A Short and Efficient Synthesis of 3-Diphenylphosphoryl- and 3-Diethoxyphosphoryl(aza)isoindolinones: Extension to the Sulfonylated Analogs

Axel Couture,* Eric Deniau, Patrice Woisel, Pierre Grandclaudon

Laboratoire de Chimie Organique Physique, URA CNRS N° 351, Université des Sciences et Technologies de Lille, F-59655 Villeneuve d'Ascq Cédex, France

Fax +33(320)436561

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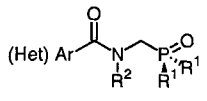
A variety of 3-diphenylphosphoryl- and 3-diethoxyphosphoryl-(aza)isoindolinones have been efficiently prepared by aryne- and hetaryne-mediated cyclization of phosphorylated α-amino carbanions derived from suitably substituted 2- and 3-halobenzamide and 3-chloropyridine-4-carboxamide derivatives. The synthesis of some 3-sulfonylated analogs by extension of this principle has been achieved.

The discovery of the biological activities of aminophosphonic acid derivatives[1] and their structural similarity to naturally occurring α-aminocarboxylic acids have promoted a widespread interest in these bifunctional compounds over the past thirty years. Indeed many of these substances display a remarkable diversity of bioactivities as witnessed by a number of articles[2] and patents[3,4] emphasizing their biological properties, especially as pesticide, insecticide, and herbicide agents.[5] Consequently, considerable effort has been devoted to the synthesis and investigation of the biological value of a wide array of α-aminophosphonic acid derivatives and particularly of the *N*-acyl derivative **1**. The standard syntheses of this class of compounds usually involve acylation of the appropriate amino(alkyl)methylphosphonates and phosphane oxides[5,6] or the three-component condensation involving an aldehyde, a phosphane or a phosphite, and a compound bearing a carboxamide function.[7] They are also accessible by treatment of *N*-acylamino(bromo)-methylphosphonic esters with mixed organocuprates,[8] by dehydrogenation of *N*,*N*-dialkylaminomethylphosphonates and phosphane oxides with mercury-EDTA,[9] by treatment of a trivalent phosphorus species with an electrophilic amidoalkylation reagent,[10,11] and by a chloromethylation–phosphorylation reaction sequence from secondary carboxamides.[12] However, none of these methods allows the preparation of the cyclic analogs of **1** and particularly of the benzo- and pyrido-fused models **2** and **3**. Heterocyclic compounds containing the phthalimidine (2,3-dihydro-1*H*-isoindol-1-one) skeleton[13] and its aza congener,[14] which can be regarded as a cyclic isonicotinamide analog, have attracted considerable interest in recent years since they represent the core unit of fascinating natural and artificial bioactive compounds.[15] Among the various routes liable to give access to the cyclocondensed compounds **2** and **3**, the treatment of the *N*,*O*-hemiacetals **4** (R^4 = H) and their *O*-alkyl and *O*-acetyl derivatives with trialkyl phosphite and chlorodiphenylphosphane[16] seemed a priori the most simple, general, and tolerant of other functionalities. However, it was deemed that this strategy would be fraught with difficulties associated with the regioselective synthesis of the parent monosubstituted models **4** (Y = CH; R^3 ≠ H) and with compounds comprising a pyridyl unit **4** (Y = N; R^3 = H). Indeed, *O*-alkyl- and *O*-acetyl-*N*,*O*-acetals are usually obtained by anionic oxidation of the *N*-aryl precursors[10,16] but this procedure requires access to the necessary electrochemical apparatus and the literature only describes the preparation of cyclic carbamates. On the other hand, *O*-acetylated and nonacetylated *N*-acyl-*N*,*O*-acetals can be obtained by decarboxylation of the corresponding α-amino acids with lead tetraacetate[17] but this strategy can be only envisaged on linear systems. In fact, the more convenient route to hydroxylactams **4** (Y = CH or N; R^4 = H) involves the double metallation of the suitable secondary amides **5** (Y = CH or N) and the subsequent treatment with a formylating agent.[18] However, incorporation of an additional *ortho*-directing metallation group at a *meta*-position of the parent carboxamide **5** (e.g., Y = CH; R^3 = *O*-alkyl) forces metallation to occur at their common "in between" site,[19] thus precluding the formation of regioisomers such as **4** (Y = CH, R^3 = alkoxy, R^4 = H). The same reaction sequence applied to isonicotinic carboxamide **5** (Y = N) gives rise also to the hydroxyazalactams **4** (Y = N; R^4 = H)[20] but the procedure has been limited to the powerful anilide *ortho*-directing metallation group[21] (R^2 = aryl). To obviate these problems, the generation of the *N*,*O*-acetals **4** (Y = CH or N; R^4 = H) by reduction of the corresponding phthalimides **6** could be finally envisaged but, unfortunately, a literature report reveals that $NaBH_4$ reduction of monosubstituted phthalimides **6** (Y = CH; R^3 ≠ H) invariably gives a mixture of regioisomeric hydroxylactams.[22]



