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New highlights in the synthesis and reactivity of 1,4-dihydropyrazine derivatives

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ABSTRACT

In the course of our investigations on the synthesis of original nitrogen heterocyclic derivatives, we were interested in the synthesis and study of original 1,4-dihydropyrazine rings. To this aim the desired bis-vinylphosphate derivative was prepared from *N*-Boc piperazine-2,5-dione and then was engaged in palladium catalyzed reactions (reduction, Suzuki and Stille cross-coupling reactions). The 1,4-dihydropyrazine and the corresponding 2,5-disubstituted derivatives were obtained in fair to good yields and were then functionalized under anionic conditions. Aromatization into 1,4-pyrazines was investigated in a second stage.

1. Introduction

Identifying improved methods for heterocycle synthesis and essentially giving access to new heterocyclic scaffolds are of prime importance.[1] It is of prime importance to identify and improve the methods that best allow to synthesize heterocycles, and to give access to new heterocyclic scaffolds. As part of our interest in the application of readily available enol phosphates in the synthesis of new nitrogen heterocyclic compounds, we would like to report herein the first results of our investigations on 1,4-dihydropyrazine derivatives. The 1,4-dihydropyrazine ring system has attracted much interest as a structural unit, this is mostly due to the fact that cyclic 8π-electron conjugation has the property to give rise to the so-called 'antiaromatic' character. 1,4-Dihydropyrazine derivatives also constitute interesting electron donors in conducting charge-transfer complexes and magnetic materials.[2,4a,b] This ring system (Fig. 1) is a key structural feature of some redox-active biological molecules such as 1,5-dihydroflavin coenzymes[3] and of several marine luciferins.[4] This 1,4-diazine privileged scaffold is encountered as piperazine moieties[5] in several marine natural products showing cytotoxic and antitumor properties (i.e., dragmacidin A and B) or as pyrazine units[6] in some naturally occurring compounds. Pyrazines have been widely used in the fields of medicinal chemistry for the elaboration of the skeletons of biologically active sites[7] and in metal coordination chemistry as *N*,*N*′-bidentate ligands.[8] Despite the relevant potential of pyrazine, its chemistry[9] is

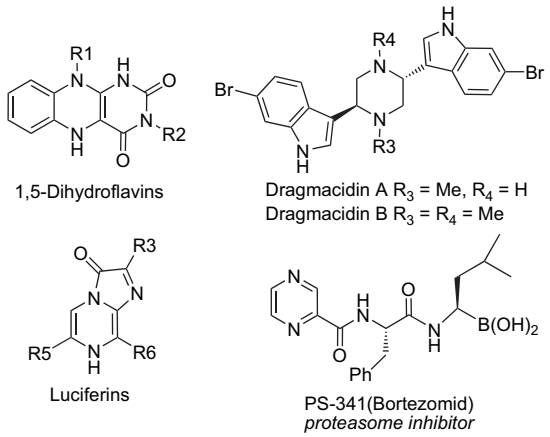

Figure 1.

under-developed in comparison with that of its isomers and pyridine. Given that a non-flexible dimerization approach is most often reported for the preparation of substituted 1,4-dihydropyrazines[10] and pyrazines, the development of new methods for their syntheses is still a great challenge.

We have recently outlined the synthesis of various 1,4-dihydropyridines **A**[11a,b] and 1,4-oxazines **B**[11c] (Fig. 2) from imide derivatives by way of Pd-catalyzed coupling reactions of the corresponding bisvinylphosphates. The first part of the work reported here is devoted to the convenient use of our strategy in the synthesis of 1,4-dihydropyrazines **C** (including R1=R2=H). Functionalization of the latter under anionic conditions as well as aromatization into pyrazines **D** is examined in a second stage.

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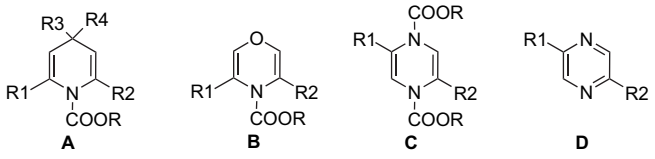


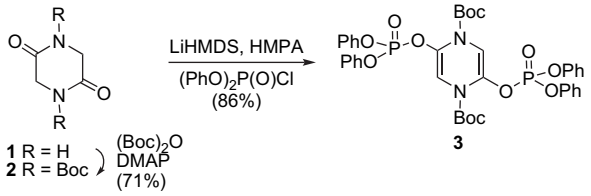
R = *t*-Bu, Ph
R_1, R_2 = aryl, heteroaryl, alcenyl, alcynyl, acyl, alkyl, hydroxyalkyl
R_3, R_4 = alkyl, allyl, hydroxyalkyl

Figure 2. Original substituted heterocycles accessible via our method.

2. Results and discussion

2.1. Synthesis and reactivity of 1,4-dihydropyrazines

In connection with our efforts to develop synthetic routes to nitrogen containing derivatives, we have undertaken a research program directed toward expanding the range of lactam-derived enol phosphates available to the organist chemist.[11,12] Taking advantage of our previous results, the original 1,4-dihydropyrazine bisvinylphosphate **3**[13] was efficiently synthesized in good yields from piperazine-2,5-dione (Scheme 1). It is worth pointing out that the presence of an electron withdrawing group on the nitrogen atoms (*tert*-butoxycarbonyl group) facilitates the stabilization of the 1,4-dihydropyrazine system. In these basic conditions at −78 °C, we didn't observe any transannular rearrangement of the enolate intermediate.[14]



Scheme 1. Preparation of the 1,4-dihydropyrazine bisvinylphosphate **3**.

In order to obtain 'symmetrical' 2,5-disubstituted 1,4-dihydropyrazines, palladium coupling reactions were then investigated. The Stille-coupling reaction was performed with various tin reagents in the presence of catalytic $Pd(PPh_3)_4$ and anhydrous LiCl in refluxing THF for 1 h and afforded the desired compounds **4a**–**d** in fair to good yields (Table 1, entries 1–4).[15] One of the attractive features of our approach lies in its inherent versatility since a wide range of reactants could be used. A Pd-catalyzed Suzuki–Miyaura coupling reaction was then studied.[16] By applying classic conditions, a range of 2,5-disubstituted 1,4-dihydropyrazine **4e**–**h** were thus isolated in satisfying yields (Table 1, entries 5–8).

