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Ketenimine and imine functions linked by an ethylene group. Intramolecular [4+2] cycloadditions leading to imidazo[1,2-*b*]isoquinolines

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Abstract—The intramolecular cyclization of imino-ketenimines where an ethylene or propylene chain is linking the nitrogen atoms of both functionalities is studied. The propylene tethered imino-ketenimines remain unchanged under thermal conditions, whereas their ethylene counterparts undergo a formal [4+2] cycloaddition, in which the ketenimine function acts as all-carbon diene and the imine as dienophile, to yield imidazo[1,2-*b*]isoquinolines. An X-ray crystal structure determination reveals that these cycloadducts incorporate an hydroxyl group at the benzylic carbon C10.

1. Introduction

Ketenimines are nitrogenated heterocumulenes that have attracted considerable interest as substrates for the synthesis of heterocycles, largely through processes involving cycloaddition reactions.[1a] In contrast to alkenes, the cycloaddition chemistry of heterocumulenes is dominated by the 'symmetry forbidden' [2+2] mode.[1b,c]

Over the past several years we have been involved in the study of the participation of ketenimines in formal pericyclic processes. As part of these studies we have reported that when an imine and a ketenimine function are simultaneously and conveniently supported on an allylic or *ortho*-benzylic scaffold, they are able to cycloadd in an intramolecular manner for yielding the corresponding [2+2] adducts.[2] We have also demonstrated that imino-ketenimines in which both reactive functionalities are connected through their nitrogen atoms by an *ortho*-phenylene tether cyclized intramolecularly following different reaction modes, such as [2+2] and [4+2] cycloadditions, and ene-type reactions.[3] These results have proven that the length and type of the tether linking the N atoms of the ketenimine and imine functions are crucial in determining the particular course of the intramolecular cyclization of these imino-ketenimines.

In this context, we were interested in checking the feasibility of [2+2] and/or [4+2] intramolecular cycloadditions of imino-ketenimines bearing ethylene or propylene tethers, more flexible that the rigid or semi-rigid tethers which we have used in previous experiments. Herein we disclose the results obtained from this study in which we have utilized imino-ketenimines bearing two phenyl groups on the terminal carbon atom of their ketenimine functions.

2. Results and discussion

The condensation of 2-azidoethylamine **1**[4] and 3-azidopropylamine **2**[4] with aromatic aldehydes yielded the corresponding imines in nearly quantitative yields.[5] Staudinger reaction[6] of those imines with triphenylphosphane and further treatment of the resulting *P*,*P*,*P*-triphenyl-λ^5-phosphazenes with diphenyl ketene in anhydrous toluene gave rise to solutions of the imino-ketenimines **7** and **8**, which also contained the by-product of the aza-Wittig type reaction,[7] $Ph_3P{=}O$ (Scheme 1).

Heterocumulenes **8** remained unchanged, as followed by IR (C=C=N absorption near 2000 cm^{-1}), when their toluene solutions were heated at reflux temperature overnight, and also under stronger thermal conditions (sealed tube, 140°C, 15 h).

In contrast, when the toluene solutions containing imino-ketenimines **7** were heated under reflux for 2 h the cumulenic band disappeared in their IR spectra. The most

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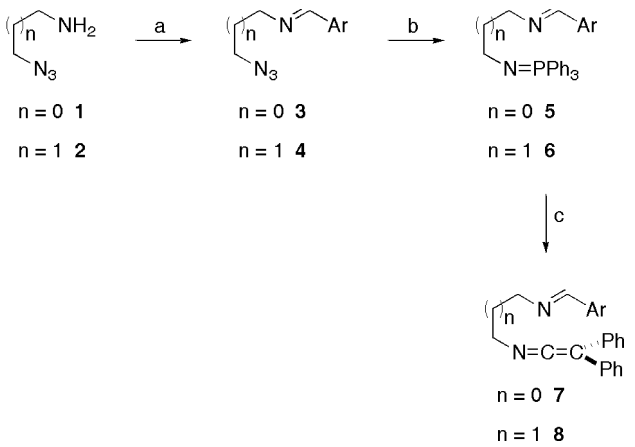
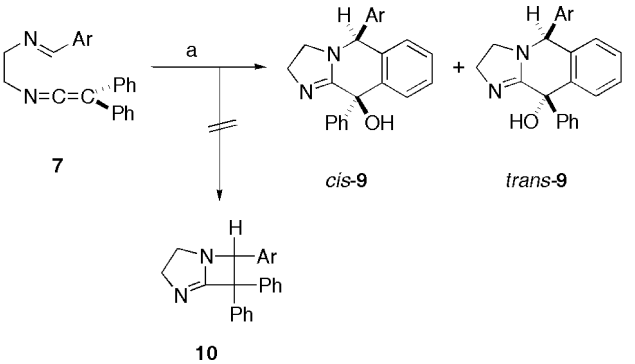