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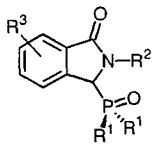

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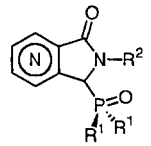

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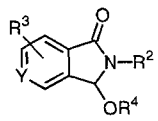

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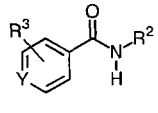

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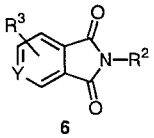

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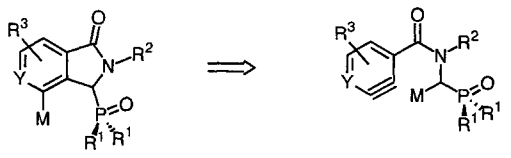
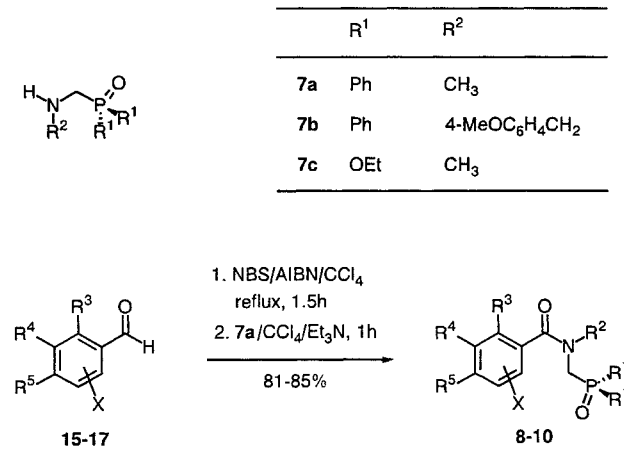
We wish, therefore, to report in this paper a conceptually and tactically new approach to a variety of diversely substituted iso(aza)indolinones possessing a pendant phosphoryl unit at the 3-position of the lactam nucleus. Our strategy hinges upon the intramolecular addition of phosphorylated α-amino carbanions across an aryne or heteroaryne intermediate as depicted in the retrosynthetic Scheme 1.

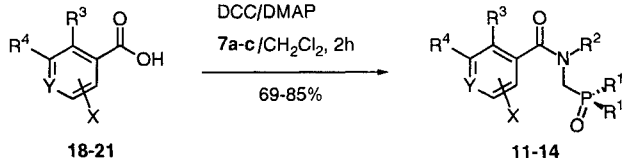


Scheme 1

The strategy of intramolecular trapping of benzyne intermediates by a side-chain nucleophile introduced independently by Huisgen[23] and Bunnet[24] has been successfully applied in the course of the last twenty years to the synthesis of a number of natural products and to a variety of heterocyclic and homocyclic systems.[25] However, applications of this concept to the elaboration of five-membered benzo mononitrogen heterocycles where the nitrogen is not attached to the original aromatic ring are extremely rare and, to the best of our knowledge, the preparation of cyanoisoindolines by treatment of *N*-2-chlorobenzyl-*N*-methylaminoacetonitrile is the only example mentioned in the literature.[26] This is undoubtedly due to the difficulties linked to the generation of α-aminocarbanions even though several procedures have been recently proposed to solve this problem.[27] On the other hand, phosphorylated α-amino carbanions have been mainly involved in the generation of the enamine and enamide functions in a variety of open-chain[28] and cyclized[29] products obtained via the classical Horner and Wadsworth–Emmons reactions but their nucleophilicity[30] has been thus far barely used with the exception of the electrophilic *C*-alkylation of free aminomethylphosphonates and phosphane oxides via their activated *N*-benzylidene imines[31] or carbamate[32] derivatives. With the aim of opening a new route to phosphorylated isoindolinones and their aza analogs, a number of phosphorylated halobenzamides and pyridine-4-carboxamides were therefore synthesized and subsequently submitted to appropriate basic treatment. Initially, the parent carboxamides **8–14** were prepared by coupling the free *N*-alkyldiphenylphosphoryl- and *N*-alkyldiethoxyphosphorylamines **7a–c**, readily accessible by a procedure recently developed in our laboratory,[32] with a suitable acylating agent. Thus, the halobenzamide derivatives **8–10** were efficiently obtained by adapting a recently reported procedure[33] for the direct conversion of aromatic carboxaldehydes into secondary and tertiary aromatic carboxamides (Scheme 2, Tables 1 and 2). The syntheses of the alkoxy derivatives **11–13** and of the 3-chloropyridine-4-carboxamide derivative **14** were achieved by reacting the phosphorylated amines **7a–c** with the corresponding halogen-substituted aromatic and heteroaromatic carboxylic acids **18–21** under standard conditions (Scheme 3, Tables 1 and 2).