With these results in hand, it was deemed appropriate to investigate the reduction of the vinyl phosphate groups. To the best of our knowledge, so far, there has been no description of the 1,4-dihydropyrazine **5** in the literature. By treatment of the bisvinylphosphate **3** with triethylammonium formate, palladium acetate, and triphenylphosphine in THF,[11a] the basic heterocyclic system **5** was isolated in moderate yield (45% yield). Fair yields (inferior to 20%) were also obtained by testing other conditions (different sources of palladium(0) or various hydride sources: Et_3Al/$Pd(PPh_3)_4$,[18] Et_3SiH/$Pd(PPh_3)_4$[19]). The slight instability of this non-substituted 1,4-dihydropyrazine system could explain why the yield was so moderate. However, the original derivative **5** might hopefully find some useful applications as a building block in heterocyclic and medicinal chemistry (Scheme 2).

With a view to valorize this 1,4-dihydropyrazine scaffold and to access more complex heterocycles, we then focused on studying their reactivity toward organometallic reagents. Taking into account our previous results in the 1,4-oxazine series,[11c] we investigated the functionalization of these derivatives under anionic conditions. This method, which offers the opportunity to easily introduce various substituents onto these structures, should be particularly useful to develop libraries for the development of biologically relevant 1,4-diazine derivatives. Hence, we decided to introduce various substituents at C-3 on the 2,5-diphenyl-1,4-dihydropyrazine **4e**, chosen as a model compound, or at C-2 on the 1,4-dihydropyrazine **5**. The best results were obtained using LDA as a base at −78 °C in the presence or absence of HMPA.[20] The 2-lithio derivatives were trapped by a range of electrophiles (5 equiv) leading to the required original trisubstituted derivatives **6a**–**e** or monosubstituted compound **7** in fair to good yields (Table 2). This strategy allowed easy access to a great diversity of 1,4-dihydropyrazines since further transformations of the resulting compound **6** or **7** could easily be envisaged.

2.2. Access to 2,5-disubstituted pyrazines

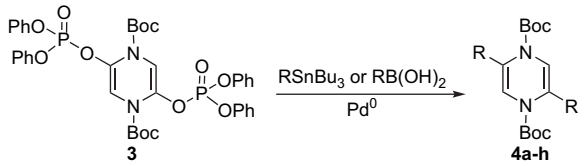
We next focused on pyrazines, which are widely used intermediates in medicinal chemistry.[7] With the aim to prepare various derivatives of this type, we examined the behavior of 1,4-dihydropyrazine derivatives under acidic conditions (Table 3). Treatment of 2,5-disubstituted dihydropyrazines with anhydrous TFA in dichloromethane for 2 h afforded in fair to good yields the corresponding pyrazines **8a**–**d**, previously undescribed that could not otherwise be easily accessible.[21] By substituting TMSI for TFA, the reaction time was improved (30 min instead of 2 h). However, a low reactivity was encountered in some cases (Table 3, entries 2 and 4) during this deprotection/aromatization step, which was probably due to the lack of solubility of some intermediates in organic solvents.

Given that the fluorescence properties of pyrazines are known,[22] the photophysical properties of the previously synthesized molecules were examined in $CHCl_3$ solution by UV–vis and fluorescence spectroscopies. The 2,5-disusbtituted pyrazines considered exhibited clear fluorescence properties that are reported in Table 4. Further studies aiming to develop new molecular probes by anchoring various substituted pyrazine units to more complex molecules are currently being explored in our laboratory. This approach should provide significant facts that could lead to the development of highly selective and sensitive chemical sensors with use of pyrazine derivatives.

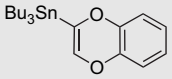
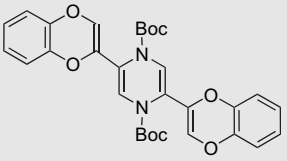
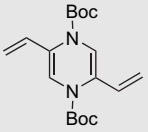
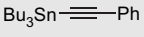
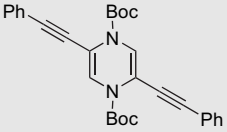
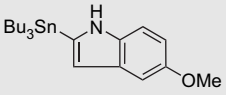
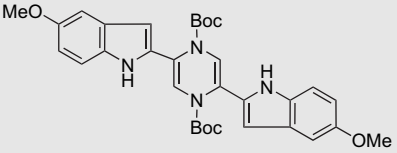
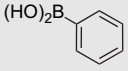
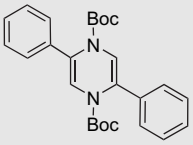
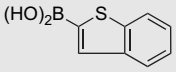
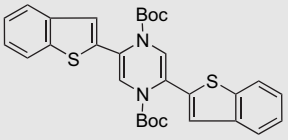
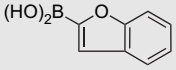
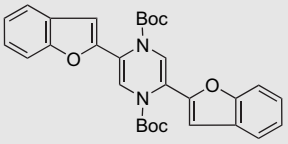
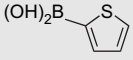
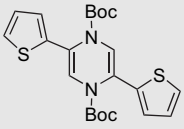
3. Conclusion

To conclude, the procedures described here represent a convenient access to 1,4-dihydropyrazine and pyrazine derivatives via vinyl phosphate intermediates. Few methods are available for their syntheses, however, a review of the literature revealed that if the parent molecules are easily prepared on the other hand the corresponding substituted compounds are frequently difficult to obtain. Subsequent to our study, it is worth noting that the presence of different functional groups in many positions of these heterocycles makes such compounds useful for further structural modifications and suitable as intermediates for more complex structures or biologically active compounds. Besides the mild and simple conditions of this procedure, its versatility allows to access valuable combinatorial libraries. Further studies are now underway in our laboratory with a view to exploit the potentiality offered by this original heterocyclic system.

