at the carbon adjacent to the nitrogen atom and, consequently, initiates the formation of the transient dehydropyridine **17**[38] (Y = N, R^2 = H, R^1 = 4-methoxybenzyl). Addition of the suitably placed carbon nucleophile across the pyridyne moiety results in the phosphorylated azaisoindolone **14** (Scheme 3).

Recent developments of the aryne-mediated cyclization approach have been mainly focused on the regioselective introduction of additional substituents onto the original aromatic nucleus of the newly formed heterocycle by quenching the organometallic intermediate generated in the course of the cyclization step with selected electrophiles.[15b, 17, 18] We were eager to gain insight about the mechanistic pathway operative in the formation of the phosphorylated lactams **11-14**. For this purpose compound **7d** was treated with KHMDS under the previously determined optimal conditions and the reaction mixture was quenched with D_2O. That deuterium had been incorporated at the benzylic position of the heterocyclic moiety of the resulting phosphorylated lactam **12** was made immediately evident by the disappearance in the ^{1}H NMR spectrum of the doublet assigned to the methine proton (δ = 5.18 ppm, J_{HP} = 10.8 Hz) coupled to the phosphoryl group. It is very likely that the metallated isoindolinone **18** is first formed by cyclization of the aryne anion **17** (Scheme 3). Metal shift to the more acidic phosphorylated benzylic position gives rise to **19** and accounts for the regioselective introduction of deuterium at the 3-position of the isoindolinone ring. It was obvious that this additional feature would have important implication for the synthesis of 3-(aryl and alkyl)methyleneisoindolinones **1** and particularly of the targeted models **2, 3, 4**. Indeed it was anticipated that straightforward access to these compounds could be designed starting with the "opened" phosphorylated *o*-halogeno(hetero)aryl carboxamides and precluding isolation of the intermediate phosphorylated isoindolones which could be trapped *in situ* with appropriate carbonyl compounds. Dephosphorylation of the adduct under classical Horner reaction conditions could then open a new route to the isoindolinones incorporating the (di)enamide *exo* function. A representative range of phosphorylated amides was therefore treated with KHMDS (2.2 equiv.) in THF at -78 °C. After gradual warming to room temperature, the reaction mixture was re-cooled to -30 °C and subsequently quenched with selected aromatic and aliphatic carboxaldehydes (Scheme 4). We were pleased to observe that this protocol generated exclusively, in a consistently clean reaction, the desired 3-(alkyl and aryl)methyleneisoindolones. The results of a representative series of products obtained by this method are presented in Table 3 where it may be seen that this simple procedure affords excellent yields of the 2-alkyl-3-(aryl and alkyl)methylene-2,3-dihydro-*1H*-isoindol-1-ones **3, 21-25,** and particularly of the previously unattainable 2,3-dihydro-3-isobutylidene-2-(4-methoxyphenyl)methyl-*1H*-pyrrolo[3,4-*c*]pyridin-1-one (**24**), in both *E* and *Z* forms. The configurational assignments were determined by homonuclear NOE NMR experiments by irradiation of the N-CH_2 or N-CH_3 protons and evaluation of enhancement of the intensity of the vinylic proton. The method is tolerant of a wide variety of phosphorylated amides and carbonyl compounds. Addition of carbanionic species to carbonyl compounds are usually limited to using non enolizable aldehydes and ketones. Normal Horner-Wittig addition reactions do not suffer from this limitation[39] and consequently the transient metallated phosphorylated lactam **19** could be trapped indifferently with benzaldehyde, isobutyraldehyde and the highly enolizable phenylacetaldehyde. The high degree of conjugation of the final compounds **3, 21-25** due to the simultaneous presence of a styrenic

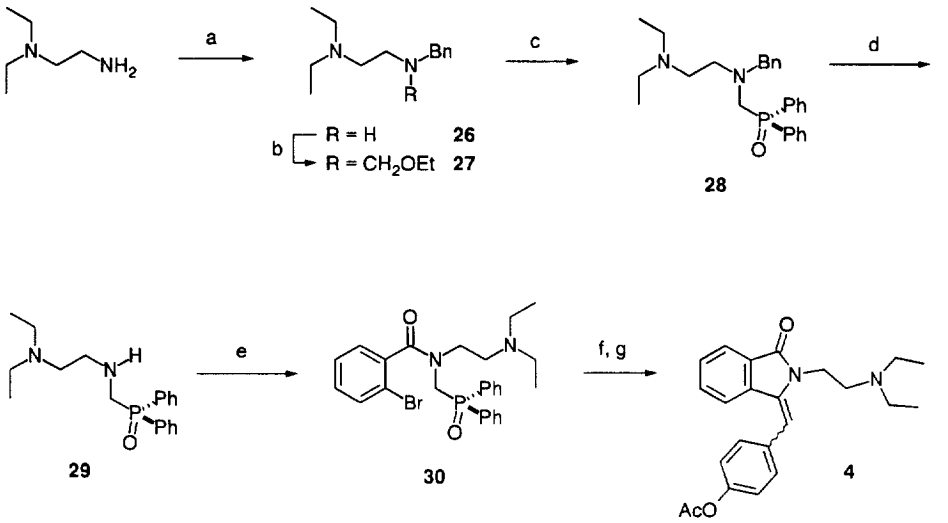


Scheme 4: (a) KHMDS (2.2 equiv.),THF, -78 °C to rt, 2 h; (b) R^3CHO, THF, -30 °C; (c) -30 °C to rt, 0.5 h; (d) aqueous HCl.

Table 3. 3-(Alkyl and aryl)methyleneisoindolinones 21-25, 3 Prepared

amide	3-alkylidene isoindolinone	R^1	R^2	Y	R^3	*Z*:*E*	yield %
7c	**21**	4-$MeOC_6H_4CH_2$	H	CH	Bn	40:60	71
7d	**22**	4-$MeOC_6H_4CH_2$	O-CH_2-O-CH		Bn	25:75	75
7e	**23**	Me	OPr	CH	Ph	55:45	85
7f	**24**	4-$MeOC_6H_4CH_2$	H	N	*i*-Pr	95:5	65
7g	**25**	Me	H	CH	Ph	55:45	60
7h	**3**	4-$MeOC_6H_4CH_2$	OPr	CH	Bn	25:75	68

or stilbenic unit and of the (di)enamide function possessing a marked polyenic character and the presence of the weakly bound potassium counterion in the adduct **20** prone to facilitate alkene formation[31b] account for the efficiency of the process.[40] Compound **21** is the direct precursor of the targeted hydroxy derivative **2** (AKS 186)[1d] and as a further demonstration of the utility of this alkyl and arylidene isoindolinone synthesis a new synthetic approach to the diethylaminoethyl derivative **4** was devised and is briefly described below (Scheme 5). Owing to unpredictable difficulties associated with the synthesis of the requisite phosphorylated diamine **29** *via* the chloromethylation phosphorylation protocol developed in our laboratory[28c], an alternative method was adopted.