Scheme 2



Scheme 3

Table 1. Phosphorylated Compounds Prepared

Entry	X	Y	R^1	R^2	R^3	R^4	R^5	Starting Materials	Phosphorylated Amides (Yield %)[a]	Phosphorylated Isoindolinones (Yield %)[a]
1	2-Br	CH	Ph	Me	H	H	H	**15** + **7a**	**8** (84)	**22** (71)
2	2-Br	CH	Ph	Me	H	OPr	H	**16** + **7a**	**9** (81)	**23** (69)
3	3-Br	CH	Ph	Me	H	H	OMe	**17** + **7a**	**10** (85)	–
4	2-Cl	CH	OEt	Me	H	H	OBn	**18** + **7c**	**11** (79)	**24** (65)
5	2-F	CO	Ph	4-$MeOC_6H_4CH_2$	H	H	OBn	**19** + **7b**	**12** (84)	**25** (78)
6	2-F	CH	Ph	4-$MeOC_6H_4CH_2$	OMe	H	OBn	**20** + **7b**	**13** (85)	**26** (75)
7	3-Cl	N	Ph	Me	H	H	–	**21** + **7a**	**14** (69)	**27** (60)

[a] Yield calculated after recrystallization.

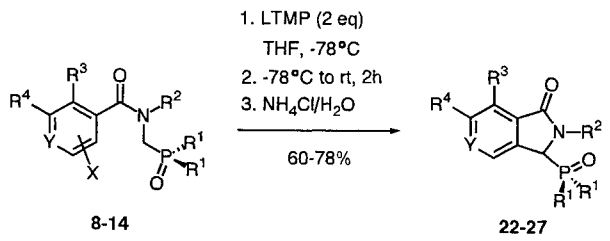
Table 2. Phosphorylated Carboxamides **8–14** Prepared

Product	mp (°C)	Molecular Formula[a]	^{1}H NMR δ (ppm), J (Hz)	^{13}C NMR δ (ppm), J (Hz)	^{31}P NMR δ (ppm)
8	124–125	$C_{21}H_{19}BrNO_2P$	3.06 (s, 3H), 4.33 (m, 1H), 4.89 (br d, J = 14.5, 1H), 6.63 (dd, J = 2.0, 7.4, 1H), 7.12–7.25 (m, 2H), 7.41–7.53 (m, 6H)	37.9, 46.7 (d, J = 76), 118.6, 127.4, 127.5, 128.5–129.1 (m), 130.3, 131.2 (d, J = 9), 132.3 (br), 132.7, 137.4, 168.9 (d, J = 2)	30.8
9	136–137	$C_{24}H_{25}BrNO_3P$	1.00 (t, J = 7.3, 3H), 1.71–1.80 (m, 2H), 3.07 (s, 3H), 3.72 (t, J = 6.3, 3H), 4.24 (dd, J = 7.8, 16.8, 1H), 4.94 (dd, J = 4.1, 16.8, 1H), 6.07 (d, J = 3.0, 1H), 6.69 (dd, J = 3.0, 8.8, 1H), 7.31 (d, J = 8.8, 1H), 7.47–7.57 (m, 6H), 7.93–8.00 (m, 4H)	10.4, 22.4, 37.9, 46.9 (d, J = 77), 69.9, 108.6, 112.9, 117.4, 128.6 (d, J = 11), 128.8 (d, J = 12), 131.3 (d, J = 12), 132.3 (d, J = 10) 133.5, 137.9, 158.5, 168.8	31.2
10	125–126	$C_{22}H_{21}BrNO_3P$	3.16 (s, 3H), 3.87 (s, 3H), 4.54 (br s, 2H), 6.78 (d, J = 8.3, 1H), 6.96 (br d, J = 8.3, 1H), 7.12 (s, 1H), 7.44–7.61 (m, 6H), 7.82–7.96 (m, 4H)	39.6, 48.0 (d, J = 73), 56.2, 111.2, 111.4, 127.6, 128.4, 128.7 (d, J = 11.5), 131.1 (d, J = 10), 131.2 (d, J = 98), 132.1, 132.3 (d, J = 3), 156.9, 169.6	31.8
11	oil	$C_{13}H_{19}ClNO_4P$	1.35 (t, J = 7.1, 6H), 2.98 (s, 3H), 4.03 (d, J = 11.5, 2H), 4.21 (q, J = 7.1, 4H), 7.25–7.39 (m, 4H)	16.4 (d, J = 6), 39.1, 42.9 (d, J = 153.5), 62.4 (d, J = 6.5), 127.0, 128.4, 129.8, 135.5, 171.0	22.4
12	155–156	$C_{35}H_{31}FNO_4P$	3.75 (s, 3H), 4.45 (d, J = 4.9, 2H), 4.71 (s, 2H), 5.00 (s, 2H), 6.62 (d, J = 11.1, 1H), 6.70 (d, J = 8.9, 1H), 6.84 (m, 3H), 7.15 (d, J = 8.2, 2H), 7.28–7.40 (m, 5H), 7.40–7.58 (m, 6H), 7.82–7.95 (m, 4H)	42.6 (d, J = 77), 52.7, 55.3, 70.4, 102.8 (d, J = 25), 111.3 (d, J = 4), 114.1, 115.8 (d, J = 18), 127.3, 127.4, 128.3, 128.6 (d, J = 12), 128.7, 129.5, 131.1 (d, J = 98), 131.2 (d, J = 10), 132.2 (d, J = 3), 135.9, 159.1 (d, J = 249), 159.3, 161.0 (d, J = 10), 166.9	30.0
13	126–127	$C_{29}H_{27}FNO_4P$	3.55 (s, 3H), 3.75 (s, 3H), 4.35 (dd, J = 6.0, 15.5, 1H), 4.59 (dd, J = 5.1, 15.5, 1H), 4.63 (d, J = 15.0, 1H), 4.74 (d, J = 15.0, 1H), 6.57–6.66 (m, 2H), 6.82 (d, J = 8.5, 2H), 7.18–7.26 (m, 3H), 7.41–7.55 (m, 6H), 7.81–8.04 (m, 4H)	42.1 (d, J = 99), 52.3, 55.3, 55.8, 106.7, 108.3 (d, J = 22), 113.2 (d, J = 21), 114.0, 127.3, 128.4 (d, J = 12), 128.6 (d, J = 12), 129.7, 131.1 (d, J = 9), 131.4 (d, J = 10), 132.1, 156.9 (d, J = 9), 159.1 (d, J = 245), 159.2, 164.2	30.9
14	168–169	$C_{20}H_{18}ClN_2O_2P$	(s, 3H), 4.45 (br s, 1H), 4.75 (br s, 1H), 7.08 (dd, J = 1.9, 7.6, 1H), 7.19 (dd, J = 4.8, 7.6, 1H), 7.50–7.58 (m, 6H), 7.90–7.97 (m, 4H), 8.37 (dd, J = 1.9, 4.8, 1H)	36.4, 45.5 (d, J = 76), 120.2, 126.4, 127.6 (d, J = 12), 130.1 (d, J = 10), 131.3, 141.3, 146.9, 148.6, 164.6	29.3