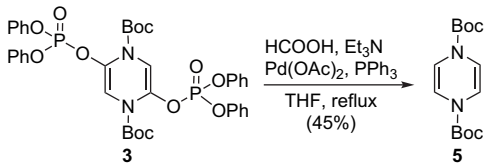
Table 1
Suzuki and Stille coupling reactions on the bisvinylphosphate **3**



3 **4a-h**

Entry	Reagents	Products (yield %)
1[a]		 **4a** (80)
2[a]		 **4b** (68)
3[a]		 **4c** (41)
4[a]		 **4d** (25)
5[b]		 **4e** (72)
6[b]		 **4f** (87)
7[b]		 **4g** (94)
8[b]		 **4h** (61)

[a] Conditions: 10 mol % $Pd(PPh_3)_4$, 5 equiv $RSnBu_3$, 6 equiv LiCl, THF, 1 h, reflux.[17]
[b] Conditions: (i) 10 mol % $PdCl_2(PPh_3)_2$, THF, rt, 15 min; (ii) 5 equiv $RB(OH)_2$, 3 equiv Na_2CO_3 2 M, EtOH, reflux, 2 h.



3 **5**

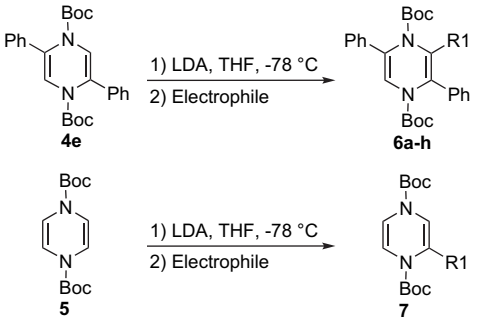
Scheme 2. Catalyzed palladium reduction of the bisvinylphosphate **3**.

4. Experimental part

4.1. General

All the solvents used for reactions were distilled prior to use according to the standard procedures. THF was distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane was distilled over CaH_2 and methanol from magnesium

Table 2
Functionalization of the 1,4-dihydropyrazines **4e** and **5**

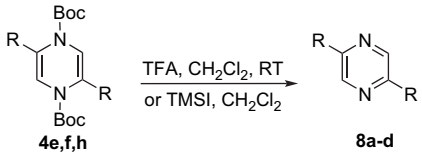


Entry	Electrophiles	Products (Yield %)
1[a]	Bu_3SnCl	**6a** (62)
2[a]	Me_3SiCl	**6b** (63)
3[a]	CHO, MeO, OMe, OMe	**6c** (75)
5[a]	DMF	**6d** (85)
6[a]	$NCCO_2Me$	**6e** (60)
7[b]	$NCCO_2Me$	**7** (65)

[a] Conditions: (i) 2.5 equiv LDA, THF, −78 °C, 1 h; (ii) 2 equiv HMPA, −78 °C, 10 min; (iii) 5 equiv electrophile, −78 °C, 30 min.
[b] Conditions: (i) 1.2 equiv LDA, THF, −78 °C, 20 min; (ii) 5 equiv electrophile, −78 °C, 30 min.

turnings. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F_{254}) plates. The compounds were visualized by UV irradiation and/or spraying with a solution of potassium permanganate, followed by charring at 150 °C. Column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of the compounds were recorded on an Infrared Fourier Transform spectrophotometer using NaCl plates or KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a spectrometer at 250 MHz or at 400 MHz. Chemical shifts are given in parts per million from tetramethylsilane (TMS) as an internal standard. Either an ionspray or an electronic impact method was used to record mass spectra. Petroleum ether (P.E.) had a 40–60 °C boiling point range.

Table 3
Access to 2,5-disubstituted pyrazines **8a–d**[a]



Entry	Reagents	Products (Yield %)
1	**4e**	**8a**[18] (100)
2	**4f**	**8b** (64)
3	**4h**	**8c** (80)
4	**4d**	**8d** (20)

[a] Conditions: 10 equiv TFA, CH_2Cl_2, rt, 2 h or 5 equiv TMSI, CH_2Cl_2, rt, 30 min.

Table 4
Relative fluorescence intensities of pyrazines **8a–c**: maximum absorption wavelength (λ_{abs}), molar absorption coefficients (ε), maximum emission wavelength (λ_{em}), and fluorescence quantum yield (Φ_f)

Entry	Compounds	λ_{abs} nm	ε 10^3 M^{-1} cm^{-1}	log ε	λ_{em} nm	Φ_f
1[a]	**8a**	326	12	4.1	374	0.05
2[a]	**8b**	367	94.2	5.0	417	0.15
3[a]	**8c**	390	8.30	3.9	418 433	0.40

[a] Solution in $CHCl_3$: **8a**: $c=7.76\times10^{-5}$ mol L^{-1}; **8b**: $c=8.20\times10^{-6}$ mol L^{-1}; **8c**: $c=5.23\times10^{-5}$ mol L^{-1}.

4.2. Preparation of the *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-(diphenyloxy-phosphoryloxy)-[1,4]-dihydropyrazine (3)

A solution of LiHMDS (1 M in hexane, 7.9 mL, 7.95 mmol, 2.5 equiv) in THF (20 mL) was cooled to −78 °C under argon. Subsequently, a solution of *N*,*N*-bis-(*tert*-butoxycarbonyl)-piperazine-2,5-dione **2**[23] (1.00 g, 3.18 mmol, 1 equiv) in THF (5 mL), distilled diphenyl chlorophosphate (1.40 mL, 6.67 mmol, 2.1 equiv), and distilled HMPA (1.50 mL, 8.90 mmol, 2.8 equiv) were added dropwise over 5 min. After 1 h at −78 °C, water (50 mL) was added and the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 7:3) to give **3** (2.13 g, 86%) as a white solid; mp=75–76 °C. IR (cm^{-1}): 2980, 1735, 1596, 1489, 1346 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 18H), 6.36 (d, $J_{H-P}=2.5$ Hz, 2H), 7.16 (t, $J=7.5$ Hz, 4H), 7.24–7.33 (m, 16H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 27.7 (q), 83.2 (s), 107.7 (d, $J^3_{C-P}=5$ Hz), 107.9 (d), 119.7 (d), 119.8 (d), 125.6 (d), 129.7 (d), 134.8 (s, $J^2_{C-P}=10.5$ Hz), 135.0 (s), 148.9 (s), 149.8

(s, J^2_{C-P}=7.5 Hz), 150.0 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{38}H_{40}N_2O_{12}^{23}NaP_2$: 801.1954; found 801.1948.