Scheme 1. *Reagents and conditions*: (a) Ar–CHO, Et_2O, $MgSO_4$, room temperature, 12 h; (b) PPh_3, Et_2O, reflux, 2 h; (c) $Ph_2C{=}C{=}O$, toluene, room temperature, 30 min.

significant data in the ^1H NMR spectra of the final reaction mixtures were two singlets in the 5.0–5.5 ppm region, in all cases integrating around a 7:3 relative ratio. In their ^{13}C NMR spectra, these mixtures showed two sets of very close signals of different intensity in the 45–75 ppm region, each set accounting for two methylene, one methine and one quaternary carbon atoms. These preliminary data were consistent with the formation of two diastereoisomers, and, consequently, were not in accord with the formation of the [2+2] cycloadducts **10**, which would only bear a single stereogenic carbon atom. Column chromatography (silica gel, ethyl acetate/methanol, 3:2 v/v) of the final reaction mixtures allowed the separation of the corresponding *cis*- and *trans*- 5-aryl-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo-[1,2-*b*]isoquinolines **9**, in moderate combined yields (40–62%) (Scheme 2) (Table 1).



Scheme 2. *Reagents and conditions*: (a) toluene, reflux, 2 h.

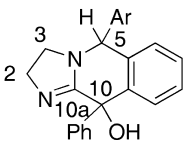
Table 1. Compounds *cis*-**9** and *trans*-**9**

Compound	Ar	*cis*/*trans*[a]	*cis*-**15** (%)[b]	*trans*-**15** (%)[b]
9a	4-Cl–C_6H_4	35:65	17	24
9b	4-Br–C_6H_4	34:66	25	31
9c	4-NC–C_6H_4	33:67	17	23
9d	3,5-$(CH_3O)_2$-C_6H_3	30:70	26	36
9e	4-O_2N–C_6H_4	33:67	25	26

[a] Determined in the final reaction mixtures by ^1H NMR analysis.
[b] After the chromatographic purification.

The structure determination of compounds **9** was not straightforward following their spectroscopic data. Of particular relevance were their mass spectra, which showed molecular ions at 16 units more than those expected from the elemental composition of the starting imino-ketenimines, indicating the incorporation of just one oxygen atom in their structures. Their IR spectra, showing absorptions in the 3200–3100 cm^{-1} zone, but not vibrations attributable to amide C=O groups, seemed indicative of an O–H group. However, in their ^1H NMR spectra the OH proton was obscured by other signals in most of the cases. Their ^{13}C NMR spectra (Table 2) showed that the ethylene group was intact (two methylene carbons in the 49–53 ppm region), the original aldimine carbon must be now an aliphatic methine carbon (62–66 ppm), and the two cumulenic carbons in **7** should be now two new quaternary carbons, one in the aliphatic region, near 72 ppm, and the other around 168 ppm, which most probably belongs to a C=N function. Interestingly, the two phenyl groups in **7** are now non equivalents, and in one of them an original methine carbon is now a quaternary one.

Table 2. Relevant ^{13}C NMR shifts of compounds **9**



Compound	C2 (ppm)	C3 (ppm)	C5 (ppm)	C10 (ppm)	C10a (ppm)
cis-**9a**	50.1	52.1	62.1	72.3	168.6
trans-**9a**	52.3	52.6	65.6	72.1	168.1
cis-**9b**	50.0	52.0	62.1	72.3	168.6
trans-**9b**	52.3	52.6	65.7	72.2	168.2
cis-**9c**	49.9	51.9	62.5	72.3	168.4
trans-**9c**	52.5	53.0	65.7	72.3	168.1
cis-**9d**	49.9	51.8	62.8	72.3	168.8
trans-**9d**	52.3	52.6	66.6	72.0	168.0
cis-**9e**	50.0	51.9	62.2	72.3	168.4
trans-**9e**	52.1	52.8	65.3	72.3	168.2

An X-ray structure determination of the minor isomer of compound **9d** [Ar=3,5-$(CH_3O)_2$–C_6H_3] was definitive for unequivocally establishing the structure of the major and minor diastereoisomers resulting from the thermal treatment of ketenimines **7**. The analyzed minor isomer was found to be the *cis* diastereoisomer of **9d** (Fig. 1), where the hydroxyl group at C10 and the aryl substituent at C5 (C4 and C11 respectively in the crystallographic numbering) present a relative *cis* disposition. By virtue of the closely similar spectroscopic data of both isomers obtained from each ketenimine **7**, the other diastereoisomer, the major one, is assumed to be *trans*-**9** in each case.