[a] Satisfactory microanalyses were obtained for all new compounds: C ± 0.29, H ± 0.30, N ± 0.27.

A wide variety of base–solvent combinations can be employed for benzyne generation from haloarylated models[34] but amidic bases[35] in aprotic solvent have proven to be the reagents of choice to perform this operation with respect to the ease of manipulation and ready accessibility. In particular, the hindered base lithium tetramethylpiperidide (LTMP) has found extensive use in coupling reactions since it minimizes undesirable side reactions such as aryne reaction with the amide base used for its generation, reprotonation of the aryl anion species, and hydride transfer from the α-carbon.[36] Accordingly, the phosphorylated halobenzamide and pyridure-4-carboxamide derivatives **8–14** were treated with LTMP (2 equivalents) in THF at low temperature (−78 °C). The reaction mixture was warmed to room temperature (2 hours) and, to our delight, standard workup furnished the expected phosphorylated annulated compounds **22–27** in excellent yields (Scheme 4, Tables 1 and 3). All cyclizations were conducted under the conditions reported in Scheme 4 and no attempt was made to optimize yields for individual substrates. The results of a representative series of compounds prepared by this method are presented in Table 1 where it may be seen that this simple procedure affords excellent yields of phosphorylated isoindolin-1-ones **22–26** and the 2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one **27**. As can be seen from Table 1, the nature of the halide and its location on the original aromatic nucleus do not play a critical role in the efficiency of the annulation process. However, somewhat better yields have been obtained with the 2-fluoro derivatives **12** and **13**, probably due to easier halide expulsion and aryne formation. Surprisingly, compound **10** failed to give the desired cyclocondensation product in spite of the cooperative effect of the 1,3-interrelated halide and carboxamide *ortho*-directing metallation groups in promoting metallation at their common site.[21] We can only suspect that the bulky bromine and carbonyl groups provide sufficient steric inhibition to deprotonation of this site by LTMP.