4.3. General procedure (A) for Stille-type coupling reactions

4.3.1. N,N-Bis-(tert-butoxycarbonyl)-2,5-di(benzo[b][1,4]dioxin-3-yl)-[1,4]-dihydropyrazine (**4a**)

To a stirred solution of bisvinylphosphate **3** (0.30 g, 0.38 mmol, 1 equiv) in THF (5 mL), benzodioxin-2-yl-tributyltin (0.561 g, 1.90 mmol, 5 equiv) and LiCl (0.096 g, 2.28 mmol, 6 equiv) were added under argon. Then, the flask was evacuated and backfilled with argon three times. Under argon, $Pd(PPh_3)_4$ (0.048 g, 0.04 mmol, 10 mol %) was added, and the mixture was refluxed for 1 h. After cooling, the reaction mixture was filtered through Celite and was washed with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) to give **4a** (0.166 g, 80%) as a yellow oil. IR (cm^{-1}): 3432, 1705, 1494 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.43 (s, 18H), 6.13 (s, 2H), 6.49 (s, 2H), 6.64–6.68 (m, 4H), 6.81–6.85 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.0 (q), 83.0 (s), 109.5 (d), 116.2 (d), 118.2 (d), 122.5 (d), 124.3 (d), 124.7 (d), 131.8 (s), 142.0 (s), 142.4 (s), 146.2 (s), 149.7 (s). MS (IS): m/z=547 [MH]$^+$, 569 [M+Na]$^+$.

4.3.2. N,N-Bis-(tert-butoxycarbonyl)-2,5-di(vinyl)-[1,4]-dihydropyrazine (**4b**)

Compound **4b** was prepared according to the general procedure (A) reported for **4a** starting from **3** (0.300 g, 0.38 mmol, 1 equiv) and tributylvinyltin (0.610 mL, 1.90 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 9:1) afforded **4b** as a white solid; mp=119–120 °C. IR: 3434, 1702, 1643, 1368, 1340, 1163, 1133, 765 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.49 (s, 18H), 5.10 (d, J=11.0 Hz, 2H), 5.30 (d, J=17.0 Hz, 2H), 6.22 (dd, J=17.0 and 11.0 Hz, 2H), 6.38 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.3 (q), 82.4 (s), 113.7 (t), 118.7 (d), 128.7(s), 128.9 (s), 129.7 (d), 150.2 (s). MS (IS): m/z=335 [MH]$^+$, 357 [M+Na]$^+$. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.74; H, 7.79; N, 8.19.

4.3.3. N,N-Bis-(tert-butoxycarbonyl)-2,5-bis-(2-phenylethynyl)-[1,4]-dihydropyrazine (**4c**)

Compound **4c** was prepared according to the general procedure (A) reported for **4a** starting from **3** (0.300 g, 0.38 mmol, 1 equiv) and tributylphenyltin (0.460 mL, 0.65 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) afforded **4c** (0.051 g, 41%) as a yellow solid; mp=160–161 °C. IR: 2979, 1724, 1369, 1289, 1153, 1105, 756 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.40 (s, 18H), 6.56 (s, 2H), 7.18–7.21 (m, 5H), 7.30–7.34 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.3 (s), 82.1 (s), 83.0 (s), 90.3 (s), 111.3 (s), 122.7 (s), 125.0 (d), 128.4 (s), 128.5 (s), 133.7 (s), 151.1 (s). MS (IS): m/z=483 [MH]$^+$, 495 [M+Na]$^+$.

4.3.4. N,N-Bis-(tert-butoxycarbonyl)-2,5-bis-(5-methoxy-1H-indol-2-yl)-[1,4]-dihydropyrazine (**4d**)

Compound **4d** was prepared according to the general procedure (A) reported for **4a** starting from **3** (0.149 g, 0.19 mmol, 1 equiv) and 5-methoxy-1*H*-indol-2-yl-tributyltin (0.420 mL, 0.96 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) afforded **4d** (0.027 g, 25%) as a yellow solid; mp=155–156 °C. IR: 3404, 1681, 1640 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6) δ: 1.19 (s, 18H), 3.80 (s, 6H), 6.45 (s, 2H), 6.46 (s, 2H), 6.76 (dd, J=9.0 and 2.5 Hz, 2H), 7.05 (d, J=2.50 Hz, 2H), 7.28 (d, J=9.0 Hz, 2H), 10.35 (se, 2H, NH). ^{13}C NMR (100.6 MHz, acetone-d_6) δ: 28.8 (q), 59.7 (q), 83.3 (s), 102.4 (d), 103.4 (d), 113.4 (d), 114.0 (d), 120.3 (d), 126.9 (s), 130.7 (s), 133.7 (s), 134.3 (s), 151.8 (s), 156.2 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{32}H_{36}N_4O_6^{23}Na$: 595.2532; found 595.2538.

