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A New Synthetic Route to 2-Alkyl-4-aryl-1(*2H*)-isoquinolones and 2-Alkyl-4-aryl-1,2,3,4-tetrahydroisoquinolines

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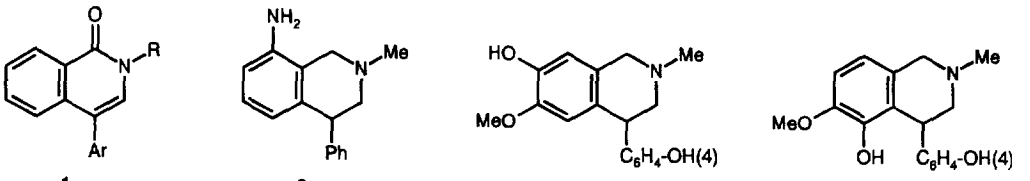
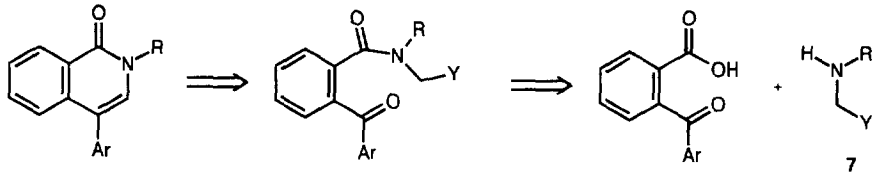
Abstract: 4-Aryl and heteroaryl-1(*2H*)-isoquinolones have been prepared by base promoted cyclization of phosphorylated *o*-aroyl and heteroaroyl benzamides. Subsequent reduction of the carbonyl and styryl functions of the annulated products has given rise to 4-aryl-1,2,3,4-tetrahydroisoquinolines.

In recent years members of the isoquinolone class of compounds have generated considerable interest from the synthetic community as witnessed by recent articles dealing with their synthesis and emphasizing their pharmaceutical and medicinal activities.[1] In particular the 1(*2H*)-isoquinolone skeleton constitutes the framework of a large variety of plant alkaloids and drugs.[2] It can also give access through relatively simple chemical transformations to the isoquinoline ring system and the importance of isoquinoline derivatives,[3] many of which are pharmacologically active, as intermediates in synthesis of natural products and medicinal chemistry is well documented.[4] Consequently the methods of synthesis of these heterobicyclic compounds are still the object of considerable attention. Paradoxically, in spite of extensive work in this field, few efforts have been devoted to the synthesis of 4-aryl-1(*2H*)-isoquinolones **1** although several articles and patents dealing with their medicinal activities[5] as cholesterol biosynthesis inhibitors[6] and as antiulcer,[7] anticholesteremic,[8] anticholinergic[9] and anticonvulsive[10] agents have recently appeared in the litterature. Furthermore these compounds may be regarded as precursors of 4-aryl-1,2,3,4-tetrahydroisoquinoline derivatives which have stimulated much interest in their synthesis[11] owing to their potent pharmacological activity.[12] For example 4-phenyl-2-methyl -1,2,3,4-tetrahydroisoquinoline is an agonist of dopamine receptors[13] and the antidepressant drug Nomifensine **2**[14] has a close relationship to the Amaryllidaceae alkaloids Cherylline **3**[15] and its biogenetic isomer Latifine **4**[16] isolated from leaves of *Crinum latifolium*, a plant used as a rubefacient and tonic.[17]



1 2 3 4

Several synthetic strategies have been developed for the preparation of 4-aryl-1(*2H*)-isoquinolone derivatives but few have demonstrated broad synthetic utility. Indeed such compounds may be obtained by treatment of the corresponding 4-arylisocoumarines with a suitable primary amine.[18] They are also the result of an aryl group migration observed upon acid-catalyzed dehydration of 2-substituted-3-aryl-4-hydroxy-1(*2H*)-isoquinolone resulting from the reaction of phtalide lithium salts with Schiff's bases.[19] They have been also incidentally obtained by reaction of 3-aryl-1-indanones with butyl nitrite in the presence of sodium methoxide.[20] Actually the most convenient synthetic route to these heterobicyclic compounds relies on the regiospecific dilithiation of 2-arylmethyl-*N*-methybenzamides[21] or *O*-methyl-2-arylmethylbenzohydroxamate[22] followed by trapping of the dilithio species with dimethylformamide (DMF) and subsequent dehydration of the resulting 4-aryl-3-hydroxy-*N*-methyl or *N*-methoxy-1(*2H*)-isoquinolone respectively. However the feasibility of this process has not been demonstrated on models incorporating competitive deprotonation sites or entities sensitive to organometallic reagents.



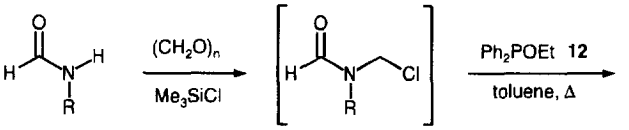
1 5 6 7

Scheme 1

The introduction of new and simple methodologies to form α-nitrogen carbon-carbon bonds is of considerable interest and synthetic methods based on carbanion chemistry are now commonplace in any rationally designed synthetic endeavour. Paradoxically, few reported strategies hinge upon the intramolecular attack of an α-carboxamido carbanion on a vicinal carbonyl moiety in suitable benzamide derivatives **5**. This is undoubtedly due to the difficulties associated with the generation and reaction of α-metallo amines[23] even though several recently developed procedures have solved this problem.[24] Recently K. Unverferth[10] reported a new isoquinolone synthesis involving base-catalysed condensation of *o*-aroyl-*N*-cyanomethylbenzamides **5** (Y = CN) and E. Bisagni[1b] has postulated the intermediacy of dilithiated species deriving from compounds of structure **5** (Y = Ph, R = H) in the synthesis of 3,4-diarylisoquinoline derivatives from hydroxyarylmethyl-isoindolones. Unfortunately the different compounds prepared by these methods were invariably substituted at the three positions of the six-membered heterocyclic ring.