Scheme 5: (a) $NaBH(OAc)_3$ (1.5 equiv.), PhCHO, DCE, rt, 1.5 h; (b) $(CH_2O)_n$, EtOH, benzene, 80 °C, 8 h; (c) Ph_2PCl, THF, rt, 0.5 h, then reflux 2 h; (d) H_2, 20% $Pd(OH)_2/C$, 80 °C, 20 h; (e) **8g**, DCC, DMAP, CH_2Cl_2, rt, 8 h; (f) KHMDS (2.2 equiv.), THF, -78 °C to rt, 2 h; (g) 4-acetoxybenzaldehyde (**31**), THF, -30 °C to rt, 0.5 h then aqueous NH_4Cl.

Initially the reductive amination of benzaldehyde with diethylaminoethylamine in dichloroethane according to the recently developed procedure of Abdel-Magid[41] afforded the *N*-benzylated derivative **26**. Mannich-type condensation with paraformaldehyde in ethanol furnished the mixed *N,O*-acetal **27** which, without isolation, was treated with chlorodiphenylphosphine[42] to yield the polysubstituted diamine **28**. Catalytic hydrogenolysis delivered the phosphorylated amine **29** with a satisfactory overall yield (55 %). The coupling reaction between the diamine **29** and 2-bromobenzoic acid (**8g**) (DCC, DMAP, CH_2Cl_2) proceeded uneventfully to generate the aromatic carboxamide **30** equipped with the phosphoryl group. Exposure of compound **30** to KHMDS followed by addition of 4-acetoxybenzaldehyde (**31**) gave direct access to the 2-diethylaminoethyl-2,3-dihydro-3(4-acetoxyphenyl)methylene-*1H*-isoindol-1-one (**4**) in excellent yield (86%) thus demonstrating the feasibility and versatility of this process.

Further studies based on this (hetero)aryne route to other heterobicyclic systems are in progress.

EXPERIMENTAL SECTION

General. The melting points were taken on a Reichert-Thermopan apparatus and are not corrected. All proton, carbon and phosphorus NMR spectra were taken with $CDCl_3$ as solvent at 300, 75 and 121 MHz respectively on a Bruker AM 300 spectrometer. Tetrahydrofuran (THF) and Et_2O were freshly distilled over $LiAlH_4$ and CH_2Cl_2, CCl_4, hexanes, toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and

assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Microanalyses were performed by the CNRS microanalysis center and mass spectra were obtained in a Riber 10-10 apparatus.

The phosphorylated amines **9, 10** were prepared from the corresponding formamides according to the procedure described in ref. 28c.

1-Diphenylphosphinyl-*N*-[(4-methoxyphenyl)methyl]methanamine (9): mp 78-79 °C; ^{1}H NMR δ 2.05 (br. s, 1H), 3.38 (d, J_{HP} = 7.8 Hz, 2H), 3.76 (s, 3H), 3.78 (s, 2H), 6.81 (d, J_{AB} = 8.7 Hz, 2H), 7.13 (d, J_{AB} = 8.7 Hz, 2H), 7.40-7.51 (m, 6H), 7.69-7.76 (m, 4H); ^{13}C NMR δ 48.0 (d, J_{CP} = 81 Hz), 54.4 (d, J_{CP} = 14 Hz), 55.2, 113.8, 128.6 (d, J_{CP} = 12 Hz), 129.5, 131.1(d, J_{CP} = 9 Hz), 131.8 (d, J_{CP} = 97 Hz), 131.9 (d, J_{CP} = 3 Hz), 158.8; ^{31}P NMR δ 29.8; MS (EI) *m/z* 351 (M^+, 98), 201 (10), 121 (100). Anal. Calcd for $C_{21}H_{22}NO_2P$: C, 71.78; H, 6.31; N, 3.99. Found: C, 72.01; H, 6.05; N, 3.77.

1-Diphenylphosphinyl-*N*-methylmethanamine (10): mp 77-78 °C (lit.[43] liquid); ^{1}H NMR δ 1.73 (br. s, 1H), 2.47 (s, 3H), 3.42 (d, J_{HP} = 7.7 Hz, 2H), 7.39-7.55 (m, 6H), 7.71-7.82 (m, 4H); ^{13}C NMR δ 38.5 (d, J_{CP} = 15 Hz), 51.5 (d, J_{CP} = 80 Hz), 55.2, 128.6 (d, J_{CP} = 12 Hz), 131.6(d, J_{CP} = 9 Hz), 131.9 (d, J_{CP} =3 Hz), 132.0 (d, J_{CP} = 97 Hz); ^{31}P NMR δ 29.0; MS (EI) *m/z* 245 (M^+, 8), 202 (100).

General Procedures for the Synthesis of the Halogenated Aromatic and Heteroaromatic Carboxamides 7a-h. Method A. The 3-fluoro and 2-bromobenzoic acids **8a,g** are commercially available. The 3-chloropyridine-4-carboxylic acid **8f** was prepared according to a previously described procedure.[44] A solution of the appropriate 2- or 3-halogenobenzoic and pyridinecarboxylic acid derivatives **8a,g** and **8f** respectively (4 mmol) in anhydrous CH_2Cl_2 (20 mL) was added with stirring under Ar to a cooled (0 °C) solution of the phosphorylated amines **9, 10** (4 mmol), dicyclohexylcarbodiimide (DCC, 0.8 g, 4 mmol), 4-dimethylaminopyridine (DMAP, 50 mg, 0.4 mmol) in anhydrous CH_2Cl_2. The mixture was then stirred at room temperature for 2 h, then filtered on Celite® and the solvent was evaporated to dryness. Flash column chromatography (silica gel 0.040-0.063 mm) of the crude products using acetone-hexane (7:3) as eluent followed by recrystallization from hexane-toluene afforded the phosphorylated carboxamides **7a,f,g** (Table 1).