4.4. General procedure (B) for Suzuki–Miyaura-type coupling reactions

4.4.1. N,N-Bis-(tert-butoxycarbonyl)-2,5-diphenyl-[1,4]-dihydropyrazine (**4e**)

To a solution of bisvinylphosphate **3** (0.300 g, 0.38 mmol, 1 equiv) in THF (5 mL) under argon, $PdCl_2(PPh_3)_2$ (0.027 g, 0.04 mmol, 10 mol %) was added. The flask was evacuated and backfilled with argon three times, and the mixture was stirred for 15 min. Then, phenylboronic acid (0.231 g, 1.90 mmol, 5 equiv), Na_2CO_3 2 M (1.35 mL, 2.7 mmol, 3 equiv), and a few drops of EtOH were added. The mixture was refluxed for 2 h. After cooling, the reaction mixture was filtered through Celite and was washed with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) to give **4e** (0.133 g, 72%) as a white solid; mp=188–189 °C. IR: 2980, 1708, 1670, 1489 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.07 (s, 18H), 6.46 (s, 2H), 7.20–7.35 (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.0 (q), 81.9 (s), 118.3 (d), 126.1 (d), 127.7 (d), 128.3 (d), 131.5 (s), 135.5 (s), 150.5 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{26}H_{30}N_2O_4^{23}Na$: 457.2103; found 457.2104.

4.4.2. N,N-Bis-(tert-butoxycarbonyl)-2,5-bis-(benzo[b]thiophen-2-yl)-[1,4]-dihydropyrazine (**4f**)

Compound **4f** was prepared according to the general procedure (B) reported for **4e** starting from **3** (0.300 g, 0.38 mmol, 1 equiv) and benzo[*b*]thiophen-2-boronic acid (0.252 g, 1.90 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) afforded **4f** (0.180 g, 87%) as a yellow solid; mp=168–169 °C. IR: 3018, 1706, 1640 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.28 (s, 18H), 6.74 (s, 2H), 7.26 (s, 2H), 7.27–7.35 (m, 4H), 7.69–7.79 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 27.9 (q), 82.9 (s), 120.1 (d), 121.7 (d), 122.3 (d), 123.5 (d), 124.6 (d), 124.7 (d), 125.8 (s), 137.4 (s), 139.1 (s), 139.5 (s), 150.1 (s). MS (IS): m/z=569 [M+Na]$^+$. Anal. Calcd for $C_{30}H_{30}N_2O_4S_2$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.95; H, 5.38; N, 5.04.

4.4.3. N,N-Bis-(tert-butoxycarbonyl)-2,5-bis-(benzofuran-2-yl)-[1,4]-dihydropyrazine (**4g**)

Compound **4g** was prepared according to the general procedure (B) reported for **4e** starting from **3** (0.300 g, 0.38 mmol, 1 equiv) and benzo[*b*]furan-2-boronic acid (0.221 g, 1.90 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) afforded **4g** (0.180 g, 87%) as a beige solid; mp=168–169 °C. IR: 3018, 1713, 1454 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.25 (br s, 18H), 6.74 (s, 2H), 6.91 (s, 2H), 7.18–7.30 (m, 4H), 7.42 (d, J=8.0 Hz, 2H), 7.53 (dd, J=6.5 and 1.5 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 27.8 (q), 82.8 (s), 104 (d), 111.0 (d), 120.2 (s), 120.3 (s), 120.4 (s), 121.0 (d), 121.9 (s), 123.1 (d), 124.6 (d), 128.4 (d), 149.6 (s), 149.9 (s), 154.4 (s). MS (IS): m/z=515 [MH]$^+$, 537 [M+Na]$^+$.

4.4.4. N,N-Bis-(tert-butoxycarbonyl)-2,5-di(thiophen-2-yl)-[1,4]-dihydropyrazine (**4h**)

Compound **4h** was prepared according to the general procedure (B) reported for **4e** starting from **3** (0.300 g, 0.38 mmol, 1 equiv) and thiophen-2-boronic acid (0.338 g, 1.90 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) afforded **4h** (0.180 g, 87%) as a yellow oil. IR (cm^{-1}): 2980, 1707, 1368, 1335. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.29 (s, 18H), 6.57 (s, 2H), 6.96 (dd, J=5.0 and 3.5 Hz, 2H), 7.02 (dd, J=3.5 and 1.0 Hz, 2H), 7.23 (dd, J=5.0 and 1.0 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 27.8 (q), 82.4 (s), 118.7 (d), 124.6 (d), 125.1 (d), 125.9 (d), 126.8 (s), 137.4 (s), 150.2 (s). HRMS

(TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{22}H_{26}N_2O_4^{23}NaS_2$: 469.1231; found 469.1243.

4.5. Preparation of the *N*,*N*-bis-(*tert*-butoxycarbonyl)-[1,4]-dihydropyrazine (5)

To a solution of bisvinylphosphate **3** (1.00 g, 1.28 mmol, 1 equiv) in DME (5 mL), $Pd(OAc)_2$ (0.023 g, 0.10 mmol, 8 mol %) and PPh_3 (0.053 g, 0.21 mmol, 0.16 equiv) were added under argon. Then, the flask was evacuated and backfilled with argon three times and was stirred for 5 min. At room temperature, this solution was then transferred dropwise into a degassed solution of formic acid (0.240 mL, 6.40 mmol, 5 equiv) and triethylamine (1.10 mL, 7.68 mmol, 6 equiv) in DME (5 mL). The reaction mixture was refluxed for 2 h. After cooling, the mixture was filtered through Celite and was washed with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) to give **5** (0.165 g, 45%) as a white solid; mp=104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 18H), 5.77 (s, 2H), 5.89 (br s, 2H), 5.94 (br s, 2H), 6.04 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 28.3 (q), 81.8 (s), 81.9 (s), 110.5 (d), 111.0 (d), 111.6 (d), 112.0 (d), 148.4 (s), 148.5 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{14}H_{22}N_2O_4^{23}Na$: 305.1477; found 305.1482.