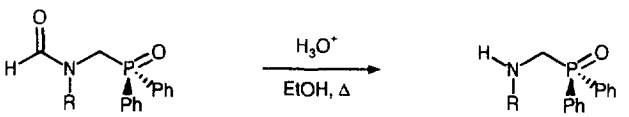
Among the different groups usually adopted for the stabilization of α-amino carbanions,[25-28] the phosphorylated entity is undoubtedly one of the most reliable.[29] Indeed the oxophosphinyl moiety can be connected to a carboxamido group by extremely diverse synthetic routes.[30] Deprotonation of the methylene or methyne linking the two functional groups proceeds rapidly and efficiently even at low temperature[31] and the phosphoryl moiety may be easily removed by different means, namely via Horner or Wadsworth-Emmons reaction[32] or by appropriate thermal or acidic treatment as already illustrated with certain amines[31,33] and carbamates.[34] Retrosynthetically it was then envisaged that 2-substituted-4-aryl-1(*2H*)-isoquinolones **1** could be obtained by base-induced intramolecular cyclization of *o*-aroyloxophosphinylmethylbenzamides **5** (R = alkyl, Ar = aryl, Y= $P(O)R^1_2$) (scheme 1). We then embarked on the search for a synthetic strategy for the elaboration of these polyfunctionalized compounds.

Recent years have witnessed a flurry of synthetic methodologies for the elaboration of *N*-acylaminophosphonic acid derivatives[30] due to their biological activities[35] and their role as precursors of the phosphorus analogs of natural α-amino carboxylic acid derivatives.[36] Among the various routes liable to give access to compounds of structure **5** (X = $P(O)R_2$) the coupling reaction between the appropriate *o*-aroyl benzoic acid derivatives **6** and a suitable *N*-alkyl-*N*-oxophosphinylmethylamine **7** (Y = $P(O)R_2$) emerged as the most simple, general and tolerant of other functionalities. An initial requirement was then to develop a simple and clean synthesis of these phosphorylated secondary amines and particularly of the aminodiphenylphosphine oxides **7** (Y = $P(O)Ph_2$) since it has been established that diphenylphosphine oxides show superior properties notably in the Horner reaction, compared to phosphonium salts and phosphonates.[37]



8, 9 **10, 11**

	R
8, 10, 13, 15	Me
9, 11, 14, 16	$PhCH_2$



13, 14 **15, 16**

Scheme 2

Compounds **15**, **16** were easily obtained after initial treatment of the appropriate formamides **8**, **9** with paraformaldehyde and chlorotrimethylsilane[38] (scheme 2). The reaction of the transient *N*-alkyl- *N*-chloro-methylformamides **10**, **11** with ethyl diphenylphosphinite **12** afforded the phosphorylated formamides **13**, **14** and subsequent hydrolysis (10% HCl) in ethanol induced the removal of the formamido protective group[39]

Table 1. Parent Compounds and Isoquinolones **20a-f**, **21a**, **25** Prepared

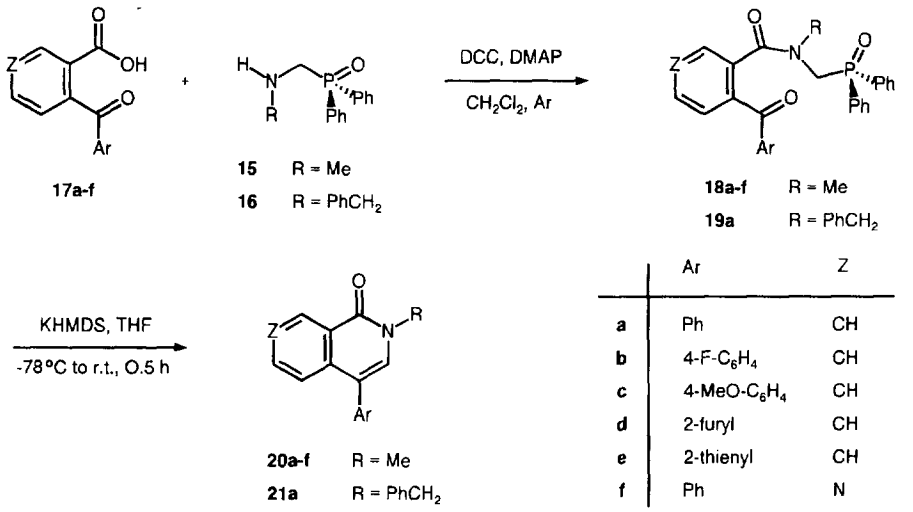
Compound	R	Ar	Z	m.p. (°C)	Yield* (%)
13	Me			130-131 lit.[52]: 130	82
14	Ph-CH_2			124-125	80
15	Me			77-78	85
16	Ph-CH_2			101-102	82
18a	Me	Ph	CH	101-102	90
18b	Me	4-F-C_6H_4	CH	111-112	85
18c	Me	4-MeO-C_6H_4	CH	148-149	86
18d	Me	2-furyl	CH	153-154	82
18e	Me	2-thienyl	CH	144-145	80
18f	Me	Ph	N	105-106	81
19a	Ph-CH_2	Ph	CH	132-133	83
20a	Me	Ph	CH	181-182 lit.[58]: 181-182	90
20b	Me	4-F-C_6H_4	CH	198-199	88
20c	Me	4-MeO-C_6H_4	CH	137-138	90
20d	Me	2-furyl	CH	78-79	65
20e	Me	2-thienyl	CH	133-134	64
20f	Me	Ph	N	231-232	85
21a	Ph-CH_2	Ph	CH	146-147 lit.[19]: 145-146	80
23				139-140	97
24		Ph	CH	151-152	82
25		Ph	CH	229-230	89

* Yields are of purified products

giving rise to the *N*-methyl and *N*-benzyl-diphenyloxophosphinylmethylamines, **15** and **16** respectively, in almost quantitative yields (Table 1).

The *o*-aroyl and heteroaroylbenzoic or nicotinic acid derivatives **17a-c,e** and **17f** were obtained by Friedel Crafts reaction between the appropriate aromatic anhydrides and anisole, thiophene and benzene respectively whilst the *o*-furoyl derivative **17d** was synthesized by applying the Parham protocol[40] to the dilithiated species deriving from 2-bromobenzoic acid and 2-methyl furoate.

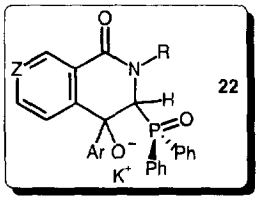
The coupling reaction between the *o*-aroylbenzoic acid **17a-e** or nicotinic acid **17f** and the phosphorylated amine **15**, **16** was effected under classical conditions (DCC, DMAP, CH_2Cl_2) and the phosphorylated aromatic carboxamides **18a-f** and **19a** were obtained with excellent yields by this protocol (scheme 3, Table 1).