***N*-Diphenylphosphinylmethyl-*N*-(4-methoxyphenyl)methyl-3-fluorobenzamide (7a):** mp 154-155 °C; ^{1}H NMR δ 3.76 (s, 3H), 4.44 (d, J_{HP} = 5.0 Hz, 2H), 4.71 (s, 2H), 6.67 (d, J_{HF} = 8.5 Hz, 1H), 6.77-6.84 (m, 3H), 7.02-7.12 (m, 3H), 7.22-7.26 (m, 1H), 7.47-7.56 (m, 6H), 7.88-7.95 (m, 4H); ^{13}C NMR δ 42.8 (d, J_{CP} = 77 Hz), 52.9, 55.2, 114.0 (d, J_{CF} = 22.5 Hz), 114.2, 116.7 (d, J_{CF} = 30 Hz), 112.3 (d, J_{CF} = 3 Hz), 127.3, 128.7 (d, J_{CP} = 12 Hz), 129.2, 130.4 (d, J_{CP} = 8 Hz), 131.1 (d, J_{CP} = 97 Hz), 131.2 (d, J_{CP} = 9 Hz), 132.3 (d, J_{CP} = 3 Hz), 137.4 (d, J_{CF} = 7 Hz), 159.3, 162.4 (d, J_{CF} = 247 Hz), 170.1; ^{31}P NMR δ 31.4; MS (EI) *m/z* 473 (M^+, 8), 123 (100). Anal. Calcd for $C_{28}H_{25}FNO_3P$: C, 71.03; H, 5.32; N, 2.96. Found: C, 71.24; H, 5.15; N, 3.12.

***N*-Diphenylphosphinylmethyl-*N*-(4-methoxyphenyl)methyl-3-chloropyridine-4-carboxamide (7f):** mp 172-173 °C ; ^{1}H NMR (two rotamers A/B, 90:10) δ 3.76 (s, 3H, A), 3.78 (s, 3H, B), 4.15 (d, J_{AB} = 15.0

Hz, 1H, B), 4.35 (dd, J = 5.1, 14.7 Hz, 1H, A), 4.43 (d, J_{AB} = 15.1 Hz, 1H, A), 4.56 (dd, J = 5.1, 16.2 Hz, 1H, A), 4.75 (d, J_{AB} = 15.1 Hz, 1H, A), 5.71 (d, J_{AB} = 15.0 Hz, 1H, B), 6.79 (d, J = 4.9 Hz, 1H), 6.82 (d, J_{AB} = 8.5 Hz, 2H), 7.14 (d, J_{AB} = 8.5 Hz, 2H), 7.39-7.62 (m, 6H), 7.78-8.00 (m, 4H), 8.42 (d, J = 4.9 Hz, 1H with overlapping with B), 8.53 (s, 1H, A), 8.59 (s, 1H, B); ^{13}C NMR (rotamer A) δ 42.2 (d, J_{CP} = 75.5 Hz), 52.4, 55.3, 114.0, 114.3, 121.9, 126.3, 128.7 (d, J_{CP} = 12 Hz), 130.4, 131.1 (m), 132.4 (m), 142.3, 147.9, 150.1, 159.5, 165.8; ^{31}P NMR δ 24.5 (B), 30.4 (A); MS (EI) *m/z* 492 (M^+, <1), 490 (M^+, 2), 146 (100). Anal. Calcd for $C_{27}H_{24}ClN_2O_3P$: C, 66.06; H, 4.93; N, 5.71. Found: C, 66.31; H, 4.79; N, 5.51.

***N*-Diphenylphosphinylmethyl-*N*-methyl-2-bromobenzamide (7g):** mp 124-125 °C; ^{1}H NMR δ 3.06 (s, 3H), 4.33 (m, 1H), 4.89 (br.d, J_{HP} = 14.5 Hz, 1H), 6.63 (dd, J = 2.0, 7.4 Hz, 1H), 7.12-7.25 (m, 2H), 7.41-7.53 (m, 6H), 7.85-8.05 (m, 4H); ^{13}C NMR δ 37.9, 46.7 (d, J_{CP} = 76 Hz), 118.6, 127.4, 127.5, 128.5-129.1 (m), 130.3, 131.2 (d, J_{CP} = 9 Hz), 132.3 (br. s), 132.7, 137.4, 168.9 (d, J_{CP} = 2 Hz); ^{31}P NMR δ 30.8; MS (EI) *m/z* 429 (M^+, 2), 427 (M^+, 2), 185 (90), 183 (100). Anal. Calcd for $C_{21}H_{19}BrNO_2P$: C, 58.90; H, 4.47; N, 3.27. Found: C, 58.75; H, 4.45; N, 3.33.

Method B: Initially the 2-bromopiperonal **8d**[45] and 2-bromo-4-propyloxybenzaldehyde **8e**[46] were synthesized according to already reported procedures. To a preheated solution (95 °C) of the aromatic carboxaldehydes **8b-e** (12 mmol) in CCl_4 (200 mL) were sequentially added 2,2'-azobisisobutyronitrile (AIBN, 20 mg, 0.3 mmol) and *N*-bromosuccinimide (NBS, 2.8 g, 15 mmol). The heterogeneous mixture was refluxed for 20 min, cooled to rt and subsequently cooled to 0 °C with an ice-water bath. A solution of the phosphorylated amines **9, 10** (14 mmol) and Et_3N (1.8 g, 18 mmol) in CCl_4 (20 mL) was added dropwise with stirring and the reactional mixture was stirred at rt for an additional 1 h. The solid material was removed by filtration and washed with CCl_4 (20 mL). The filtrate was extracted with water (2 x 50 mL), brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a viscous oil which was purified as in Method A to afford the phosphorylated carboxamides **7b-e,h** (Table 1).