4.6. General procedure (C) for the preparation of trisubstituted derivatives 6a–6e

*4.6.1. N,N-Bis-(tert-butoxycarbonyl)-2-(tributylstannyl)-3,6-diphenyl-[1,4]-dihydropyrazine (**6a**)*

Lithium diisopropylamide 1.8 M in THF/heptane/ethylbenzene (0.250 mL, 0.54 mmol, 2.5 equiv) was added dropwise, at −78 °C, to a solution of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-diphenyl-[1,4]-dihydropyrazine **4e** (0.080 g, 0.18 mmol, 1 equiv) in THF (4 mL). After stirring for 1 h at −78 °C, distilled HMPA (0.060 mL, 0.36 mmol, 2 equiv) was added and then dropwise a solution of tributyltin chloride (0.240 mL, 0.90 mmol, 5 equiv) in THF (1 mL). After 1 h, the mixture was diluted with EtOAc and quenched with water. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) to give **6a** (0.081 g, 62%) as a yellow oil. IR: 2955, 1710, 1358 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (t, J=8.0 Hz, 9H), 1.09 (s, 9H), 1.10 (s, 9H), 1.15–1.46 (m, 18H), 9.81 (s, 1H), 7.19–7.43 (m, 10H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 12.2 (t), 13.8 (q), 27.5 (t), 27.8(q), 27.9 (q), 29.0 (t), 81.0 (s), 81.8 (s), 119.4 (d), 124.8 (d), 126.0 (d), 127.2 (d), 128.0 (d), 128.2 (d), 131.0 (s), 131.0 (s), 136.7 (s), 138.4 (s), 141.2 (s), 152.0 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{38}H_{56}N_2O_4^{23}Na^{120}Sn$: 747.3159; found 747.3183.

*4.6.2. N,N-Bis-(tert-butoxycarbonyl)-2-(trimethylsilyl)-3,6-diphenyl-[1,4]-dihydropyrazine (**6b**)*

Compound **6b** was prepared according to the general procedure (C) reported for **6a** starting from **4e** (0.100 g, 0.23 mmol, 1 equiv) and trimethylsilyl chloride (0.145 mL, 1.15 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2) afforded **6b** (0.073 g, 63%) as an oil. IR: 2980,1694, 1588 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 9H), 1.07 (br s, 18H), 6.99 (s, 1H), 7.34 (m, 10H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 0.9 (q), 1.2 (2C, t), 27.5 (q), 27.9 (q), 81.1 (s), 82.1 (s), 125.3 (d), 125.5 (s), 128.0 (d), 128.4 (d), 128.7 (d), 129.6 (s), 132.6 (s), 138.3 (s), 145.6 (s), 151.6 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{29}H_{38}N_2O_4^{23}NaSi$: 529.2486; found 529.2511.

*4.6.3. N,N-Bis-(tert-butoxycarbonyl)-2-(hydroxy(3,4,5-trimethoxy)-methyl)-3,6-diphenyl-[1,4]-dihydropyrazine (**6c**)*

Compound **6c** was prepared according to the general procedure (C) reported for **6a** starting from **4e** (0.080 g, 0.18 mmol, 1 equiv) and 3,4,5-trimethoxybenzaldehyde (0.177 g, 0.90 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc/Toluene, 5:3:2) afforded **6c** (0.085 g, 75%) as a white solid; mp=91–92 °C. IR (cm^{-1}): 3378, 2979, 1715, 1625. ^{1}H NMR (400 MHz, acetone-d_6) δ: 1.07 (s, 9H), 1.13 (s, 9H), 3.63 (s, 6H), 3.75 (3H), 5.29 (d, J=10.5 Hz, 1H), 6.54 (s, 1H), 6.57–6.59 (m, 2H), 6.66 (d, J=10.5 Hz, 1H), 7.10–7.20 (m, 6H), 7.47–7.56 (m, 4H). ^{13}C NMR (100.6 MHz, acetone-d_6) δ: 28.7 (q), 28.7 (q), 57.4 (q), 61.8 (q), 73.5 (d), 84.1 (s), 84.4 (s), 104.9 (d), 122.2 (d), 126.6 (d), 129.1 (d), 129.8 (d), 130.3 (d), 130.4 (s), 130.8 (d), 132.7 (s), 136.5 (s), 137.3 (s), 139.6 (s), 140.4 (s), 140.6 (s), 151.8 (s), 155.5 (s), 156.1 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{36}H_{42}N_2O_8^{23}Na$: 653.2838; found 653.2847.

*4.6.4. N,N-Bis-(tert-butoxycarbonyl)-2-formyl-3,6-diphenyl-[1,4]-dihydropyrazine (**6d**)*

Compound **6d** was prepared according to the general procedure (C) reported for **6a** starting from **4e** (0.080 g, 0.18 mmol, 1 equiv) and DMF (0.070 mL, 0.90 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2) afforded **6d** (0.096 g, 85%) as a yellow solid; mp=145–146 °C. IR (cm^{-1}): 2980, 1815, 1720, 1364. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (s, 9H), 1.25 (br s, 9H), 7.09 (s, 1H), 7.27–7.57 (m, 10H), 9.32 (br s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 27.5 (q), 27.9 (q), 82.0 (s), 84.2 (s), 125.3 (d), 125.5 (s), 128.0 (d), 128.4 (d), 128.7 (d), 129.8 (d), 130.5 (d), 131.7 (s), 131.9 (s), 149.8 (s), 151.3 (s), 186.0 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{27}H_{30}N_2O_5^{23}Na$: 485.2052; found 485.2049.

*4.6.5. N,N-Bis-(tert-butoxycarbonyl)-2-methoxycarbonyl-3,6-diphenyl-[1,4]-dihydropyrazine (**6e**)*

Compound **6e** was prepared according to the general procedure (C) reported for **6a** starting from **4e** (0.1 g, 0.23 mmol, 1 equiv) and methyl cyanoformate (0.070 mL, 1.15 mmol, 5 equiv). Flash column chromatography on silica gel (petroleum ether/EtOAc, 8:2) afforded **6e** (0.067 g, 60%) as a yellow solid; mp=65–66 °C. IR (cm^{-1}): 2970, 1732, 1634, 1360. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (br s, 18H), 3.69 (s, 3H), 6.69 (br s, 1H), 7.27–7.36 (m, 6H), 7.51 (m,4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 27.4 (q), 51.8 (q), 81.8 (s), 83.1 (s), 119.3 (d), 125.4 (s), 128.0 (d), 128.4 (d), 128.6 (d), 129.9 (d), 130.5 (d), 131.7 (s), 131.8 (s), 135.0 (s), 141.1 (s), 142.9 (s), 151.9 (s), 163.3 (s). MS (IS): m/z=515 [M+Na]$^+$.