Compound *cis*-**9d** crystallized in the triclinic space group. The core tricyclic system presents a slightly folded conformation, with a 170° angle between the mean planes of the fused benzene and imidazole rings. The pyramidalization degree of the N1 nitrogen atom (crystallographic numbering) is considerable ($\sum\alpha$=346.8°).

Inside the unit cell, the molecules are associated forming dimers by intermolecular H bonds between the OH group of

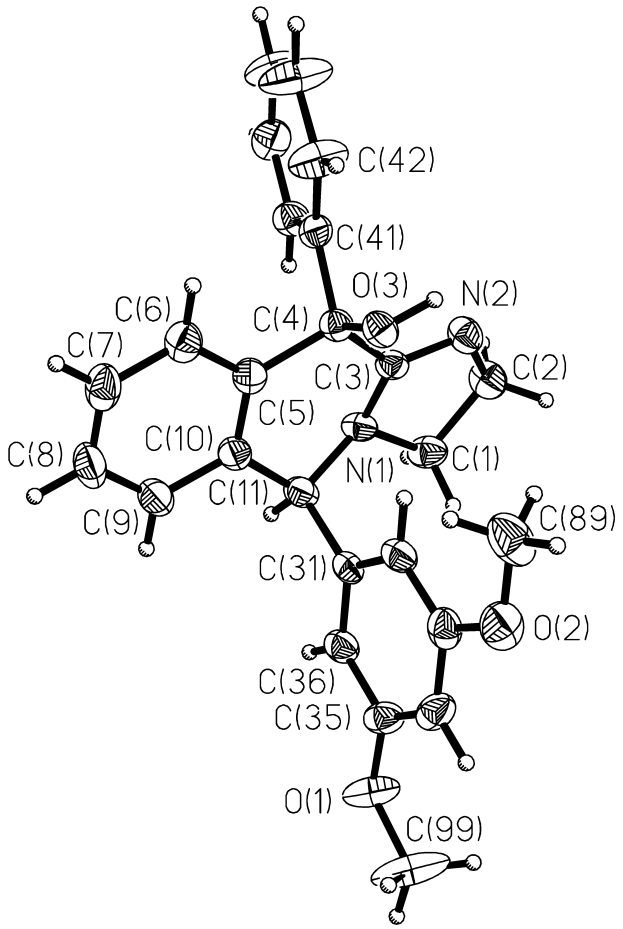


Figure 1. Molecular structure of compound *cis*-**9d** showing the numbering used in the crystallographic work.

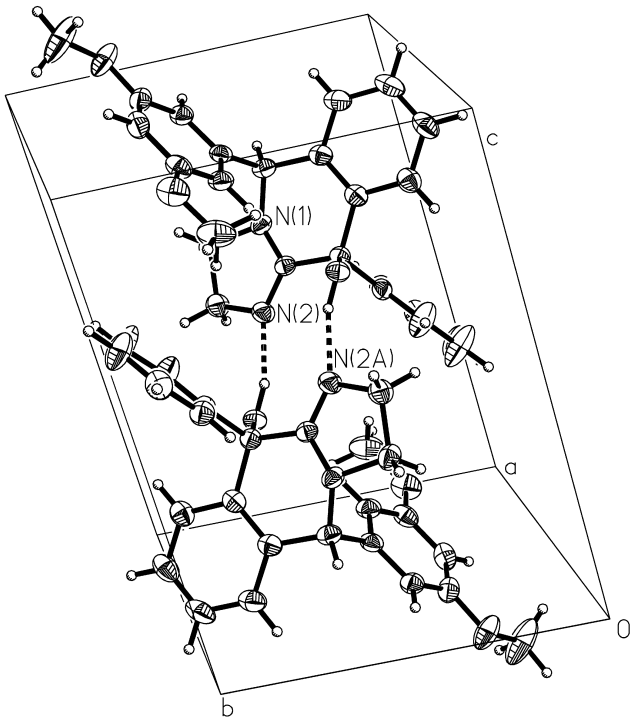
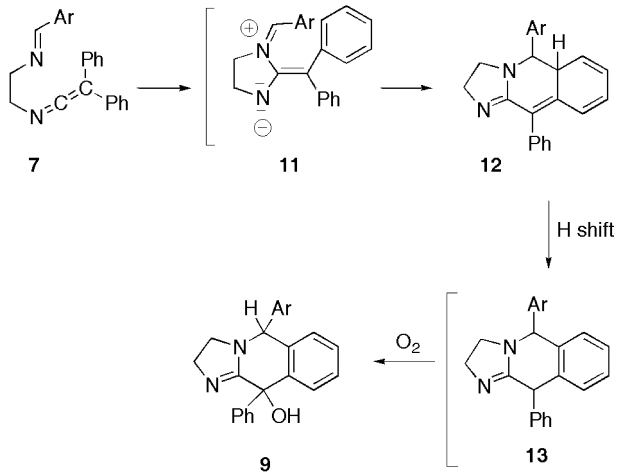