	Ar	Z
a	Ph	CH
b	4-F-C_6H_4	CH
c	4-MeO-C_6H_4	CH
d	2-furyl	CH
e	2-thienyl	CH
f	Ph	N

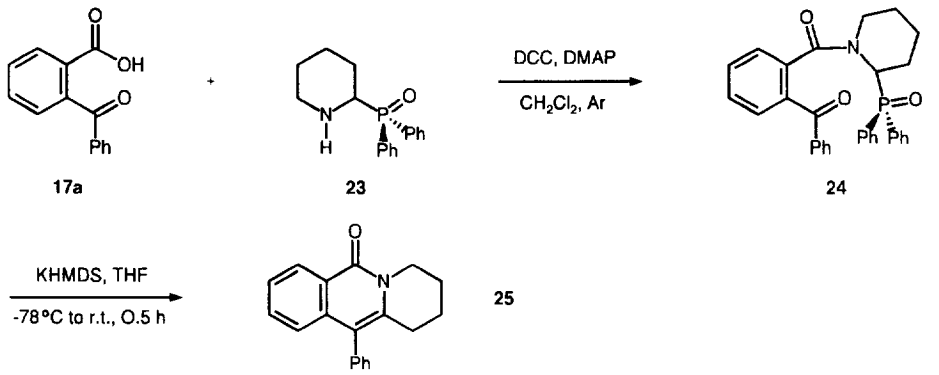
Scheme 3

As anticipated, deprotonation of the methylene group in **18a-f** and **19a** with potassium bis(trimethylsilylamide) (KHMDS) proceeded rapidly and efficiently at -78°C in tetrahydrofuran. Warming the reaction mixture to room temperature for 0.5 h ensured the completion of the annelation reaction as indicated by the concomitant disappearance of the characteristic orange color of the anions deriving from **18** and **19** and the formation of potassium diphenylphosphinate. The results of a representative series of products obtained by this method are presented in the Table 1 where it may be seen that this procedure affords excellent yields of thetargeted 4-aryl-1(*2H*)-isoquinolone derivatives **20a-f** and **21a**. The method is tolerant with a wide variety of aromatic and heteroaromatic substituents and allows the construction of fused models comprising a pyridine



constituent unit. The efficiency of this new annulation process is actually the combined result of the remarkable nucleophilicity of the phosphoryl stabilized aminocarbanion, of the high degree of conjugation of the final compounds and finally of the presence of the weakly bound potassium counterion in the primary adduct **22**.

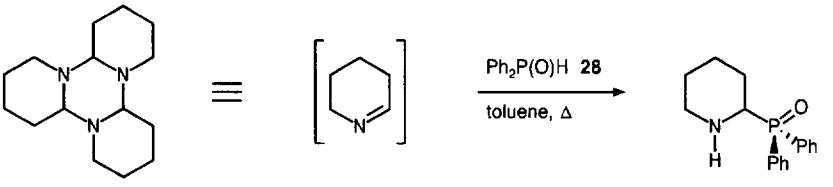
Furthermore the scope of these reactions can be broadened to include the preparation of condensed polycyclic models as illustrated by the synthesis of 1,2,3,4-tetrahydro-11-phenyl-*6H*-benzo[*b*]quinolizine-6-one **25** issued from the base-induced ring closure of the phosphorylated carboxamide **24** (scheme 4, Table 1).



17a **23** **24** **25**

Scheme 4

The procedure noticeably differs from the foregoing process by the synthesis of the cyclic phosphorylated amine **23** which can not be obtained following the protocol depicted in scheme 2. A general and common route to amino phosphonates and phosphine oxides usually involves the thermal addition of trivalent phosphorus derivatives to Schiff's bases[41] which are either preformed or generated *in situ*. However the thermal instability of the 1-piperideine **27** (scheme 5) and its propensity to polymerize[42] represent a significant impediment to enlargement of this method to the synthesis of the phosphorylated piperidine **23**. This problem was circumvented by treating directly the tripiperidine **26**, *i.e.* dodecahydro-*1H*, *6H*, *11H*-tripyrido[1,2-*a* : 1',2'-*c* : 1",2"-*e*]triazine, which can be regarded as synthetic equivalent of 1-piperideine **27**, with diphenylphosphine oxide **28** (scheme 5). The connection of the aminophosphorylated moiety proceeded uneventfully and the basic treatment of the phosphorylated carboxamide **24** delivered the cyclohexyl fused isoquinolone **25** with a very satisfying yield (scheme 4, Table 1).