The simplicity and efficiency of this short and clean annulation process prompted continuation of this work towards the synthesis of isoindolinone derivatives incorporating other pendant functionalities at the 3-position of



Scheme 4

the heterocyclic nucleus, particularly the sulfonyl group. To this end, some *N*-(phenylsulfonylmethyl)-2-chlorobenzamides **34** and **35** were prepared by treatment of the chloromethylation products **30,** and **31**, derived from the parent secondary 2-halobenzamides **28** and **29**, with thiophenol and subsequent oxidation with MCPBA (Scheme 5). Treatment of the sulfonylated amides **34** and **35**, with LTMP under the previously determined conditions gave only modest yields of the target sulfonylated lactams and attempts to improve the efficiency by varying the base (LDA) and solvent (diethyl ether, THF/hexane) were unrewarding. Reasoning that the desired intramolecular benzyne addition would be favored with a more nucleophilic amino carbanion, we decided to expose the sulfonylated amides **34** and **35**, to LTMP in the presence of 12-crown-4 (1 equivalent) and we observed that this protocol now effected the desired cyclization to give the sulfonylated lactams **36** and **37**, in very satisfactory yields (Scheme 5).

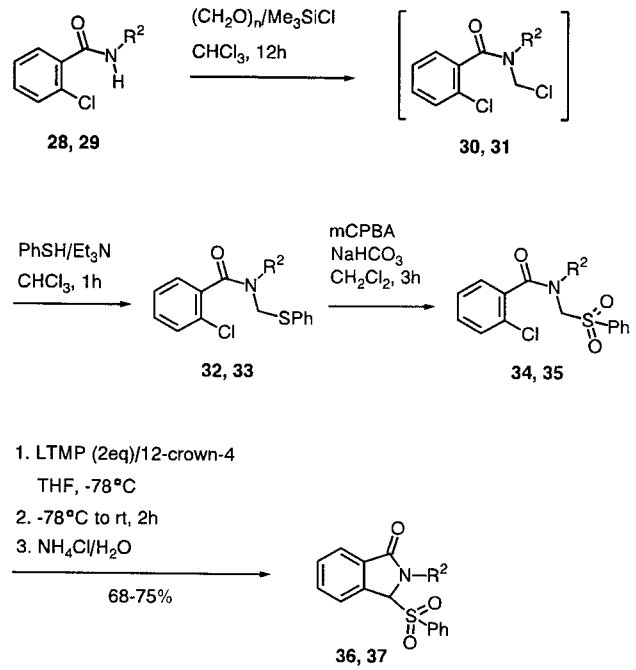
In conclusion, we have demonstrated that the aryne-mediated cyclization approach provides a ready access to a variety of hardly accessible phosphorylated and sulfonylated isoindolinone derivatives. The procedure allows the regioselective introduction of substituents onto the aromatic nucleus fused to the newly formed heterocyclic ring. It also tolerates the presence of diverse alkoxy groups and a pyridyl unit which can be of interest for further synthetic planning. Furthermore, the easy access to the corresponding sulfonylated compounds enlarges the scope of this conceptually new process, demonstrates the versatility of the strategy, and endows the procedure with considerable synthetic potential.

Melting point determinations were carried out on a Reichert-Thermopan apparatus and are uncorrected. ^1H, ^{13}C, and ^{31}P NMR spectra were measured at 300, 75, and 121 MHz, respectively, on a Bruker AM 300 spectrometer as solutions in $CDCl_3$ with TMS as internal standard or H_3PO_4 as external standard. Elemental analyses were determined by the CNRS microanalysis centre; for new compounds satisfactory microanalyses were obtained: C ± 0.32, H ± 0.28, N ± 0.28. For flash chromatography, Merck silica gel 60