***N*-Diphenylphosphinylmethyl-*N*-(4-methoxyphenyl)methyl-2-chlorobenzamide (7b):** mp 162-163 °C; ^{1}H NMR (two rotamers A/B, 90:10) δ 3.73 (s, 3H, A), 3.75 (s, 3H, B), 4.27 (d, J_{AB} = 14.6 Hz, 1H, B), 4.47 (ddd, J = 5.6, 15.4, 16.9 Hz, 2H), 4.51 (d, J_{AB} = 14.9 Hz, 1H, A), 4.76 (d, J_{AB} = 14.9 Hz, 1H, A), 5.75 (d, J_{AB} = 14.6 Hz, 1H, B), 6.80-6.86 (m, 3H), 7.13-7.29 (m, 5H), 7.46-7.51 (m, 6H), 7.85-8.00 (m, 4H); ^{13}C NMR (rotamer A) δ 42.0 (d, J_{CP} = 76.5 Hz), 52.5, 55.2, 114.1, 126.9, 127.0, 128.2, 128.7 (d, J_{CP} = 9 Hz), 129.8, 129.9, 130.4, 130.6, 131.1 (d, J_{CP} = 9 Hz), 131.3 (d, J_{CP} = 10 Hz), 132.2, 132.3, 134.9, 159.3, 168.2; ^{31}P NMR δ 25.4 (B), 30.8 (A); MS (EI) *m/z* 489 (M^+, <1), 454 (23), 215 (37), 201 (23), 141 (33), 139 (100). Anal. Calcd for $C_{28}H_{25}ClNO_3P$: C, 68.64; H, 5.14; N, 2.86. Found: C, 68.57; H, 4.99; N, 3.01.

***N*-Diphenylphosphinylmethyl-*N*-(4-methoxyphenyl)methyl-2-bromobenzamide (7c):** mp 148-149 °C; ^{1}H NMR (two rotamers A/B, 93:7) δ 3.75 (s, 3H, A), 3.77 (s, 3H, B), 4.08 (d, J_{AB} = 14.5 Hz, 1H, B), 4.40-4.54 (m, 3H), 4.77 (d, J_{AB} = 15.0 Hz, 1H, A), 5.76 (d, J_{AB} = 14.5 Hz, 1H, B), 6.77-6.84 (m, 3H), 7.09-7.25 (m, 5H), 7.42-7.60 (m, 6H), 7.84-8.03 (m, 4H); ^{13}C NMR (rotamer A) δ 41.9 (d, J_{CP} = 76 Hz), 52.6, 55.2, 114.1, 119.4, 126.9, 127.4, 128.3, 128.6 (d, J_{CP} = 11.5 Hz), 128.7 (d, J_{CP} = 12 Hz), 129.9, 130.5, 131.2 (d, J_{CP} = 10

Hz), 131.5 (d, J_{CP} = 10.5 Hz), 132.2, 132.3, 133.1, 137.0, 159.3, 168.9; ^{31}P NMR δ 25.3 (B), 30.8 (A); MS (EI) *m/z* 533 (M^+, <1), 454 (32), 215 (44), 201 (32), 185 (97), 183 (100). Anal. Calcd for $C_{28}H_{25}BrNO_3P$: C, 62.93; H, 4.72; N, 2.62. Found: C, 63.17; H, 4.65; N, 2.91.

***N*-Diphenylphosphinylmethyl-*N*-(4-methoxyphenyl)methyl-5-bromo-1,3-benzodioxole-4-carboxamide (7d):** mp 157-158 °C; ^{1}H NMR δ 3.77 (s, 3H), 4.44 (d, J_{HP} = 5.3 Hz, 2H), 4.55 (d, J_{AB} = 14.9 Hz, 1H), 4.78 (d, J_{AB} = 14.9 Hz, 1H), 5.95 (s, 2H), 6.20 (s, 1H), 6.84 (d, J_{AB} = 8.5 Hz, 2H), 6.90 (s, 1H), 7.23 (d, J_{AB} = 8.5 Hz, 2H), 7.31-7.61 (m, 6H), 7.84-8.03 (m, 4H); ^{13}C NMR δ 42.0 (d, J_{CP} = 79 Hz), 52.7, 55.2, 102.1, 108.1, 110.6, 113.0, 114.1, 126.9, 128.6 (d, J_{CP} = 11.5 Hz), 128.7 (d, J_{CP} = 12 Hz), 129.9, 131.0, 131.2 (d, J_{CP} = 10 Hz), 131.4 (d, J_{CP} = 10 Hz), 132.2, 132.3, 147.4, 149.0, 159.3, 168.5; ^{31}P NMR δ 30.9; MS (EI) *m/z* 579 and 577 (M^+, <1), 229 (96), 227 (100). Anal. Calcd for $C_{29}H_{25}BrNO_5P$: C, 60.22; H, 4.36; N, 2.42. Found: C, 60.07; H, 4.64; N, 2.27.

***N*-Diphenylphosphinylmethyl-*N*-methyl-2-bromo-5-propoxybenzamide (7e):** mp 136-137 °C; ^{1}H NMR δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.71-1.80 (m, 2H), 3.07 (s, 3H), 3.72 (t, *J* = 6.3 Hz, 2H), 4.24 (dd, *J* = 7.8, 16.8 Hz, 1H), 4.94 (dd, *J* = 4.1, 16.8 Hz, 1H), 6.07 (d, *J* = 3.0 Hz, 1H), 6.69 (dd, *J* = 3.0, 8.8 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.47-7.57 (m, 6H), 7.93-8.00 (m, 4H); ^{13}C NMR δ 10.4, 22.4, 37.9, 46.8 (d, J_{CP} = 77 Hz), 69.9, 108.6, 112.9, 117.4, 128.6 (d, J_{CP} = 11 Hz), 128.8 (d, J_{CP} = 12 Hz), 131.3 (d, J_{CP} = 12 Hz), 132.3 (d, J_{CP} = 10 Hz), 133.5, 137.9, 158.5, 168.8; ^{31}P NMR δ 31.2; MS (EI) *m/z* 487 (M^+, 15), 485 (M^+, 15), 243 (98), 241 (100), 201 (37). Anal. Calcd for $C_{24}H_{25}BrNO_3P$: C, 59.27; H, 5.18; N, 2.88. Found: C, 59.25; H, 4.99; N, 2.61.