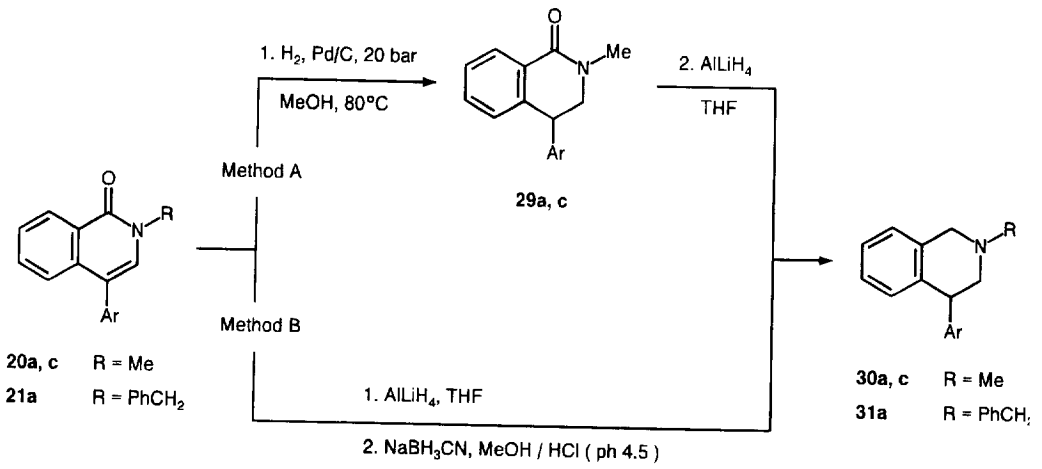


26 **27** **23**

Scheme 5

The simplicity and efficiency of this short and clean procedure and the high yields of 2-substituted-4-aryl-1(*2H)*-isoquinolones prompted continuation of this work toward the synthesis of 2-alkyl-4-aryl-1,2,3,4-tetrahydroisoquinolines. The synthetic utility[43] and the potent pharmalogical activity[12,16,44] of compounds of this type have attracted the attention of synthetic organic chemists in recent years and consequently several efficient synthetic procedures have been explored.[11,45] The most popular syntheses are based on the use of *N*-alkyl-*N*-benzyl-2-amino-1-phenylethanols as key intermediates, which are usually cyclized in acidic media.[12f, 17b, 46] They are also accessible by a nickel-assisted Barbier reaction of *N*-(2-iodobenzyl)phenacylamine and subsequent treatment of the intermediate isoquinolin-4-ols,[47] by reduction of quaternary salts of 4-arylisoquinolines obtained by palladium-catalyzed cross-coupling reactions of dialkyl(4-isoquinolyl)borane with aromatic organic halides[48] and by fluoride ion induced desilylation of *trans*-2-methyl-1-arylisoindoliunium iodides.[45b] Recently S.G. Davies *et al.* have developed an original and elegant method which recommends the 4-exo-deprotonation of tricarbonyl(*N*-alkyl-1,2,3,4-tetrahydro-isoquinoline)chromium and subsequent electrophilic addition of tricarbonyl(fluorobenzene)chromium followed by decomplexation.[49]

Two different protocols have been adopted for the convertion of the 2-alkyl-4-aryl-1(2H)-isoquinolones **20a,c** and **21a** to the 2-alkyl-4-aryl-1,2,3,4-tetrahydroisoquinolines **30a,c**, **31a** (scheme 6) which alternate the reduction of the styryl and carbonyl functions. Catalytic hydrogenation (H_2, Pd/C, MeOH) of **20a,c** afforded quantitatively their 3,4-dihydroderivatives as exemplified by isolation and characterization of the intermediate **29a**. The subsequent reduction of the carbonyl function ($LiAlH_4$, ether) gave ready access to the desired 4-aryltetrahydroisoquinolines **30a,c** (scheme 6, method A, Table 2).



Scheme 6

The presence in the parent arylisoquinolone of substituent sensitive to hydrogenolysis prompted us to develop an alternative route to these arylated polyhydroisoquinolines. The preliminary reduction of the

carbonyl function of compounds **20a,c** and **21a** followed by reduction of the styryl moiety of the transient unstable enamines ($NaBH_3CN$, MeOH, HCl) furnished the targeted 2-methyl and 2-benzyl-1,2,3,4-tetrahydro-isoquinolines **30a,c** and **31a** with fairly good yields (scheme 6, method B, Table 2).

Table 2. 2-Alkyl-4-aryl-1,2,3,4-tetrahydroisoquinolines **30a,c** and **31a** Prepared.

Compound	R	Ar	m.p. (°C)	Yield (%)	
				Method A	Method B
30a	Me	Ph	-	77	81
30c	Me	4-MeO-C_6H_4	121-122 lit.[48]: 121-122	69	79
31a	Ph-CH_2	Ph	-	-	77

In conclusion we have developed a general and versatile method for the preparation of 1(2H)isoquinolones flanked indifferently with aromatic and heteroaromatic units at position 4. The use of readily available starting materials and the possibility to reach ultimately 4-aryl-1,2,3,4,-isoquinolines endow the procedure with considerable synthetic potential.

EXPERIMENTAL SECTION

^1H NMR (100 MHz), ^{13}C NMR (75 MHz) and ^{31}P NMR (121 MHz) spectra were recorded on a Bruker AM 300 spectrometer. All ^1H, ^{13}C and ^{31}P spectra were run relative to tetramethylsilane and H_3PO_4as the internal standard . Chemical shifts are expressed in ppm. Abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet), br. (broad). Mass spectra were registred on a Riber 10-10 apparatus. For flash column chromatography Merck silica gel 60 (230-400 mesh ASTM) was used. Tetrahydrofuran (THF) was freshly distilled over $LiAlH_4$ and dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) over CaH_2 . Methanol (MeOH) was distilled over magnesium turnings and iodine. 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 syringe techniques. Elemental analyses were determined by the CNRS microanalysis centre.

General Procedure for the Synthesis of the Phosphorylated Carboxamides and amines* 13, 14 *and* 15, 16 *respectively.

N-Methyl and *N*-benzyl formamide, **8**, **9** respectively (0.05 mol) were treated with paraformaldehyde (0.05 mol) dried over P_2O_5 and chlorotrimethylsilane (0.15 mol) in boiling $CHCl_3$ (150 mL) for c.a. 2 h.[38,50] The reaction mixture was filtered on celite^R, the solvent was removed on a rotary vacuum evaporator (water aspirator; 35°C) and the crude chloromethylcarboxamide derivatives **10**, **11** were treated with ethyl diphenylphosphinite **12**[51] (11.5 g, 0.05 mol) in boiling toluene (20 mL) for 1 h. The solvent was evaporated to dryness and the crude product was triturated with Et_2O, filtered. Compounds **13**, **14** were finally recrystallized from hexane-toluene.

A solution of the phosphorylated carboxamide **13**, **14** in ethanol (20 mL) was refluxed in the presence of 10% aqueous HCl for 0.5 h. The mixture was made alkaline by the slow addition of 30% aqueous NH_4OH and then saturated with NH_4Cl. The mixture was extracted twice with CH_2Cl_2 then dried ($MgSO_4$) and evaporated to give a crude solid which was finally purified by flash column chromatography on silica using acetone-hexane (9:1) as eluent and recrystallized from hexane-toluene.

N-*methyl*-N-*diphenylphosphinoylmethylformamide* **13**[52] .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 2.91 and 3.14 (3H, two s, two rotamers, NCH_3), 4.03 and 4.28 (2H, two d, J_{HP} 4.1 and 5.7, two rotamers, NCH_2P), 7.43-7.53 (6H, m, H_{arom}), 7.75-7.87 (5H, m, H_{arom} + CHO); *m/z* (%): 273 (M^+, 12), 201 ($POPh_2$, 100), 72 (30).