4.7. *N*,*N*-Bis-(*tert*-butoxycarbonyl)-2-methoxycarbonyl-[1,4]-dihydropyrazine (7)

Lithium diisopropylamide 1.8 M in THF/heptane/ethylbenzene (0.140 mL, 0.25 mmol, 1.2 equiv) was added dropwise at −78 °C, to a solution of *N*,*N*-bis-(*tert*-butoxycarbonyl)-[1,4]-dihydropyrazine **5** (0.060 g, 0.21 mmol, 1 equiv) in THF (2 mL). After 15 min of stirring at −78 °C, the solution of methyl cyanoformate (0.833 mL, 1.05 mmol, 5 equiv) in THF (1 mL), previously dried over molecular sieves (4 Å), was added dropwise. After 2 h of stirring, the mixture was diluted with EtOAc and quenched with water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2) to give **7** (0.072 g, 65%) as a yellow oil. IR (cm^{-1}): 2980, 1732, 1634, 1371 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39 (s, 9H), 1.47 (s, 9H), 3.71 (s, 3H), 6.07 (d, J=3.5 Hz, 1H), 6.31 (d, J=3.5 Hz, 1H), 7.02 (s, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 27.4 (q), 27.5 (q), 51.8 (q),

81.6 (s), 83.2 (s), 113.7 (d), 114.9 (d), 125.1 (d), 148.0 (s), 149.3 (s), 163.1 (s). HRMS (TOF ES$^+$) m/z [M+Na]$^+$ calcd for $C_{16}H_{24}N_2O_6^{23}Na$: 363.1532; found 363.1528.

4.8. General procedure (D) for the preparation of the pyrazines

4.8.1. 2,5-Diphenylpyrazine (**8a**)

Method 1: to a solution of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-diphenyl-[1,4]-dihydropyrazine **4e** (0.080 g, 1.80 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1.00 mL, 1.80 mmol, 10 equiv) with fast stirring at room temperature for 2–4 h (TLC control). The reaction mixture was then diluted with CH_2Cl_2 and was quenched with saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was washed with Et_2O, filtered, and concentrated to afford **8a** as a beige solid (0.041 g, 100%).

Method 2: to a solution of **4e** (0.080 g, 1.80 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added trimethylsilyl iodide (1.30 mL, 1.10 mmol, 4.8 equiv) at room temperature. After 30 min of stirring, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The compound **8a** (0.037 g, 73%) was isolated by using the same work-up as described in method 1.

Mp=195–196 °C. IR (cm^{-1}): 3382, 1652, 1636, 1106, 1078 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ: 7.45–7.55 (m, 6H), 8.06 (m, 4H), 9.08 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 126.9 (d), 129.2 (d), 129.9 (d), 136.4 (s), 141.4 (d), 150.8 (s). HRMS (EI) m/z [M]$^+$ calcd for $C_{16}H_{12}N_2$: 232.1000; found 232.0985.

4.8.2. 2,5-Dithiophenylpyrazine (**8b**)

Compound **8b** was prepared according to the method described for **8a**. Yellow solid isolated in 64% yield; mp=93 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.17 (t, 2H, J=4.5 Hz), 7.48 (d, 2H, J=4.8 Hz), 7.68 (d, 2H, J=3.6 Hz), 8.88 (s, 2H). HRMS (EI) m/z [M]$^+$ calcd for $C_{12}H_8N_2S_2$: 244.0128; found 244.0132.

4.8.3. 2,5-Dibenzothiophenylpyrazine (**8c**)

Compound **8c** was prepared according to the method described for **8a**. Orange solid isolated in 80% yield; mp >250 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.38–7.42 (m, 3H), 7.85 (m, 5H), 7.97 (s, 1H), 9.07 (s, 1H). HRMS (EI) m/z [M]$^+$ calcd for $C_{20}H_{12}N_2S_2$: 344.0441; found 344.0430.

4.8.4. 2,5-Bis-(5-methoxy-1H-indol-2-yl)-pyrazine (**8d**)

Compound **8d** was prepared according to the method described for **8a**. Brown solid isolated in 20% yield; mp >250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.78 (s, 6H), 6.80 (dd, 2H, J=2.2 and 9 Hz), 7.08 (d, 2H, J=2 Hz), 7.25 (br s, 2H), 7.37 (d, 2H, J=9 Hz), 9.21 (s, 2H), 11.68 (br s, 2H). HRMS (EI) m/z [M]$^+$ calcd for $C_{22}H_{18}N_4O_2$: 370.4102; found 370.4104.

4.9. Fluorescence study

Absorption spectra were obtained with an UVIKON XL Double Beam ultraviolet–visible (UV/VIS) spectrophotometer (Secomam, France). Stock solutions for absorption measurements were prepared in $CHCl_3$ and diluted at absorbance 0.01–0.05 for fluorescence measurements to minimize the 'inner-filter effect'. Fluorescence emission spectra (excitation wavelength 326 nm for **8a**, 367 nm for **8b**, 390 nm for **8c**, and 2 nm bandwidth) were recorded at room temperature in silica cells of 1 cm pathlength using a Jobin-Yvon Fluoromax 2 spectrofluorimeter. Emission spectra were corrected with the computer program supplied with the instrument. Fluorescence quantum yields were determined by the standard method using quinine sulfate in 0.5 N H_2SO_4 solution as reference. The refractive index of the solution was taken into account in the calculation (Figs. 3 and 4).