***N*-Diphenylphosphinylmethyl-*N*-(4-methoxyphenyl)methyl-2-bromo-5-propoxybenzamide (7h):** mp 154-155 °C; ^{1}H NMR δ 0.99 (t, *J* = 7.4 Hz, 3H),1.68-1.80 (m, 2H), 3.67-3.76 (m, 2H), 3.77 (s, 3H), 4.40 (dd, *J* = 5.8, 15.2 Hz, 1H), 4.51-4.56 (m, 2H), 4.77 (d, J_{HP} = 15.2 Hz, 1H), 6.22 (d, *J* = 3.0 Hz, 1H), 6.69 (dd, *J* = 3.0, 9.1 Hz, 1H), 6.83 (d, J_{AB} = 8.8 Hz, 2H), 7.24 (d, J_{AB} = 8.8 Hz, 2H), 7.33 (d, *J* = 9.1 Hz, 1H), 7.40-7.55 (m, 6H), 7.85-8.04 (m, 4H); ^{13}C NMR δ 10.4, 22.4, 41.9 (d, J_{CP} = 76 Hz), 52.7, 55.2, 70.0, 109.3, 113.8, 114.1, 117.6, 129.6, 128.7 (d, J_{CP} = 10.5 Hz), 128.6 (d, J_{CP} = 12 Hz), 130.0, 131.3, (d, J_{CP} = 8.5 Hz), 131.4 (d, J_{CP} = 10 Hz), 132.2, 132.3, 133.8, 137.6, 158.3, 159.3, 168.7; ^{31}P NMR δ 30.9; MS (EI) *m/z* 593 and 591 (M^+, <1),.243 (95), 241 (100) Anal. Calcd for $C_{31}H_{31}BrNO_4P$: C, 62.85; H, 5.27; N, 2.36. Found: C, 63.02; H, 5.14; N, 2.17.

General Procedure for the Synthesis of the Phosphorylated Isoindolinones 11-14. A commercial solution of KHMDS in toluene (Aldrich, 0.5 M, 4 mL, 2 mmol) was added dropwise over a period of 0.25 h to a stirred solution of the parent phosphorylated amides **7a-f** (1 mmol) in THF (20 mL) at -78 °C under Ar. The solution was stirred for 0.25 h at this temperature after which it was allowed to warm to rt within 2 h. After this, several drops of dilute HCl (10%), water (10 mL), Et_2O (30 mL) were subsequently added. The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. TLC analysis indicated the presence of a single product which was finally purified by recrystallization from hexane-toluene.

2,3-Dihydro-3-diphenylphosphinyl-2-(4-methoxyphenyl)methyl-*1H*-isoindol-1-one (11): mp 173-174 °C; ^{1}H NMR δ 3.74 (s, 3H), 4.30 (d, J_{AB} = 14.8 Hz, 1H), 5.28 (d, J_{HP} = 11.0 Hz, 1H), 5.34 (d, J_{AB} = 14.8

Hz, 1H), 6.75-6.81 (m, 3H), 7.11 (d, J = 8.6 Hz, 2H), 7.28-7.71 (m, 13H); ^{13}C NMR δ 44.7, 55.2, 60.0 (d, J_{CP} = 73 Hz), 114.0, 124.0, 104.4, 128.7 (d, J_{CP} = 11 Hz), 128.8 (d, J_{CP} =10.5 Hz), 129.8, 131.4 (d, J_{CP} = 2 Hz), 131.6 (d, J_{CP} = 8.5 Hz), 132.0 (d, J_{CP} =9 Hz), 132.6 (d, J_{CP} = 3 Hz),, 132.9, 133.0, 138.9, 159.1, 168.8; ^{31}P NMR δ 30.9; MS (EI) *m/z* 453 (M^+, 13), 201 (20), 121 (100). Anal. Calcd for $C_{28}H_{24}NO_3P$: C, 74.16; H, 5.33; N, 3.09. Found: C, 74.30; H, 5.21; N, 3.27.

2,3-Dihydro-3-diphenylphosphinyl-2-(4-methoxyphenyl)methyl-*1H*-dioxolo[4,5-*e*]isoindol-1-one (12): mp 214-215 °C; ^{1}H NMR δ 3.77 (s, 3H), 4.05 (d, J_{AB} = 14.8 Hz, 1H), 5.18 (d, J_{HP} = 10.8 Hz, 1H), 5.26 (d, J_{AB} = 14.8 Hz, 1H), 5.98 (dd, J = 1.0, 10.3 Hz, 2H), 6.32 (s, 1H), 6.78 (d, J_{AB} = 8.5 Hz, 2H), 7.01 (d, J_{AB} = 8.5 Hz, 2H), 7.09 (s, 1H), 7.44-7.52 (m, 6H), 7.56-7.70 (m, 4H); ^{13}C NMR δ 44.8, 55.3, 59.8 (d, J_{CP} = 73 Hz), 102.0, 103.5, 104.4, 114.0, 126.8, 127.7 (d, J_{CP} = 19. Hz), 128.8 (d, J_{CP} = 11.5 Hz), 128.85 (d, J_{CP} =11.5 Hz), 129.6, 131.6 (d, J_{CP} =8.5 Hz), 131.9 (d, J_{CP} = 9 Hz), 132.9 (d, J_{CP} = 3Hz), 133.0 (d, J_{CP} = 2.5 Hz), 148.8, 151.2, 159.05, 168.9; ^{31}P NMR δ 30.2; MS (EI) *m/z* 497 (M^+, 100), 296 (37), 295 (34), 121 (46). Anal. Calcd for $C_{29}H_{24}NO_5P$: C, 70.02; H, 4.86; N, 2.82. Found: C, 70.27; H, 4.59; N, 2.76.

2,3-Dihydro-3-diphenylphosphinyl-2-methyl-6-propoxy-*1H*-isoindol-1-one (13): mp 181-182 °C; ^{1}H NMR δ 1.00 (t, J = 7.4 Hz, 3H), 1.74-1.81 (m, 2H), 3.11 (s, 3H), 3.89 (t, J = 6.6 Hz, 2H), 5.29 (d, J_{HP} = 10.6 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.86 (dd, J = 2.4, 8.5 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.30-7.71 (m, 10H); ^{13}C NMR δ 10.4, 22.4, 30.4, 63.5 (d, J_{CP} = 77 Hz), 69.9, 107.0, 120.0, 124.6, 128.7 (d, J_{CP} = 8.5 Hz), 128.8 (d, J_{CP} = 11.5 Hz), 130.15, 131.6 (d, J_{CP} = 9 Hz), 131.8 (d, J_{CP} = 8.5 Hz), 132.8, 133.9, 159.8, 168.7; ^{31}P NMR δ 30.7; MS (EI) *m/z* 405 (M^+, 36), 204 (100), 201 (64). Anal. Calcd for $C_{24}H_{24}NO_3P$: C, 71.10; H, 5.97; N, 3.45. Found: C, 71.36; H, 6.04; N, 3.18.