N-*benzyl*-N-*diphenylphosphinoylmethylformamide* **14** :

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.89 and 4.16 (2H, two d, J_{HP} 3.8 and 5.4, two rotamers, NCH_2P), 4.67 and 4.74 (2H, two s, two rotamers, NCH_2Ph), 7.25-7.34 (5H, m, H_{arom}), 7.46-7.54 (6H, m, H_{arom}), 7.78-7.85 (4H, m, H_{arom}), 7.97 (1H, two s, two rotamers, CHO); *m/z* (%): 349 (M^+, 14), 215 (CH_2POPh_2, 91), 201 ($POPh_2$, 62), 91 (100); Anal. Calcd for $C_{21}H_{20}NO_2P$: C, 72.20; H, 5.77; N, 4.01; O, 9.16; P, 8.87. Found: C, 72.01; H, 5.86; N, 4.25; O, 8.90; P, 8.59.

N-*diphenylphosphinoylmethyl*-N-*methylamine* **15**[52] .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 1.60(1H, br. s, NH), 2.45 (3H, s, NCH_3), 3.40 (2H, d, J_{HP} 7.6, NCH_2P), 7.39-7.78(10H, m, H_{arom}); *m/z* (%): 245 (M^+, 8), 202 (100).

N-*diphenylphosphinoylmethyl*-N-*benzylamine* **16** :

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 1.32 (1H, br. s, NH), 3.41 (2H, d, J_{HP} 7.8, NCH_2P), 3.86 (2H, NCH_2Ph), 7.23-7.78 (15H, m, H_{arom}); *m/z* (%): 321 (M^+, 1), 214 (11), 201 (27), 120 (79), 91 (100); Anal. Calcd for $C_{20}H_{20}NOP$: C, 74.75; H, 6.27; N, 4.36; O, 4.98; P, 9.64. Found: C, 74.98; H, 6.01; N, 4.57; O, 5.23; P, 9.36.

***Synthesis of the phosphorylated piperidine* 23** .

A solution of the tetracyclic triazine **26**[53] (4 g, 0.05 mol) and diphenylphosphine oxide **28**[54] (10 g, 0.05 mol) was refluxed in toluene (50 mL) for 2 h. The solvent was removed under vacuum in a rotary evaporator and the crude solid was recrystallized from hexane-toluene.

2-Diphenylphosphinoylpiperidine **23** :

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 1.30-1.85 (7H, m, CH_2 + NH), 2.55 (1H, m), 3.10 (1H, m), 3.35 (1H, dq, *J 2.5*, J_{HP} 7.1, NCHP), 7.39-7.60 (6H, m, H_{arom}), 7.72-7.81 (2H, m, H_{arom}), 7.91-8.00 (2H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 130.9, 129.8; CH, 132.0, 131.9, 131.8, 131.5, 128.7, 128.6, 128.5, 128.4, 56.6 (J_{CP} 83.8); CH_2, 47.4 (J_{CP} 13.4), 26.3, 25.4, 24.8 (J_{CP} 12.6); *m/z* (%): 285 (M^+, 1), 201 (22), 84(100); Anal. Calcd for $C_{17}H_{20}NOP$: C, 71.56; H, 7.07; N, 4.91; O, 5.61; P, 10.86. Found: C, 71.41; H, 7.08; N, 5.05; O, 5.53; P, 10.76.

***General Procedure for the Synthesis of the Starting Compounds* 18a-f, 19a *and* 24** .

The *o*-aroylbenzoic acids **17a,b** are commercially available. The *o*-aroyl and *o*-heteroaroylbenzoic and nicotinic acid derivatives **17c**,[55] **17d**,[40] **17e**[56] and **17f**[57] were prepared according to previously described procedures.

A suspension of the appropriate *o*-aroylbenzoic and nicotinic acid derivative (4 mmol) in anhydrous CH_2Cl_2 (20 mL) was added with vigorous stirring under Ar to a cooled solution (O°C) of the phosphorylated amine **15, 16** (4 mmol), dicyclohexylcarbodiimide (DCC, 0.8 g, 4 mmol), dimethylaminopyridine (DMAP, 0.1 g, 0.4

mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 2 h, then filtered on celite^R and the solvent was evaporated on a rotary vacuum evaporator. The crude phosphorylated carboxamides **18a-f**, **19a** and **24** were purified by flash column chromatography using acetone-hexane (65:35) as eluent and finally recrystallized from hexane-toluene (Table 1).

N-*diphenylphosphinoylmethyl*-N-*methyl-2-benzoylbenzamide* **18a** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.13 (3H, s, NCH_3), 4.51 (2H, d, J_{HP} 5.4, NCH_2P), 6.51 (1H, dd, *J* 4.1, 2.9, H_{arom}), 7.33-7.54 (12H, m, H_{arom}), 7.72-7.75 (2H, m, H_{arom}), 7.86-7.93 (4H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 196.2, 170.8, 137.5, 136.8, 136.4, 132.2; CH, 133.1, 131.6, 131.2, 131.1, 130.4, 130.2, 130.1, 128.7, 128.6, 128.3, 128.2, 126.9; CH_2, 46.9 (J_{CP} 77.7); CH_3, 39.0; ^{31}P NMR ($CDCl_3$, δ): 31.5; *m/z* (%): 453 (M^+, 1), 209 (100), 201 (53); Anal. Calcd for $C_{28}H_{24}NO_3P$: C, 74.16; H, 5.33; N, 3.09; O, 10.58; P, 6.83. Found: C, 74.02; H, 5.51; N, 3.26; O, 10.72; P, 6.46.

N-*diphenylphosphinoylmethyl*-N-*methyl-2-(4-fluorbenzoyl)benzamide* **18b** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.16 (3H, s, NCH_3), 4.53 (2H, d, J_{HP} 5.4, NCH_2P), 6.53 (1H, dd, *J* 5.4, 3.3, H_{arom}), 7.11-7.56 (11H, m, H_{arom}), 7.77-7.82 (2H, m, H_{arom}), 7.87-7.94 (4H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 194.7, 170.8, 137.3, 136.3, 132.9, 130.2; CH, 132.8, 132.3, 131.5, 131.2, 131.1, 129.7, 128.8, 128.6, 128.3, 126.9, 115.7, 115.4; CH_2, 46.9 (J_{CP} 77.7); CH_3, 39.1; ^{31}P NMR ($CDCl_3$, δ): 31.5; *m/z* (%): 471 (M^+, 1), 227 (100), 201 (77); Anal. Calcd for $C_{28}H_{23}FNO_3P$: C, 71.33; H, 4.92; F, 4.03; N, 2.97; P, 6.57. Found: C, 71.17; H, 5.06; F, 3.87; N, 3.15; P, 6.74.