Figure 2. View of the crystal packing and the hydrogen bond interactions in *cis*-**9d**.

a molecule as donor and the N2 atom of the second molecule as acceptor (Fig. 2), with the following bond and angle values: N···H=1.872 Å; N···O=2.743 Å; N···H–O=158.12°.

A reasonable mechanistic explanation for the conversion **7→9**, which takes into account our previous findings in the intramolecular cyclizations of imino-ketenimines leading to formal [4+2] cycloadducts,[3a,b] is the following: addition of the iminic N lone pair on the electrophilic central carbon of the ketenimine function should lead to a zwitterionic intermediate **11**, which then cyclizes to **12** by forming a bond between the iminic carbon atom and one of the *ortho*-carbons of the nearby phenyl group via a 6π electrocyclic ring-closure (Scheme 3). This cyclization path of the intermediates **11** seems to be more favorable than the alternative conrotatory four-electron electrocyclization that would lead to the [2+2] cycloadduct **10**. Although we have not proven unequivocally where the hydroxylic oxygen atom in **9** comes from, we believe that a reasonable mechanistic explanation for the conversion of **12** into the final product **9** starts with an hydrogen shift to the 5,10-dihydro derivative **13**, driven by the rearomatization of the benzene nucleus, which is then spontaneously oxidized into **9** by the action of atmospheric oxygen. We tried very hard to exclude air from the reaction mixture, but probably we did not succeed as the results were invariable, and compounds **9** were still the only reaction products that we could isolate.



Scheme 3. Mechanism for the conversion **7→9**.

To the best of our knowledge, the tricyclic system imidazo[1,2-*b*]isoquinoline has been previously reported only once in the literature,[8] where it has been considered as a 'bridged' version of tolazoline (2-benzylimidazoline), an α-adrenergic blocking agent.

3. Conclusions

Two new types of imino-ketenimines **7** and **8** have been prepared, both bearing flexible carbon chains (ethylene and propylene, respectively) linking the nitrogen atoms of their two functionalities. The thermally induced intramolecular cyclization of compounds **7** yielded new derivatives of the

practically unknown imidazo[1,2-*b*]isoquinoline system by a formal [4+2] cycloaddition process. By contrary, compounds **8** remained unaltered under similar or stronger thermal conditions. In no case products derived from [2+2] cycloaddition reactions between the imine and ketenimine functions of compounds **7** and **8** were obtained.

While both types of imino-ketenimines studied here do not appear to show a common reactivity pattern, the transformations of **7** into **9** contribute to extend significantly the synthetic applicability of this class of bifunctional compounds.

4. Experimental

4.1. General methods

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 or on a Varian Unity-300. Mass spectra were recorded on a Hewlett–Packard 5993C spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 instrument.

4.2. Materials

Compounds 2-azidoethylamine **1**,[4] 3-azidopropylamine **2**[4] and diphenylketene[9] were prepared following previously reported procedures.

4.3. General procedure for the preparation of the *P*,*P*,*P*-triphenyl-λ^5-phosphazenes 5

To a solution of 2-azidoethylamine **1** (0.17 g, 2 mmol) in dry diethyl ether (20 ml) the corresponding aldehyde (2 mmol) and anhydrous $MgSO_4$ (2 g) were added. The reaction mixture was kept at room temperature for 12 h. After separation of the $MgSO_4$ by filtration, the solvent was removed under reduced pressure, and the resulting imine **3** was used in the following step without further purification.

To a solution of the corresponding imine **3** (1 mmol) in dry diethyl ether (4 ml) triphenylphosphane (0.26 g, 1 mmol) was added, and the reaction mixture was stirred at reflux temperature during 2 h. After cooling at room temperature, the solvent was removed under reduced pressure and the resulting material was crystallized from *n*-hexane/diethyl ether 10:1 (v/v).