Table 3. Phosphorylated Isoindolinones **22–27** Prepared

Product	mp (°C)	Molecular Formula[a]	^1H NMR δ (ppm), *J* (Hz)	^{13}C NMR δ (ppm), J_{CP} (Hz)	^{31}P NMR δ (ppm)
22	197–198	$C_{21}H_{18}NO_2P$	3.04 (s, 3H), 5.33 (d, *J* = 11.1, 1H), 6.84 (d, *J* = 7.5, 1H), 7.25–7.67 (m, 13H)	30.4, 63.8 (d, *J* = 72.5), 123.7, 123.8, 128.7 (d, *J* = 12), 128.8 (d, *J* = 12), 131.2, 131.6 (d, *J* = 9), 131.8 (d, *J* = 9), 132.9 (d, *J* = 2.5), 133.0 (d, *J* = 3), 138.6, 168.8	30.6
23	181–182	$C_{24}H_{24}NO_3P$	1.00 (t, *J* = 7.4, 3H), 1.74–1.81 (m, 2H), 3.11 (s, 3H), 3.89 (t, *J* = 6.6, 2H), 5.29 (d, *J* = 10.6, 1H), 6.63 (d, *J* = 8.5, 1H), 6.86 (dd, *J* = 2.4, 8.5, 1H), 6.86 (dd, *J* = 2.4, 8.5, 1H), 7.15 (d, *J* = 2.4, 1H), 7.30–7.71 (m, 10H)	10.4, 22.4, 30.4, 63.5 (d, *J* = 77), 69.9, 107.0, 120.0, 124.6, 128.7 (d, *J* = 8.5), 128.8 (d, *J* = 11.5), 130.15, 131.6 (d, *J* = 9), 131.8 (d, *J* = 8.5), 132.8, 133.9, 159.8, 168.7	30.7
24	67–68	$C_{13}H_{18}NO_4P$	1.04 (t, *J* = 7.1, 3H), 1.21 (t, *J* = 7.1, 3H), 3.25 (s, 3H), 3.72–3.78 (m, 1H), 3.86–3.91 (m, 1H), 4.07 (q, *J* = 7.1, 2H), 4.71 (d, *J* = 13.4, 1H), 7.44–7.54 (m, 2H), 7.70 (d, *J* = 7.4, 1H), 7.79 (d, *J* = 7.4, 1H)	16.2 (d, *J* = 5), 16.3 (d, *J* = 5), 29.6, 59.6 (d, *J* = 155), 63.1 (d, *J* = 7), 63.5 (d, *J* = 7), 123.6, 124.2, 128.8, 131.5, 132.1, 138.3, 168.9	18.2
25	151–152	$C_{35}H_{30}NO_4P$	3.76 (s, 3H), 4.17 (d, *J* = 14.8, 1H), 4.80 (s, 2H), 5.19 (d, *J* = 14.8, 1H), 5.30 (d, *J* = 14.8, 1H), 6.39 (s, 1H), 6.79 (d, *J* = 8.5, 2H), 6.98 (d, *J* = 8.4, 1H), 7.08 (d, *J* = 8.5, 2H), 7.25–7.49 (m, 12H), 7.55–7.68 (m, 4H)	44.7, 55.2, 59.9 (d, *J* = 74), 69.9, 108.8, 114.0, 117.5, 125.3, 125.4 (d, *J* = 3), 127.3, 128.2, 128.6, 128.7 (d, *J* = 12), 128.8 (d, *J* = 13), 129.7, 131.7 (d, *J* = 8.5), 131.9 (d, *J* = 9), 132.7 (d, *J* = 3), 132.9 (d, *J* = 2.5), 135.9, 141.3, 159.0, 161.3, 168.7	30.7
26	185–186	$C_{29}H_{26}NO_4P$	3.75 (s, 3H), 3.86 (s, 3H), 4.14 (d, *J* = 14.8, 1H), 5.20 (d, *J* = 11.1, 1H), 5.29 (d, *J* = 14.8, 1H), 6.44 (d, *J* = 7.4, 1H), 6.79 (m, 3H), 7.10 (d, *J* = 8.4, 2H), 7.18–7.26 (m, 1H), 7.35–7.72 (m, 10H)	39.4, 55.2, 55.9, 59.7 (d, *J* = 74), 110.8, 113.9, 116.2, 128.3, 128.7 (d, *J* = 11.5), 130.0, 131.6 (d, *J* = 9), 132.0 (d, *J* = 8.5), 132.8, 132.9, 141.6, 157.5, 159.0, 167.8	30.5
27	194–195	$C_{20}H_{17}N_2O_2P$	3.12 (s, 3H), 5.50 (d, *J* = 10.7, 1H), 7.40–7.63 (m, 11H), 8.17 (s, 1H), 8.67 (d, *J* = 4.5, 1H)	30.5, 62.8 (d, *J* = 71), 117.4, 128.8, 129.0 (d, *J* = 12), 129.2 (d, *J* = 12), 131.5 (d, *J* = 9), 131.8 (d, *J* = 9), 133.4 (d, *J* = 2.5), 140.4, 145.6, 149.7, 167.1	29.9

[a] Satisfactory microanalyses were obtained for all new compounds: C ± 0.26, H ± 0.19, N ± 0.27.



R^2	
Me	28, 30, 32, 34, 36
Bn	29, 31, 33, 35, 37

Scheme 5

(230–400 mesh ASTM) was used. Tetrahydrofuran (THF) was freshly distilled over $LiAlH_4$ and 2,2,6,6-tetramethylpiperidine over CaH_2. Dry glassware for moisture-sensitive reactions was obtained by oven drying and assembly under Ar. An inert atmosphere was obtained with a stream of Ar and glassware equipped with rubber septa; reagent transfer was performed by the syringe technique.

The phosphorylated amines **7a–c**[32] were prepared according to previously reported procedures. The aldehydes **15** and **17**, and the acid **18** are commercially available.