N-*diphenylphosphinoylmethyl*-N-*methyl-2-(4-methoxybenzoyl)benzamide* **18c** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.14 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 4.53 (2H, d, J_{HP} 5.1, NCH_2P), 6.48-6.50 (1H, m, H_{arom}), 6.90 (2H, d, *J* 9.0, H_{arom}), 7.25-7.32 (2H, m, H_{arom}), 7.33-7.60 (7H, m, H_{arom}), 7.70-7.80 (2H, d, *J* 9.0, H_{arom}), 7.86-7.93 (4H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 207.2, 174.1, 148.3, 130.7, 129.6, 128.3, 127.2; CH, 132.7, 132.4, 131.2, 130.1, 130.0, 129.5, 128.7, 113.6; CH_2, 46.9 (J_{CP} 104.1); CH_3, 55.5, 39.3; ^{31}P NMR ($CDCl_3$, δ): 31.6; *m/z* (%): 483 (M^+, 1), 239 (100), 201 (36); Anal. Calcd for $C_{29}H_{26}NO_4P$: C, 72.04; H, 5.42; N, 2.90; O, 13.24; P, 6.41. Found: C, 72.25; H, 5.48; N, 3.15; O, 13.01; P, 6.23.

N-*diphenylphosphinoylmethyl*-N-*methyl-2-(2-furoyl)benzamide* **18d** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.13 (3H, s, NCH_3), 4.57 (2H, d, J_{HP} 4.8, NCH_2P), 6.45-6.48 (1H, m, H_{arom}), 6.52-6.55 (1H, dd, *J* 3.6, 1.7 H_{furan}), 7.13 (1H, d, *J* 3.6, H_{furan}), 7.36-7.39 (2H, m, H_{arom}), 7.48-7.52 (6H, m, H_{arom}), 7.64 (1H, d, *J* 0.9, H_{arom}), 7.71-7.77 (1H, m, H_{furan}), 7 .87-7.94 (4H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 183.2, 171.0, 151.9, 137.3, 135.4, 130.4; CH, 147.5, 132.2, 131.4, 131.2, 131.1, 129.5, 128.6, 128.4, 126.9, 121.2, 112.4; CH_2, 46.9 (J_{CP} 78.1); CH_3, 39.0; ^{31}P NMR ($CDCl_3$, δ): 31.3; *m/z* (%): 443 (M^+, 1), 201 (44), 199 (100); Anal. Calcd for $C_{26}H_{22}NO_4P$: C, 70.42; H, 5.00; N, 3.16; O, 14.43; P, 6.98. Found: C, 70.59; H, 4.78; N, 3.35; O, 14.70; P, 6.75.

N-*diphenylphosphinoylmethyl*-N-*methyl-2-(2-thenoyl)benzamide* **18e** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.13 (3H, s, NCH_3), 4.57 (2H, d, J_{HP} 5.2, NCH_2P), 6.48-6.51 (1H, m, H_{arom}), 7.10 (1H, dd, *J* 4.9, 3.9, $H_{thiophene}$), 7.36-7.40 (2H, m, H_{arom}), 7.48-7.55 (7H, m, H_{arom} + $H_{thiophene}$), 7.69-7.71 (2H, m, H_{arom} + $H_{thiophene}$), 7.87-7.94 (4H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 182.3, 170.7, 143.4, 137.2, 135.6, 131.2, 129.4; CH, 135.5, 135.0, 132.2, 131.1, 128.7, 128.6, 128.3, 128.1, 127.0; CH_2, 46.9 (J_{CP} 77.9); CH_3, 39.1; ^{31}P NMR ($CDCl_3$, δ): 31.4; *m/z* (%): 459 (M^+, 1), 202 (100), 201 (26), 155 (34);

Anal. Calcd for $C_{26}H_{22}NO_3PS$: C, 67.96; H, 4.83; N, 3.05; O, 10.45; P, 6.74; S, 6.98. Found: C, 68.15; H, 4.75; N, 3.29; O, 10.57; P, 6.84; S, 6.40.

N-*diphenylphosphinoylmethyl*-N-*methyl-3-benzoyl-2-pyridinecarboxamide* **18f** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.28 (3H, s, NCH_3), 4.45 (2H, d, J_{HP} 6.0, NCH_2P), 7.31-7.39 (1H, m, $H_{pyridine}$), 7.40-7.54 (8H, m, H_{arom}), 7.54-7.62 (1H, m, H_{arom}), 7.70-7.79 (3H, m, H_{arom}) 7.81-7.90 (4H, m, H_{arom}), 8.61 (1H, d, *J 4.8*, $H_{pyridine}$); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 194.5, 168.4, 154.5, 153.9, 136.0; CH, 150.0, 136.7, 133.6, 132.2, 131.2, 131.1, 130.1, 128.7, 128.6, 122.9; CH_2, 47.6 (J_{CP} 72.7); CH_3, 38.6; ^{31}P NMR ($CDCl_3$, δ): 30.5; *m/z* (%): 454 (M^+, 1), 201 (100); Anal. Calcd for $C_{27}H_{23}N_2O_3P$: C, 71.36; H, 5.10; N, 6.16; O, 10.56; P, 6.82. Found: C, 71.24; H, 5.36; N, 5.94; O, 10.22; P, 7.24.

N-*diphenylphosphinoylmethyl*-N-*benzyl-2-benzoylbenzamide* **19a** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 4.44 (2H, br. s, NCH_2P), 4.80 (2H, s, NCH_2Ph), 6.70 (1H, dd, *J* 5.7, 3.2, H_{arom}), 7.23-7.59 (18H, m, H_{arom}), 7.74-7.91 (5H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 196.8, 171.3, 138.5, 137.7, 137.4, 135.8, 132.8; CH, 133.7, 132.7, 131.9, 131.8, 131.6, 131.1, 131.0, 130.6, 129.9, 129.3, 129.2, 128.9, 128.5, 128.4; CH_2, 55.1, 42.8 (J_{CP} 76.5); ^{31}P NMR ($CDCl_3$, δ): 28.6; *m/z* (%): 529 (M^+, 1), 349 (3), 201 (32), 91 (100); Anal. Calcd for $C_{34}H_{28}NO_3P$: C, 77.11; H, 5.33; N, 2.64; O, 9.06; P, 5.85. Found: C, 77.25; H, 5.02; N, 2.89; O, 9.15; P, 5.74.