4.3.1. *N*-[2-(4-Chlorobenzylideneamino)ethyl]-*P*,*P*,*P*-triphenyl-λ^5-phosphazene (5a). Yield 62%, colorless prisms, mp 99°C; IR (Nujol) ν 1647, 1595, 1512, 1435, 1379, 1300, 1205, 1162, 749, 724, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.44 (dt, 2H, J=18.6, 6.3 Hz), 3.81 (t, 2H, J=6.3 Hz), 7.26–7.65 (m, 19H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.4 (d, $^2J_{PC}$=4.5 Hz), 66.4 (d, $^3J_{PC}$=16.7 Hz), 128.3 (d, $^3J_{PC}$=11.5 Hz), 128.7, 129.2, 131.6 (d, $^1J_{PC}$=95.3 Hz), 131.2 (d, $^4J_{PC}$=2.3 Hz), 132.6 (d, $^2J_{PC}$=8.6 Hz), 135.2 (s), 136.1 (s), 160.1; ^{31}P NMR ($CDCl_3$) δ 12.13. Anal. calcd for $C_{27}H_{24}ClN_2P$: C, 73.22; H, 5.46; N, 6.32. Found: C, 73.46; H, 5.29; N, 6.19.

4.3.2. *N*-[2-(4-Bromobenzylideneamino)ethyl]-*P*,*P*,*P*-triphenyl-λ^5-phosphazene (5b). Yield 63%, colorless prisms, mp 91°C; IR (Nujol) ν 1644, 1588, 1439, 1345, 1190, 1120, 841, 749, 724, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.44 (dt, 2H, J=18.6, 6.3 Hz), 3.81 (t, 2H, J=6.3 Hz), 7.35–7.41 (m, 6H), 7.44–7.50 (m, 7H), 7.58–7.65 (m, 6H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.3 (d, $^2J_{PC}$=4.6 Hz), 66.4 (d, $^3J_{PC}$=17.2 Hz), 124.5 (s), 128.4 (d, $^3J_{PC}$=11.5 Hz), 129.5, 131.2 (d, $^4J_{PC}$=2.3 Hz), 131.6, 131.9 (d, $^1J_{PC}$=94.8 Hz), 132.6 (d, $^2J_{PC}$=9.2 Hz), 135.6 (s), 160.2; ^{31}P NMR ($CDCl_3$) δ 11.84. Anal. calcd for $C_{27}H_{24}BrN_2P$: C, 66.54; H, 4.96; N, 5.75. Found: C, 66.76; H, 5.09; N, 5.59.

4.3.3. *N*-[2-(4-Cyanobenzylideneamino)ethyl]-*P*,*P*,*P*-triphenyl-λ^5-phosphazene (5c). Yield 75%, colorless prisms, mp 131–133°C; IR (Nujol) ν 2226, 1644, 1590, 1437, 1345, 1266, 1184, 1119, 749, 724, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.46 (dt, 2H, J=18.5, 6.3 Hz), 3.86 (t, 2H, J=6.3 Hz), 7.34–7.48 (m, 9H), 7.55–7.73 (m, 10H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.1 (d, $^2J_{PC}$=4.6 Hz), 66.4 (d, $^3J_{PC}$=17.2 Hz), 113.4 (s), 118.7 (s), 128.4 (d, $^3J_{PC}$=11.5 Hz), 128.4, 131.3 (d, $^4J_{PC}$=2.7 Hz), 132.4 (d, $^1J_{PC}$=98.2 Hz), 132.3, 132.5 (d, $^2J_{PC}$=9.0 Hz), 140.5 (s), 159.6; ^{31}P NMR ($CDCl_3$) δ 11.84. Anal. calcd for $C_{28}H_{24}N_3P$: C, 77.58; H, 5.58; N, 9.69. Found: C, 77.79; H, 5.42; N, 9.43.

4.3.4. *N*-[2-(3,5-Dimethoxybenzylideneamino)ethyl]-*P*,*P*,*P*-triphenyl-λ^5-phosphazene (5d). Yield 79%, colorless prisms, mp 112°C; IR (Nujol) ν 1645, 1596, 1440, 1342, 1302, 1205, 1151, 841, 751, 722, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (dt, 2H, J=18.4, 6.6 Hz), 3.78–3.88 (m, 8H), 6.48 (t, 1H, J=2.3 Hz), 6.81 (d, 2H, J=2.3 Hz), 7.34–7.47 (m, 9H), 7.58–7.68 (m, 6H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.3 (d, $^2J_{PC}$=4.9 Hz), 55.5, 66.3 (d, $^3J_{PC}$=17.6 Hz), 103.1, 105.6, 128.3 (d, $^3J_{PC}$=11.5 Hz), 131.2 (d, $^4J_{PC}$=2.5 Hz), 132.6 (d, $^2J_{PC}$=9.0 Hz), 131.73 (d, $^1J_{PC}$=95.3 Hz), 138.7 (s), 160.7 (s), 161.5; ^{31}P NMR ($CDCl_3$) δ 11.96. Anal. calcd for $C_{29}H_{29}N_2O_2P$: C, 74.34; H, 6.24; N, 5.98. Found: C, 74.59; H, 6.07; N, 5.86.