2-Bromo-5-propoxybenzaldehyde (16):
Compound **16** was synthesized by bromination of 2-propoxybenzaldehyde following the procedure described for the corresponding 2-methoxy derivative;[37] overall yield: 72%.

^{1}H NMR ($CDCl_3$): δ = 0.98 (t, J = 7.4 Hz, 3H), 1.71–1.79 (m, 2H), 3.87 (t, J = 6.5 Hz, 2H), 6.95 (dd, J = 3.2, 8.8 Hz, 3H), 7.31 (d, J = 3.2 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 10.22 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 10.4, 22.4, 70.0, 113.3, 117.6, 123.5, 133.9, 134.5, 158.8, 191.8.

The acid **19**[38] was readily accessible by benzylation[39] of the commercial 2-fluoro-4-hydroxybenzonitrile and subsequent basic hydrolysis ($KOH/H_2O/EtOH$).[40] 2-Fluoro-6-methoxybenzoic acid **(20)**[40] and 3-chloropyridine-4-carboxylic acid **(21)**[41] were prepared according to reported procedures.

Phosphorylated Halobenzamides 8–10; General Procedure:
N-Bromosuccinimide (2.8 g, 15 mmol) and AIBN (20 mg) were added portionwise to a solution of the appropriate aldehyde **15–17** (12 mmol) in anhyd purified CCl_4 (200 mL) preheated with an oil bath maintained at 95°C. The solution was heated at reflux for 1.5 h, cooled to 0°C, and a solution of the phosphorylated amine **7a** (12 mmol) and Et_3N (18 mmol) in CCl_4 (50 mL) was added dropwise to the heterogeneous mixture with vigorous stirring. Stirring was maintained for an additional 1 h and, after filtration, the organic layer was washed with H_2O (2 × 30 mL), and dried ($MgSO_4$). Evaporation of the solvent and purification by flash column chromatography using a mixture acetone/hexane (3:2) as eluent followed by recrystallization from hexane/toluene provided the phosphorylated halobenzamides **8–10** (Table 2).

Phosphorylated 2-Halobenzamides 11–13 and 3-Chloropyridine-4-carboxamide (14); General Procedure:
A mixture of DCC (825 mg, 4 mmol), DMAP (50 mg, 0.4 mmol), phosphorylated amine **7a–c** (4 mmol), and halobenzene or pyridine-4-carboxylic acid **18–21** (4 mmol) in CH_2Cl_2 (100 mL) freshly distilled over CaH_2 was stirred under Ar at r.t. for 2 h. The mixture was filtered, the solvent removed on a rotary evaporator. Acetone (50 mL) was added and the remaining insoluble dicyclohexylurea removed by filtration. Acetone was evaporated, the crude product was dissolved in CH_2Cl_2 (100 mL), and the organic layer was subsequently treated with H_2O (2 × 20 mL) and brine, and dried ($MgSO_4$). The phosphorylated amides **11–14** (Table 2) were finally purified as described above for **8–10**.

Phosphorylated (Aza)Isoindolinones 22–27; General Procedure:
To a cooled (−78°C) solution of freshly distilled 2,2,6,6-tetramethylpiperidine (565 mg, 4 mmol) in THF (10 mL) was added dropwise a solution of BuLi in hexanes (1.6 M, 2.5 mL, 4 mmol). The mixture was stirred at −78°C for 30 min and a solution of the phosphorylated amide **8–14** (2 mmol) in THF (15 mL) was added dropwise at a rate such that the reaction temperature did not exceed −70°C. The solution was stirred for 30 min at this temperature and then warmed to r.t. within 2 h and quenched with dil NH_4Cl. The solution was partitioned between Et_2O (100 mL) and brine (50 mL) and, after workup, by the products **22–27** (Table 2) were finally purified by direct recrystallization of the crude product from hexane/toluene.

Sulfonylated Amides 34 and 35; General Procedure:
N-Methyl- and *N*-benzyl-2-chlorobenzamide (**28** and **29**), respectively, (50 mL) were treated with paraformaldehyde (50 mmol) dried over P_2O_5 and chlorotrimethylsilane (150 mmol) in boiling $CHCl_3$ (150 mL) for ca. 12 h. The mixture was filtered on Celite, the solvent was removed on a rotary evaporator, and the crude *N*-chloromethylcarboxamide derivatives **30** and **31** were treated with thiophenol (5.5 g, 50 mmol) in the presence of Et_3N (5.05 g, 50 mmol) at 0°C. The mixture was warmed to r.t. within 1 h, the solvent and excess reagents were removed under vacuum and the residue dissolved in CH_2Cl_2 (300 mL). Sodium hydrogen carbonate (10 g, 120 mmol) was added to the solution which was cooled to −5°C and vigorously stirred under Ar. 3-Chloroperoxybenzoic acid (17.5 g, 60 mmol) was then added in portions after which the mixture was stirred at r.t. for 3 h. The organic layer was washed with dil NH_4OH (22%, 4 × 50 mL), water (50 mL), brine (50 mL), and dried ($MgSO_4$). Compounds **34** and **35** were finally purified by recrystallization from hexane/toluene.