2,3-Dihydro-3-diphenylphosphinyl-2-(4-methoxyphenyl)methyl-*1H*-pyrrolo[3,4-*c*]pyridin-1-one (14): mp 205-206 °C; ^{1}H NMR δ 3.78 (s, 3H), 4.37 (d, J_{AB} = 14.7 Hz, 1H), 5.34 (d, J_{AB} = 14.7 Hz, 1H), 5.40 (d, J_{HP} = 10.5 Hz, 1H), 6.82 (d, J_{AB} = 8.6 Hz, 2H), 7.12 (d, J_{AB} = 8.6 Hz, 2H), 7.35-7.78 (m, 11H), 8.06 (s, 1H), 8.67 (d, J = 4.6 Hz, 1H); ^{13}C NMR δ 44.9, 55.3, 59.2 (d, J_{CP} = 75 Hz), 114.2, 114.3, 117.7, 128.9 (d, J_{CP} = 12 Hz), 129.2 (d, J_{CP} = 12 Hz), 129.9, 131.5 (d, J_{CP} = 10.5 Hz), 132.0 (d, J_{CP} = 9 Hz), 133.3 (d, J_{CP} = 3 Hz), 133.4 (d, J_{CP} = 3 Hz), 140.4, 145.8, 149.6, 159.3, 166.9; ^{31}P NMR δ 30.5; MS (EI) *m/z* 454 (M^+, 21), 201 (100). Anal. Calcd for $C_{27}H_{23}N_2O_3P$: C, 71.36; H, 5.10; N, 6.16. Found: C, 71.10; H, 5.04; N, 6.28.

General Procedure for the Synthesis of the 3-[(alkyl and aryl)methylene] isoindolinones 21-25, 3. A solution of the brominated and phosphorylated aryl and heteroaryl carboxamides, **7c-e,g,h** and **7f** respectively, was treated with KHMDS (2 equiv) as previously described. After warming to rt, the reaction mixture was recooled to -30 °C and a solution of the appropriate aromatic and aliphatic aldehyde (1 equiv) was added. The solution was allowed to warm to rt over a period of 0.5 h. Water was added and the mixture was extracted with Et_2O. The ether extract was washed with water and brine, dried over Na_2SO_4 and evaporated *in vacuo*. Flash chromatography on silica gel (AcOEt-hexane, 15:85-20:80) allowed, in several cases, isolation of *Z* and *E* forms of the isoindolinones **21-25, 3** which, when necessary, were recrystallized from hexane-toluene.

2,3-Dihydro-2-[(4-methoxyphenyl)methyl]-3-(2-phenylethylidene)-*1H*-isoindol-1-one (21): *E* and *Z* isomers (ratio 60:40 from ^{1}H NMR spectrum). Pure *E* isomer: mp 105-106 °C; ^{1}H NMR δ 3.65 (d, *J* = 8.1 Hz, 2H), 3.77 (s, 3H), 5.21 (s, 2H), 5.75 (t, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 7.0 Hz, 2H), 7.09-7.29 (m, 5H), 7.49-7.64 (m, 3H), 7.91 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 32.5, 44.2, 55.3, 107.1, 114.3, 119.2, 123.3, 126.4, 127.0, 127.9, 128.2, 128.7, 129.7, 131.9, 134.3, 138.1, 140.0, 158.8, 168.4; MS (EI) *m/z* 355 (M^+, 100), 220 (34); *Z* isomer (not separated): ^{1}H NMR δ 3.77 (s, 3H), 3.95 (d, *J* = 7.9 Hz, 2H), 4.98 (s, 2H), 5.62 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.10-7.28 (m, 7H), 7.45-7.60 (m, 2H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR δ 33.2, 42.5, 55.3, 111.3, 114.0, 123.3, 123.7, 126.5, 128.2, 128.4, 128.6, 128.9, 129.1, 130.5, 132.1, 135.4, 135.5, 139.6, 158.8, 166.5. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.35; H, 5.75; N, 3.72.

2,3-Dihydro-2-[(4-methoxyphenyl)methyl]-3-(2-phenylethylidene)-*1H*-1,3-dioxolo[4,5-*e*]isoindol-1-one (22): non separable *E* and *Z* isomers (ratio 75:25 from ^{1}H NMR spectrum). ^{1}H NMR δ (*E* isomer) 3.60 (d, *J* = 8.1 Hz, 2H), 3.77 (s, 3H), 5.14 (s, 2H), 5.53 (t, *J* = 8.1 Hz, 1H), 6.05 (s, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.99 (s, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.22-7.29 (m, 5H); (*Z* isomer) 3.77 (s, 3H), 3.85 (d, *J* = 7.9 Hz, 2H), 4.91 (s, 2H), 5.50 (t, *J* = 7.9 Hz, 1H), 6.06 (s, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 6.8 Hz, 2H), 7.11-7.26 (m, 7H); ^{13}C NMR δ (*E* isomer) 32.4, 44.2, 55.3, 99.5, 102.1, 102.7, 106.5, 114.2, 122.4, 126.4, 126.9, 128.2, 128.6, 129.8, 134.2, 140.0, 148.9, 151.9, 158.8, 167.1; (*Z* isomer) 32.9, 42.4, 55.3, 102.1, 103.5, 103.6, 110.2, 114.0, 126.4, 126.9, 128.1, 128.3, 128.7, 129.8, 134.2, 135.5, 139.7, 148.9, 158.8, 166.5. MS (EI) *m/z* 399 (M^+, 100), 264 (41). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 74.98; H, 5.55; N, 3.39.

2,3-Dihydro-2-methyl-3-phenylmethylene-6-propoxy-*1H*-isoindol-1-one (23): separable *E* and *Z* isomers (ratio 45:55 from ^{1}H NMR spectrum). Pure *E* isomer: mp 99-100°C; ^{1}H NMR δ 1.01 (t, *J* = 7.4 Hz, 3H), 1.73-1.85 (m, 2H), 3.36 (s, 3H), 3.95 (d, *J* = 6.6 Hz, 2H), 6.40 (s, 1H), 6.83 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 7.31-7.43 (m, 5H); ^{13}C NMR δ 10.4, 22.4, 26.1, 69.9, 106.6, 108.6, 119.7, 124.2, 127.3, 127.6, 128.6, 129.6, 132.4, 135.4, 137.3, 160.5, 166.5; pure *Z* isomer: mp 86-87 °C; ^{1}H NMR δ 1.05 (t, *J* = 7.4 Hz, 3H), 1.83-1.90 (m, 2H), 3.01 (s, 3H), 4.00 (t, *J* = 6.6 Hz, 2H), 6.64 (s, 1H), 7.13 (dd, *J* = 2.4,, 8.5 Hz, 1H), 7.25-7.39 (m, 6H), 7.61 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR δ 10.5, 22.5, 30.6, 70.0, 105.4, 106.2, 120.5, 127.2, 128.0, 129.7, 129.9, 130.5, 135.0, 136.0, 160.4, 168.9; MS (EI) *m/z* 293 (M^+, 100), 273 (40). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.47. Found: C, 78.01; H, 6.44; N, 4.78.