4.3.5. *N*-[2-(4-Nitrobenzylideneamino)ethyl]-*P*,*P*,*P*-triphenyl-λ^5-phosphazene (5e). Yield 82%, colorless prisms, mp 116°C; IR (Nujol) ν 1642, 1598, 1515, 1439, 1342, 1312, 1189, 1120, 850, 747, 721, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (dt, 2H, J=18.7, 6.5 Hz), 3.88 (t, 2H, J=6.5 Hz), 7.36–7.48 (m, 9H), 7.57–7.64 (m, 6H), 7.76 (d, 2H, J=8.7 Hz), 8.20 (d, 2H, J=8.7 Hz), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.1 (d, $^2J_{PC}$=4.5 Hz), 66.5 (d, $^3J_{PC}$=16.6 Hz), 123.7, 128.4 (d, $^3J_{PC}$=11.1 Hz), 128.6, 131.3 (d, $^4J_{PC}$=2.5 Hz), 131.7 (d, $^1J_{PC}$=96.2 Hz), 132.5 (d, $^2J_{PC}$=9.1 Hz), 142.1 (s), 148.7 (s), 159.1; ^{31}P NMR ($CDCl_3$) δ 11.99. Anal. calcd for $C_{27}H_{24}N_3O_2P$: C, 73.69; H, 5.11; N, 7.47. Found: C, 73.53; H, 5.33; N, 9.27.

4.4. General procedure for the preparation of the 5-aryl-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinolines 9

To a solution of the corresponding *P*,*P*,*P*-triphenyl-λ^5-phosphazene **5** (1 mmol) in dry toluene (15 ml) a solution of

diphenylketene (0.19 g, 1 mmol) in the same solvent (2 ml) was added. The reaction mixture was stirred first 30 min at room temperature and then at reflux temperature for 2 h. After cooling, the toluene was removed under reduced pressure and the resulting solid was chromatographed on a silica gel column using ethyl acetate/methanol as eluent (3:2, v/v).

4.4.1. *cis*-5-(4-Chlorophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*cis*-9a). Yield 17%, colorless prisms (Et_2O), mp 216–218°C; IR (Nujol) ν 3083, 1608, 1598, 1489, 1463, 1408, 1277, 1187, 1091, 928, 751, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.13–3.29 (m, 2H), 3.55–3.78 (m, 2H), 5.26 (s, 1H), 6.67 (d, 1H, J=7.8 Hz), 7.13 (td, 1H, J=7.7, 1.5 Hz), 7.21–7.31 (m, 7H), 7.35–7.38 (m, 3H), 7.62 (dd, 1H, J=8.1, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 50.1, 52.1, 62.1, 72.3 (s), 125.8, 127.0, 127.2, 127.5, 127.6, 128.3, 128.4, 129.3, 130.3, 134.3 (s), 135.3 (s), 138.2 (s), 139.4 (s), 145.7 (s), 168.6 (s); MS *m/z* (%): 376 (M+2, 33), 375 (M+1, 60), 374 (M, 62), 263 (100). Anal. calcd for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.11; N, 7.47. Found: C, 73.83; H, 5.19; N, 7.54.

4.4.2. *trans*-5-(4-Chlorophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*trans*-9a). Yield 24%, colorless prisms ($CHCl_3/Et_2O$), mp 164°C; IR (Nujol) ν 3232, 1620, 1275, 1253, 1183, 1167, 1090, 1028, 927, 759, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.16–3.33 (m, 1H), 3.53–3.67 (m, 2H), 3.74–3.91 (m, 1H), 5.16 (s, 1H), 5.68 (br s, 1H), 6.95–7.00 (m, 3H), 7.15–7.37 (m, 9H), 7.74 (d, 1H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 52.3, 52.6, 65.6, 72.1 (s), 126.5, 126.6, 127.5, 127.7, 127.8, 127.9, 128.0, 128.7, 129.2, 133.6 (s), 134.3 (s), 137.4 (s), 140.1 (s), 145.8 (s), 168.1 (s); MS *m/z* (%): 376 (M+2, 22), 375 (M+1, 38), 374 (M, 70), 357 (100). Anal. calcd for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.11; N, 7.47. Found: C, 73.74; H, 5.25; N, 7.40.