N-*(2-benzoyl)benzoyl-2-diphenylphosphinoylpiperidine* **24** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 1.56-2.06 (5H, m, $H_{piperidine}$), 2.42-2.56 (1H, m, $H_{piperidine}$), 3.45 (1H, d, *J* 12.8, NCH_2), 3.71 (1H, dt, *J* 12.8, 2.8, NCH_2), 5.85 (1H, m, NCHP), 6.03 (1H, d, *J* 7.2, H_{arom}), 7.16 (2H, d, *J* 7.3, H_{arom}), 7.15-7.34 (2H, m, H_{arom}), 7.41-7.58 (8H, m, H_{arom}), 7.77-7.80 (2H, m, H_{arom}), 7.93-8.03 (4H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 196.4, 169.9, 137.6, 137.4, 136.9, 133.1; CH, 132.0, 131.9, 131.3, 131.2, 131.0, 130.9, 131.6, 130.3, 129.9, 128.8, 128.4, 128.0, 126.6, 47.6 (J_{CP} 105.0); CH_2, 46.9, 25.1, 24.0, 20.5; ^{31}P NMR ($CDCl_3$, δ): 35.1; *m/z* (%): 493 (M^+, 1), 292 (5), 209 (100), 201 (15), 152 (15); Anal. Calcd for $C_{31}H_{28}NO_3P$: C, 75.44; H, 5.72; N, 2.84; O, 9.73; P, 6.28. Found: C, 75.67; H, 5.96; N, 2.59; O, 9.68; P, 6.01.

***General Procedure for the Synthesis of 2-Substituted-4-aryl and heteroaryl-1(2H)-isoquinolone Derivatives* 20a-f, 21a *and* 25.**

A solution of KHMDS in toluene (0.5 M, 2 mL, 1 mmol) was added dropwise by way of a syringe to a stirred solution of the parent amides **18a-f**, **19a** and **24** (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 warmed to room temperature and stirred for an additional 0.5 h. After this, several drops of dilute HCl (10%), water (10 mL), Et_2O (20 mL), CH_2Cl_2 (20 mL) were added to it. The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. The crude products were purified by flash column chromatography using AcOEt-hexane (60:40) as eluent and finally recrystallized from hexane-toluene.

2-Methyl-4-phenyl-1(2H)-isoquinolone **20a**[58] .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.62 (3H, s, NCH_3), 7.02 (1H, s, NCH=), 7.38-7.55 (8H, m, H_{arom}), 8.50 (1H, dd, *J* 8.5, 1.0, H_{arom}); *m/z* (%): 235 (M^+, 76), 194 (18), 165 (41), 149 (32), 57 (100).

2-Methyl-4-(4-fluorophenyl)-1(2H)-isoquinolone **20b** .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.64 (3H, s, NCH_3), 7.01 (1H, s, NCH=), 7.12-7.59 (7H, m, H_{arom}), 8.50 (1H, dd, *J* 7.8, 0.9, H_{arom}); *m/z* (%): 253 (M^+, 100), 212 (30), 183 (57); Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; F, 7.50; N, 5.53. Found: C, 76.02; H, 4.95; F, 7.17; N, 5.69.

2-Methyl-4-(4-methoxyphenyl)-1(2H)-isoquinolone **20c** .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.64 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 6.98-7.01 (3H, m, NCH= + H_{arom}), 7.30-7.33 (2H, m, H_{arom}), 7.47-7.59 (3H, m, H_{arom}), 8.51 (1H, d, *J* 7.8, H_{arom}); *m/z* (%): 265 (M^+, 100), 250 (37); Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; O, 12.06. Found: C, 77.25; H, 5.41; N, 5.36; O, 12.23.

2-Methyl-4-(2-furyl)-1(2H)-isoquinolone **20d** .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.65 (3H, s, NCH_3), 6.52 (2H, d, *J* 1.2, H_{furan}), 7.35 (1H, s, NCH=), 7.50-7.55 (2H, m, H_{furan} + H_{arom}), 7.65-7.70 (1H, m, H_{arom}), 7.92 (1H, d, *J* 8.1, H_{arom}), 8.50 (1H, d, *J* 8.0, H_{arom}); *m/z* (%): 225 (M^+, 100) 224 (85), 154 (37); Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22; O, 14.21. Found: C, 74.51; H, 5.05; N, 6.24; O, 14.39.

2-Methyl-4-(2-thienyl)-1(2H)-isoquinolone **20e** .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.63 (3H, s, NCH_3), 7.12-7.15 (2H, m, $H_{thiophene}$), 7.20 (1H, s, NCH=), 7.36-7.38 (1H, dd, *J* 4.5, 1.8, $H_{thiophene}$), 7.48-7.54 (1H, ddd, *J* 8.1, 6.9, 1.2, H_{arom}), 7.60-7.63 (1H, ddd, *J* 8.1, 6.9, 1.2, H_{arom}), 7.77 (1H, d, *J* 7.7, H_{arom}), 8.50 (1H, dd, *J* 8.0, 1.0, H_{arom}); *m/z* (%): 241 (M^+, 100), 171 (30); Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; O, 6.63; S, 13.29. Found: C, 69.97; H, 4.36; N, 5.86; O, 6.51; S, 13.01.

7-Methyl-5-phenyl-1,7-naphthyridine-8(7H)one **20f** .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.71 (3H, s, NCH_3), 7.12 (1H, s, NCH=), 7.30-7.51 (6H, m, H_{arom}), 7.95 (1H, dd, *J* 6.6, 1.6, $H_{pyridine}$), 8.90 (1H, dd, *J* 4.5, 1.6, $H_{pyridine}$); *m/z* (%): 236 (M^+, 100), 207 (73); Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; O, 6.77. Found: C, 76.20; H, 4.92; N, 11.98; O, 6.90.

2-Benzyl-4-phenyl-1(2H)-isoquinolone **21a**[19] .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 5.23 (2H, s, NCH_2Ph), 7.05 (1H, s, NCH=), 7.38-7.55 (13H, m, H_{arom}) 8.50 (1H, dd, *J* 8.0, 1.0, H_{arom}); *m/z* (%): 299 (M^+, 23), 298 (40), 208 (21), 91 (100);

1,2,3,4-Tetrahydro-11-phenyl-6H-benzo[b]quinolizine-6-one **25** .