2,3-Dihydro-3-isobutylidene-2-(4-methoxyphenyl)methyl-*1H*-pyrrolo[3,4-*c*]pyridin-1-one (24): *E* and *Z* isomers (ratio 5:95 from ^{1}H NMR spectrum). *E* isomer (not separated): ^{1}H NMR (partial) δ 0.89 (d, *J* = 6.5 Hz, 6H), 5.16 (s, 2H), 5.54 (d, *J* = 10.7 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 5.2 Hz, 1H), 8.74 (d, *J* = 5.2 Hz, 1H), 9.03 (s, 1H); pure *Z* isomer: mp 125-126 °C; ^{1}H NMR δ 1.13 (t, *J* = 6.7 Hz, 6H), 3.22 (m, 1H), 3.76 (s, 3H), 4.94 (s, 2H), 5.42 (d, *J* = 9.7 Hz, 1H), 6.82 (d, J_{AB} = 9.0 Hz, 2H), 7.15 (d, J_{AB} = 9.0 Hz, 2H), 7.80 (d, *J* = 5.1 Hz, 1H), 8.75 (d, *J* = 5.1 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR δ 23.3, 27.5, 42.7, 55.2, 114.0, 117.2, 123.2, 128.4, 130.5, 131.5, 137.0, 145.0, 149.2, 158.9, 167.7; MS (EI) *m/z* 308 (M^+, 100), 173 (31). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.69; N, 8.82.

2,3-Dihydro-2-methyl-3-phenylmethylene-*1H*-isoindol-1-one (25): separable *E* and *Z* isomers (ratio 45:55 from ^{1}H NMR spectrum). NMR spectral data consistent with those previously described.[6d] Pure *E* isomer: mp 120-121 °C (lit.[6d] 116-118 °C); pure *Z* isomer: mp 104-105 °C.

2,3-Dihydro-2-(4-methoxyphenyl)methyl-3-(2-phenylethylidene)-6-propoxy-*1H*-isoindol-1-one (3): separable *E* and *Z* isomers (ratio 75:25 from ^{1}H NMR spectrum). Pure *E* isomer: mp 128-129 °C; ^{1}H NMR δ 1.06 (t, *J* = 7.4 Hz, 3H), 1.78-1.90 (m, 2H), 3.61 (d, *J* = 8.1 Hz, 2H), 3.77 (s, 3H), 4.01 (t, *J* = 6.5 Hz, 2H), 5.18 (s, 2H), 5.59 (t, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 7.1 Hz, 2H), 7.07-7.28 (m, 6H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.51 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR δ 10.5, 22.5, 32.5, 44.2, 55.3, 70.1, 105.8, 106.1, 114.3, 120.4, 121.1, 126.4, 126.9, 128.2, 128.6, 129.2, 129.7, 130.7, 134.2, 140.2, 158.8, 160.1, 168.4; MS (EI) *m/z* 413 (M^+, 100), 292 (34); pure *Z* isomer: oil, ^{1}H NMR δ 1.06 (t, *J* = 7.4 Hz, 3H), 1.78-1.90 (m, 2H), 3.77 (s, 3H), 3.90 (d, *J* = 7.9 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 4.95 (s, 2H), 5.50 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.86-7.33 (m, 8H), 7.43 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 10.5, 22.5, 33.1, 42.5, 55.3, 70.1, 107.2, 109.4, 114.0, 121.1, 124.4, 126.4, 126.9, 128.0, 128.1, 128.3, 132.3, 135.3, 139.8, 158.8, 160.1, 166.5. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.15; H, 6.68; N, 3.62.

***N*-Diphenylphosphinylmethyl-*N*-benzyl-2-(*N*-diethylamino)ethylamine (28).** *N,N*-Diethylethylenediamine (5.8 g, 50 mmol) and benzaldehyde (5.3 g, 50 mmol) were mixed in 1,2-dichloroethane (150 mL) and then treated with sodium triacetoxyborohydride (15g, 70 mmol). The mixture was stirred at rt under Ar for 12 h. The reaction mixture was quenched by adding 1N NaOH and the product was extracted with Et_2O. The ether extract was washed with brine, dried ($MgSO_4$) and the solvent removed by distillation under vacuum. The amine **26** was purified by distillation *in vacuo* ($bp_{0.02}$ 75 °C).[47] A suspension of paraformaldehyde (1g), dried over P_2O_5, amine **26** (5.2 g, 25 mmol), ethanol (1.5 mL) in toluene (100 mL) was refluxed for 8 h. After cooling and filtration on Celite® the solvents were removed in a rotary evaporator and excess paraformaldehyde was removed under vacuum (2. 10^{-2} torr). The crude *N,O*-acetal **27** was then dissolved in anhydrous THF (100 mL) and a solution of chlorodiphenylphosphine (5.5 g, 25 mmol) in THF (25 mL) was added dropwise under Ar over a period of 0.5 h. The mixture was then refluxed for 2 h, cooled to rt and K_2CO_3 (2 g) was added portionwise. Stirring was maintained for 0.25 h and the mixture was filtered on Celite® and then poured on hexane (250 mL) with vigourous stirring. The product was collected by suction, then dissolved in acetone and purification by column chromatography on silica gel using acetone-Et_3N (99:1) as eluent afforded the phosphorylated amine **28** as a colorless viscous oil (6.6 g, 63 %). ^{1}H NMR δ 0.91 (t, *J* = 7.2 Hz, 6H), 2.40-2.49 (m, 6H), 2.80 (t, *J* = 6.6 Hz, 2H), 3.40 (d, J_{HP} = 5.9 Hz, 2H), 3.77 (s, 2H), 7.06-7.08 (m, 2H), 7.16-7.18 (m, 3H), 7.39-7.47 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR δ 11.7, 46.9, 50.9, 53.0 (d, J_{CP} = 6 Hz), 54.5 (d, J_{CP} = 87 Hz), 61.0 (d, J_{CP} = 8 Hz), 126.9, 128.1, 128.4 (d, J_{CP} = 11.5 Hz), 129.1, 131.2 (d, J_{CP} = 9 Hz), 131.6 (d, J_{CP} = 3 Hz), 132.4 (d, J_{CP} = 97 Hz), 138.7; ^{31}P NMR δ 29.4; MS (EI) *m/z* 420 (M^+, 25), 334 (97), 91 (100). Anal. Calcd for $C_{26}H_{33}NO_2P$: C, 74.26; H, 7.91; N, 6.66. Found: C, 74.21; H, 8.05; N, 6.57.