N-(2-Chlorobenzoyl)-N-methylaminomethyl Phenyl Sulfone **(34)**:
yield: 57%; white solid; mp 138–139°C.

^{1}H NMR ($CDCl_3$, two rotamers A/B, 75:25): δ = 3.08 (s, 3H, A), 3.30 (s, 3H, B), 4.50 (dd, J_{AB} = 14.6 Hz, 2H, B), 4.82 (br s, 1H, A), 5.23 (br s, 1H, A), 6.39 (d, J = 7.1 Hz, 1H, B), 6.91 (d, J = 7.7 Hz, 1H, A), 7.00–7.05 (m, 1H, B), 7.21–7.35 (m, 2H), 7.52–7.77 (m, 4H), 8.02 (d, J = 7.3 Hz, 2H, A).

^{13}C NMR ($CDCl_3$): δ = 35.4 (B), 38.0 (A), 67.9 (A), 71.9 (B), 127.9, 128.2, 129.5 (B), 129.7 (A), 129.8 (A), 130.0 (B), 130.3 (A), 130.4 (B), 130.6, 131.4 (A), 131.5 (B), 135.1 (A), 135.3 (B), 137.5 (B), 138.3 (A), 169.1 (A), 169.6 (B).

N-Benzyl-N-(2-chlorobenzoyl)aminomethyl Phenyl Sulfone **(35)**;
yield: 63%; white solid; mp 135–136°C.

^{1}H NMR ($CDCl_3$, two rotamers A/B, 70:30): δ = 4.31 (d, J = 14.6 Hz, 1H, B), 4.38 (d, J = 14.6 Hz, 1H, B), 4.46 (d, J = 14.5 Hz, 1H, B), 4.61 (d, J = 15.0 Hz, 1H, A), 4.75 (d, J = 15.0 Hz, 1H, A), 4.92 (s, 2H, A), 5.81 (d, J = 14.5 Hz, 1H, B), 6.64 (d, J = 7.6 Hz, 1H, B), 7.05–7.45 (m, 8H), 7.49–7.67 (m, 4H), 8.05 (d, J = 9.0 Hz, 2H, A).

^{13}C NMR ($CDCl_3$): δ = 48.1 (B), 53.1 (A), 63.5 (A), 67.8 (B), 127.7 (A), 127.8 (B), 128.7 (A), 129.0 (A), 129.1 (B), 129.4 (B), 129.5 (A), 129.8 (A), 130.0 (A), 130.2 (B), 130.4 (B), 130.7 (A), 131.2, 131.5 (B), 131.6 (A), 134.6 (B), 134.7 (A), 135.0 (A), 135.2 (B), 137.9 (B), 138.9 (A), 169.1 (A), 169.5 (B).

Sulfonylated Lactams 36 and 37; General Procedure:

The annulation reactions of **34** and **35** were performed following the procedure already mentioned for the synthesis of the phosphorylated analogs **22–27**. However, the preparation of LTMP was achieved by addition of BuLi (1.6 M, 2.5 mL, 4 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (565 mg, 4 mmol) in THF (15 mL) containing 12-crown-4 (705 mg, 4 mmol) preliminary stored over molecular sieves. Completion of the cyclization reaction required a prolonged reaction time (3 h).

2-Methyl-3-phenylsulfonylisoindolin-1-one **(36)**: yield: 75%; white solid, mp 148–149 °C.

^{1}H NMR ($CDCl_3$): δ = 3.40 (s, 3H), 5.48 (s, 1H), 7.20–7.34 (m, 4H), 7.42–7.60 (m, 3H), 7.60 (dt, J = 1.2, 7.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ = 30.4, 81.3, 124.2, 125.6, 129.2, 129.8, 130.9, 132.6, 132.7, 132.8, 135.1, 136.2, 168.8.

2-Benzyl-3-phenylsulfonylisoindolin-1-one **(37)**: yield: 68%; white solid; mp 121–122 °C.

^{1}H NMR ($CDCl_3$): δ = 4.79 (d, J = 14.5 Hz, 1H), 5.38 (s, 1H), 5.51 (d, J = 14.5 Hz, 1H), 7.25–7.36 (m, 7H), 7.45–7.60 (m, 6H), 7.89 (dd, J = 1.0, 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ = 44.7, 70.1, 123.9, 125.2, 128.2, 128.6, 129.0, 129.3, 131.8, 132.3, 133.9, 134.5, 135.7, 135.8, 168.7.

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