4.4.3. *cis*-5-(4-Bromophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*cis*-9b). Yield 25%, colorless prisms (Et_2O), mp 200–203°C; IR (Nujol) ν 3200, 1599, 1280, 1187, 1071, 1011, 808, 768, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.14–3.28 (m, 2H), 3.50–3.73 (m, 2H), 5.23 (s, 1H), 6.65 (d, 1H, J=7.5 Hz), 7.13 (td, 1H, J=7.5, 1.2 Hz), 7.18–7.31 (m, 6H), 7.34–7.38 (m, 2H), 7.52 (d, 2H, J=8.4 Hz), 7.65 (dd, 1H, J=7.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 50.0, 52.0, 62.1, 72.3 (s), 122.4 (s), 125.8, 126.9, 127.2, 127.5, 127.6, 128.3, 128.4, 130.6, 132.2, 135.1 (s), 138.2 (s), 139.9 (s), 145.7 (s), 168.6 (s); MS *m/z* (%): 421 (M+2, 20), 420 (M+1, 20), 419 (M, 30), 401 (100). Anal. calcd for $C_{23}H_{19}BrN_2O$: C, 65.88; H, 4.57; N, 6.68. Found: C, 65.70; H, 4.61; N, 6.57.

4.4.4. *trans*-5-(4-Bromophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*trans*-9b). Yield 31%, colorless prisms (Et_2O), mp 138–140°C; IR (Nujol) ν 3187, 1625, 1277, 1140, 1073, 1012, 929, 761, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15–3.25 (m, 1H), 3.46–3.63 (m, 2H), 3.65–3.86 (m, 1H), 5.14 (s, 1H), 6.91 (d, 2H, J=8.4 Hz), 6.96 (d, 1H, J=7.8 Hz), 7.14–7.38 (m, 9H), 7.74 (dd, 1H, J=8.1, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 52.3, 52.6, 65.7, 72.2 (s), 121.8 (s), 126.7, 127.4, 127.6, 127.8, 127.9, 128.1, 129.6, 131.7, 134.2 (s), 137.5 (s), 140.7 (s), 145.8 (s), 168.2 (s); MS *m/z* (%): 421 (M+2, 48), 420 (M+1, 37), 419 (M, 50), 401 (100). Anal. calcd for $C_{23}H_{19}BrN_2O$: C, 65.88; H, 4.57; N, 6.68. Found: C, 65.95; H, 4.49; N, 6.76.

4.4.5. *cis*-5-(4-Cyanophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*cis*-9c). Yield 17%, colorless prisms (Et_2O), mp 183–185°C; IR (Nujol) ν 2228, 1607, 1596, 1277, 1189, 1177, 1134, 769, 721, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03–3.33 (m, 2H), 3.52–3.75 (m, 2H), 5.32 (s, 1H), 6.60 (d, 1H, J=7.6 Hz), 7.10–7.37 (m, 7H), 7.45 (d, 2H, J=8.1 Hz), 7.61–7.71 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 49.9, 51.9, 62.5, 72.3 (s), 112.5 (s), 118.4 (s), 125.8, 126.8, 127.6, 127.7, 128.4, 128.5, 129.6, 132.9, 134.2 (s), 138.2 (s), 145.6 (s), 146.2 (s), 168.4 (s); MS *m/z* (%): 365 (M, 20), 348 (100). Anal. calcd for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50. Found: C, 79.01; H, 5.19; N, 11.43.

4.4.6. *trans*-5-(4-Cyanophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*trans*-9c). Yield 23%, colorless prisms (CH_2Cl_2/Et_2O), mp 151–153°C; IR (Nujol) ν 3180, 2227, 1623, 1281, 1256, 1145, 1028, 928, 770, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22–3.32 (m, 1H), 3.53–3.68 (m, 2H), 3.80–3.94 (m, 1H), 5.24 (s, 1H), 7.02 (d, 1H, J=7.7 Hz), 7.10 (d, 2H, J=8.2 Hz), 7.19–7.46 (m, 9H), 7.81 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 52.5, 53.0, 65.7, 72.3 (s), 111.8 (s), 118.5 (s), 126.6, 126.8, 127.8, 127.9, 128.0, 128.2, 128.4, 132.4, 133.6 (s), 137.6 (s), 145.0 (s), 146.7 (s), 168.1 (s); MS *m/z* (%): 365 (M, 25), 348 (100). Anal. calcd for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.95; H, 5.29; N, 11.69.