***N*-Diphenylphosphinylmethyl-2-(*N*-diethylamino)ethylamine (29).** Compound **28** (4.1 g, 10 mmol) was debenzylated by hydrogenolysis over 20 % $Pd(OH)_2/C$ in MeOH (100 mL) at 80 °C. Chromatography on

silica gel with acetone-Et_3N (99:1) as eluent furnished the phosphorylated secondary amine **29** as a pale yellow oil (2.9 g, 88 %). ^1H NMR δ 0.87 (t, J = 7.1 Hz, 6H), 1.20 (br. s, 1H), 2.39 (q, J = 7.1 Hz, 4H), 2.45 (t, J = 6.1 Hz, 2H), 2.69 (t, J = 6.1 Hz, 2H), 3.46 (d, J_{HP} = 7.6 Hz, 2H), 7.36-7.50 (m, 6H), 7.72-7.79 (m, 4H); ^{13}C NMR δ 11.7, 46.9, 49.0 (d, J_{CP} = 12 Hz), 49.5 (d, J_{CP} = 80 Hz), 128.5 (d, J_{CP} = 11 Hz), 131.2 (d, J_{CP} = 9 Hz), 131.8 (d, J_{CP} = 2 Hz), 132.4 (d, J_{CP} = 101 Hz); ^{31}P NMR δ 29.3; MS (EI) *m/z* 420 (M^+, 25), 335 (25), 334 (100). Anal. Calcd for $C_{19}H_{27}NO_2P$: C, 69.07; H, 8.24; N, 8.48. Found: C, 68.92; H, 8.35; N, 8.40.

***N*-Diphenylphosphinylmethyl-*N*-(2-diethylamino)ethyl-2-bromobenzamide (30).** The synthesis of the phosphorylated bromobenzamide derivative **30** was achieved by coupling 2-bromobenzoic acid **8g** (1.1 g, 5.5 mmol) with amine **29** (1.8 g, 5.4 mmol) in CH_2Cl_2 (100 mL) in the presence of DCC (1.1 g, 5.4 mmol) and DMAP (100 mg) as previously described (Method A). Amide **30** was purified by flash column chromatography on silica gel using acetone-hexane-Et_3N (89:10:1) as eluent and obtained as a viscous yellow oil (2.3 g, 82 %). ^1H NMR δ 0.80 (t, J = 7.0 Hz, 6H), 2.30 (q, J = 7.0 Hz, 4H), 2.48 (t, J = 6.5 Hz, 2H), 3.42 (dt, J = 6.5, 15.0 Hz, 2H), 3.55 (dt, J = 6.5, 15.0 Hz, 2H), 4.68 (dd, J = 6.0, 15.5 Hz, 1H),), 4.83 (dd, J = 5.1, 15.5 Hz, 1H), 6.62 (d, J = 7.1 Hz, 1H), 7.04-7.15 (m, 2H), 7.30-7.49 (m, 7H), 7.82-7.97 (m, 4H); ^{13}C NMR δ 11.7, 44.5 (d, J_{CP} = 75 Hz), 46.9, 47.2, 51.2, 119.1, 127.2, 128.0, 128.5 (d, J_{CP} = 11.5 Hz), 128.7 (d, J_{CP} = 11.5 Hz), 130.2, 131.2 (d, J_{CP} = 10 Hz), 131.4 (d, J_{CP} = 10 Hz), 132.1, 132.2, 132.8, 137.3, 169.2; ^{31}P NMR δ 30.7; MS (EI) *m/z* 514 and 512 (M^+, 1), 416 (10), 414 (10), 201 (13), 185 (15), 183 (15), 99 (32), 86 (100). Anal. Calcd for $C_{26}H_{30}BrN_2O_2P$: C, 60.83; H, 5.89; N, 5.46. Found: C, 60.90; H, 5.78; N, 5.62.

3-(4-Acetoxyphenyl)methylene-2-(2-diethylamino)ethyl-2,3-dihydro-*1H*-isoindol-1-one (4). Compound **4** was obtained by applying the experimental protocol adopted for the preparation of the aryl and alkylmethylene isoindolinones **21-25, 3** starting from the phosphorylated benzamide **30** (1 g, 2 mmol), KHMDS (0.5 M in toluene, 8.8 mL, 4.4 mmol) and 4-acetoxybenzaldehyde[48] (330 mg, 2 mmol). Purification by flash column chromatography on silica gel using acetone-hexane-Et_3N (50:49:1) as eluent afforded the *E* and *Z* isomers (ratio 90:10 from ^1H NMR spectrum) of the targeted isoindolinone **4** (635 mg, 86 %). *E* isomer: oil; ^1H NMR δ 1.05 (t, J = 7.1 Hz, 6H), 2.32 (s, 3H), 2.62 (q, J = 7.1 Hz, 4H), 2.73 (t, J = 7.5 Hz, 2H), 3.95 (t, J = 7.5 Hz, 2H), 6.54 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.29-7.41 (m, 3H), 7.43 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 12.1, 21.2, 38.2, 47.5, 50.6, 109.1, 121.9, 123.1, 129.3, 130.4, 130.6, 131.5, 132.8, 134.9, 136.6, 150.2, 166.4, 169.4; MS (EI) *m/z* 378 (M^+, 6), 86 (100); *Z* isomer: oil; ^1H NMR δ 0.77 (t, J = 7.1 Hz, 6H), 2.20 (q, J = 7.1 Hz, 4H), 2.30 (s, 3H), 2.54 (m, 2H), 3.83 (t, J = 7.4 Hz, 2H), 6.67 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 7.4 Hz, 1H); ^{13}C NMR δ 12.1, 21.1, 39.3, 47.0, 50.2, 105.2, 119.2, 121.5, 123.2, 129.0, 130.7, 131.9, 132.4, 133.8, 135.2, 138.4, 150.1, 169.0, 169.2; MS (EI) *m/z* 378 (M^+, 4), 86 (100). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.69; H, 7.12; N, 7.65.

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