^{1}H NMR ($CDCl_3$, δ, *J* Hz): 1.73 (2H, quintet, *J* 7.1, CH_2), 1.94 (2H, quintet, *J* 7.1, CH_2), 2.56 (2H, t, *J* 7.1, CH_2), 4.22 (2H, t, *J* 5.6, CH_2), 7.00 (1H, d, *J* 7.2, H_{arom}), 7.20-7.23 (2H, m, H_{arom}), 7.36-7.47 (5H, m, H_{arom}), 8.47 (1H, dd, *J* 8.0, 1.5, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 162.4, 138.4, 137.2, 136.9, 123.9, 116.2; CH, 131.8, 131.1, 128.8, 127.7, 127.5, 125.6, 124.6; CH_2, 41.1, 26.7, 21.9, 19.0; *m/z* (%): 275 (M^+, 100), 274 (30), 260 (11), 165 (14); Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09; O, 5.81. Found: C, 82.96; H, 6.14; N, 5.09; O, 5.81.

***General Procedure for the Synthesis of the 2-Alkyl-4-aryl-1,2,3,4-tetrahydroisoquinolines* 30a,c *and* 31a .**
Method A:

A solution of the isoquinolones **20a,c** (0.4 mmol) in MeOH (30 mL) was hydrogenated (20 bar) over 10% paladium-charcoal at 80°C for 15 h. Filtration and evaporation gave the 3,4-dihydrolactame **29a,c** which were pure enough to be used directly in the next step. If required they could be purified by recrystallization in ethanol.

2-Methyl-4-phenyl-1,2,3,4-tetrahydro-1(2H)-isoquinolone **29a**[59] .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 3.06 (3H, s, NCH_3), 3.62-3.69 (1H, dd, *J* 12.4, 7.9, CH_2), 3.73-3.79 (1H, dd, *J* 12.4, 5.4, CH_2), 4.28 (1H, dd, *J* 7.9, 5.4, CH), 6.89-6.93 (1H, m, H_{arom}), 7.12-7.15 (2H, m, H_{arom}), 7.22-7.35 (5H, m, H_{arom}), 8.12-8.18 (1H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 164.6, 140.7, 140.6, 129.4; CH, 131.8, 128.8, 128.4, 128.2, 127.4, 127.2, 55.0; CH_2, 44.0; CH_3, 35.3; *m/z* (%): 237 (M^+, 100), 154 (50), 136 (40).

A solution of the dihydroisoquinolone **29a,c** (0.4 mmol) dissolved in THF (10 mL) was treated at 0°C with $LiAlH_4$ (50 mg, 13 mmol) added by small portions. The mixture was stirred at room temperature for 2 h under Ar and cooled. The excess of hydride was destroyed by the slow addition of AcOEt. The reaction product **30a,c** was filtered on celite^R and evaporated to dryness to leave an oil which was purified by flash column chromatography on silica using AcOEt-hexane (70:30) as eluent and finally recrystallized from acetone-Et_2O.

Method B:
To a solution of the isoquinolones **20a,c** and **21a** (4 mmol) in anhydrous THF (40 mL), $LiAlH_4$ (90 mg, 13 mmol) was added in small portions with cooling at 0°C. The mixture was refluxed for 2 h under Ar, then cooled. The excess of hydride was decomposed with AcOEt. Evaporation left a residue which was extracted with Et_2O-THF to give an unstable enamine. Solid $NaBH_3CN$ (75 mg, 12 mmol) was added to a solution of the residue in anhydrous MeOH (30 mL) containing a few crystals of bromocresol green. The mixture was stirred at room temperatue for 0.25 h and the colour of the solution turned to blue. Methanolic HCl was then added dropwise in order to bring the color back to yellow (pH 4.5). This process was repeated several times until the persistance of the yellow color of the solution. Water (50mL) was added, followed by 10% aqueous NaOH solution (pH = 10) and finally extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water then with brine, dried over Na_2SO_4 and evaporated in vacuo to afford an oil which was purified as previously described in *Method A*.

2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **30a**[45] .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 2.36 (3H, s, NCH_3), 2.58 (1H, dd, *J* 11.5, 8.7, CH_2), 3.04 (1H, ddd, *J* 11.5, 5.8, 1.3, CH_2), 3.62 (1H, d, *J* 14.9, CH_2), 3.77 (1H, d, *J* 14.9, CH_2), 4.28 (1H, t, *J* 6.9, CH), 6.87 (1H, d, *J* 7.4, H_{arom}), 7.03-7.32 (8H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 144.7, 137.2, 135.2; CH, 129.4, 129.1, 128.3, 126.5, 126.3, 126.2, 126.0, 46.0; CH_2, 61.9, 58.5; CH_3, 46.0; *m/z* (%): 223 (M^+, 65), 222 (24), 208 (14), 180 (62), 179 (100), 178 (42), 165 (28).

2-Methyl-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **30c**[48] .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 2.37 (3H, s, NCH_3), 2.60 (1H, dd, *J* 11.5, 8.3, CH_2), 3.01 (1H, dd, *J* 11.5, 5.5, 1.3, CH_2), 3.62-3.68 (2H, m, CH_2), 3.72 (3H, s, OCH_3), 4.12-4.33 (1H, m, CH), 6.85 (1H, d, *J* 7.5, H_{arom}), 7.03-7.22 (7H, m, H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 147.7, 138.6, 137.1, 135.4; CH, 129.3, 129.1, 128.3, 126.3, 126.1, 126.0, 113.6, 46.4; CH_2, 62.2, 59.1; CH_3, 46.2; *m/z* (%): 253 (M^+, 41), 252 (17), 238 (44), 210 (22), 199 (100), 198 (33), 185 (13).

2-Benzyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **31a** .
^{1}H NMR ($CDCl_3$, δ, *J* Hz): 2.70 (1H, dd, *J* 11.5, 7.9, CH_2), 3.10 (1H, dd, *J* 11.5, 5.4, CH_2), 3.70 (2H, s, CH_2), 3.77 (2H, d, *J* 4.0, CH_2), 4.27 (1H, t, *J* 6.7, CH), 6.91 (1H, d, *J* 7.5, H_{arom}), 7.06-7.33 (13H, m,

H_{arom}); ^{13}C NMR ($CDCl_3$, δ, *J* Hz): C, 144.8, 138.2, 137.6, 135.2; CH, 129.5, 129.2, 128.9, 128.3, 128.2, 127.0, 126.3, 126.0, 45.8; CH_2, 62.5, 59.3, 56.4; *m/z* (%): 299 (M^+, 69), 298 (52), 208 (50), 180 (54), 179 (82), 178 (41), 91 (100); Anal. Calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.06; H, 6.94; N, 4.89.

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