4.4.7. *cis*-5-(3,5-Dimethoxyphenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*cis*-9d). Yield 26%, colorless prisms (CH_2Cl_2/Et_2O), mp 223°C; IR (Nujol) ν 3170, 1614, 1601, 1296, 1274, 1207, 1163, 1067, 839, 772, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23–3.31 (m, 2H), 3.55–3.73 (m, 2H), 3.75 (s, 6H), 5.18 (s, 1H), 6.42 (t, 1H, J=2.4 Hz), 6.47 (d, 2H, J=2.4 Hz), 6.79 (d, 1H, J=7.8 Hz), 7.13 (td, 1H, J=7.5, 1.2 Hz), 7.18–7.31 (m, 4H), 7.35–7.39 (m, 2H), 7.61 (d, 1H, J=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 49.9, 51.8, 55.5, 62.8, 72.3 (s), 100.1, 106.8, 125.9, 126.9, 127.0, 127.3, 127.4, 128.0, 128.3, 135.3 (s), 138.3 (s), 143.1 (s), 145.9 (s), 161.3 (s), 168.8 (s); MS *m/z* (%): 400 (M, 23), 382 (100). Anal. calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 75.13; H, 6.19; N, 6.97.

4.4.8. *trans*-5-(3,5-Dimethoxyphenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*trans*-9d). Yield 36%, colorless prisms (Et_2O), mp 177–180°C; IR (Nujol) ν 3200, 1612, 1599, 1352, 1292, 1262, 1208, 1152, 1065, 770, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26–3.36 (m, 1H), 3.58–3.79 (m, 8H), 3.94–4.04 (m, 1H), 5.12 (s, 1H), 6.29 (d, 2H, J=2.4 Hz), 6.33 (t, 1H, J=2.4 Hz), 7.09 (d, 1H, J=8.1 Hz), 7.21–7.29 (m, 4H), 7.34 (t, 1H, J=7.5 Hz), 7.42–7.45 (m, 2H), 7.65 (dd, 1H, J=7.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 52.3, 52.6, 55.3, 66.6, 72.0 (s), 99.9, 105.9, 126.7, 126.8, 127.5, 127.8, 127.9, 128.1, 134.5 (s), 136.9 (s), 144.2 (s), 146.3 (s), 161.0 (s), 168.0 (s); MS *m/z* (%): 400 (M, 100). Anal. calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.90; H, 5.99; N, 7.11.

4.4.9. *cis*-5-(4-Nitrophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*cis*-9e). Yield 25%, colorless prisms (Et_2O), mp 186–187°C; IR (Nujol) ν 3176, 1613, 1595, 1520, 1264, 1186, 1166, 927, 776, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11–3.17 (m, 1H), 3.22–3.31 (m, 1H), 3.52–3.73 (m, 2H), 5.40 (s, 1H), 6.62 (d, 1H, J=7.5 Hz), 7.14 (td, 1H, J=7.3, 1.2 Hz), 7.22–7.39 (m, 6H), 7.53 (d, 2H, J=8.7 Hz), 7.64 (dd, 1H, J=7.8, 0.9 Hz), 8.26 (d, 2H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 50.0, 51.9, 62.2, 72.3 (s), 124.4, 125.8, 126.8, 127.6, 127.7, 127.8, 128.4, 128.7, 129.7, 134.1 (s), 138.2 (s), 145.5 (s), 148.0 (s), 148.1 (s), 168.4 (s); MS *m*/*z* (%): 385 (M, 31), 262 (100). Anal. calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.54; H, 4.90; N, 11.04.

4.4.10. *trans*-5-(4-Nitrophenyl)-10-hydroxy-10-phenyl-2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (*trans*-9e). Yield 26%, colorless prisms (Et_2O), mp 191°C; IR (Nujol) ν 3210, 1625, 1597, 1520, 1348, 1266, 1143, 1013, 763, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31–3.96 (m, 4H), 5.32 (s, 1H), 5.48 (br s, 1H), 7.03 (d, 1H, J=7.6 Hz), 7.12–7.45 (m, 9H), 7.86 (d, 1H, J=7.6 Hz), 7.98 (d, 2H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 52.1, 52.8, 65.3, 72.3 (s), 123.8, 126.6, 126.8, 127.9, 128.0, 128.2, 128.4, 128.5, 133.3 (s), 137.6 (s), 144.9 (s), 147.4 (s), 148.4 (s), 168.2 (s); MS *m*/*z* (%): 385 (M, 37), 262 (100). Anal. calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.55; H, 4.81; N, 11.13.

4.5. X-Ray diffraction study

Crystallographic data for the structure *cis*-**9d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 210719. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

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