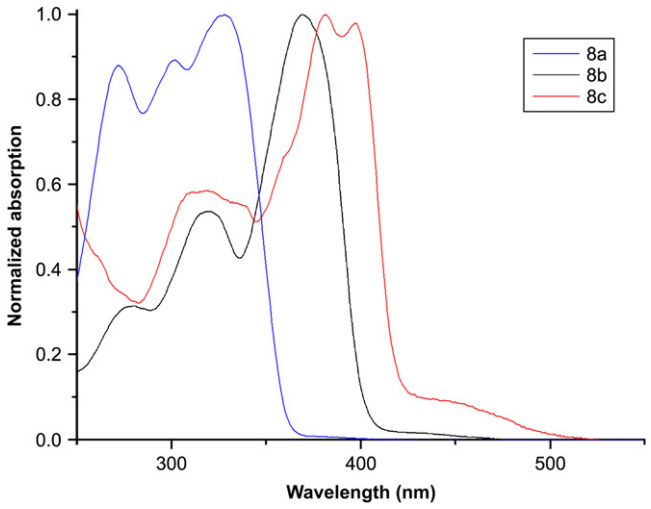


Figure 3. Normalized absorption spectra of compounds **8a**, **8b**, and **8c** in $CHCl_3$.

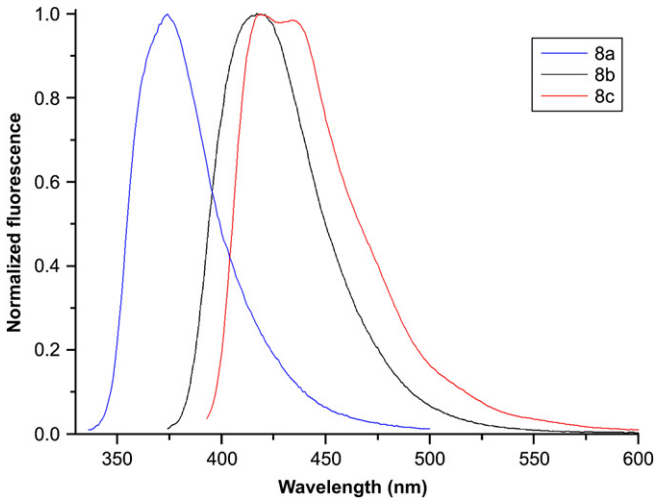


Figure 4. Normalized fluorescence spectra of compounds **8a**, **8b**, and **8c** in $CHCl_3$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.080.

References and notes

1. (a) For diversity-oriented synthesis, see: Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74; (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.
2. Borbulevych, O. Y.; Shishkin, O. V. *J. Mol. Struct.* **1998**, *446*, 11.
3. Massey, V.; Hemmerich, P. In *The Enzymes* Boyer P. D., Ed.; New York, NY, 1975; Vol. 4, p 191.

4. (a) Brook, D. J. R.; Noll, B. C.; Koch, T. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 289; (b) Brook, D. J. R.; Haltiwanger, R. C.; Koch, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 6017; (c) Goto, T.; Inoue, S.; Sugiura, S. *Tetrahedron Lett.* **1968**, 3873; (d) Teranishi, K.; Goto, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3132.
5. Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Cho, H. Y.; Jung, J. H. *J. Nat. Prod.* **2007**, *70*, 2.
6. (a) Jones, K.; Keenan, M.; Hibbert, F. *Synlett* **1996**, 509; (b) Cavalier, J.; Marchand, C.; Rees, J.; Marchand-Brynaert, J. *Synthesis* **2001**, 768; (c) Lotowski, Z.; Gryszkiewiez, A.; Borowiecka, J. B.; Nikitiuk, A.; Morzycki, J. W. *J. Chem. Res., Synop.* **1999**, 662; (d) Vazquez, J.; González, J. J. L.; Márquez, F.; Pongor, G.; Boogs, J. E. *J. Phys. Chem. A* **2000**, *104*, 2599; (e) Fourrey, J. L.; Beauhaire, J.; Yuan, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1841; (f) Shu, C. *J. Agric. Food Chem.* **1999**, *47*, 4332; (g) Janin, Y. L. *Bioorg. Med. Chem.* **2007**, *15*, 2479.
7. (a) Kim, K. B.; Crews, C. M. *J. Med. Chem.*, in press; (b) Asaki, T.; Hamamoto, T.; Sugiyama, Y.; Kuwano, K.; Kuwabara, K. *Bioorg. Med. Chem.* **2007**, *15*, 6692; (c) Corbett, J. W.; Rauckhorst, M. R.; Qian, F.; Hoffman, R. L.; Knauer, C. S.; Fitzgerald, L. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6250; (d) Buron, F.; Turck, A.; Plé, N.; Bischoff, L.; Marsais, F. *Tetrahedron Lett.* **2007**, *48*, 4327; (e) Martínez, M. M.; Sarandeses, L. A.; Sestelo, J. P. *Tetrahedron Lett.* **2007**, *48*, 8536; (f) Buron, F.; Plé, N.; Turck, A.; Queguiner, G. *J. Org. Chem.* **2005**, *70*, 2616; (g) Geiger, C.; Zelenka, C.; Weigl, M.; Frölich, R.; Wibbeling, B.; Lehmkuhl, K.; Schepmann, D.; Grüner, R.; Bednarski, P. J.; Wünsch, B. *J. Med. Chem.* **2007**, *50*, 6144; (h) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. *Mini-Rev. Med. Chem.* **2005**, *5*, 319.
8. (a) Mikuriya, M.; Yoshioka, D.; Handa, M. *Coord. Chem. Rev.* **2006**, *250*, 2194; (b) Crutchley, R. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6452; (c) Takamizawa, S.; Kohbara, M. *Dalton Trans.* **2007**, 3640; (d) Caradoc-Davies, P. L.; Hanton, L. R.; Henderson, W. *J. Chem. Soc., Dalton Trans.* **2001**, 2749.
9. (a) Barthelon, A.; Dos Santos, A.; El Kaïm, L.; Grimaud, L. *Tetrahedron Lett.* **2008**, *49*, 3208; (b) Eda, Y.; Odazaki, Y.; Mizutani, A.; Ito, Y. N.; Kawato, T. *Tetrahedron Lett.* **2008**, *49*, 2519; (c) Mamane, V.; Aubert, E.; Fort, Y. *J. Org. Chem.* **2007**, *72*, 7294; (d) Taber, D. F.; DeMatteo, P. W.; Taluskie, K. V. *J. Org. Chem.* **2007**, *72*, 1492; (e) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602; (f) Low, M. Y.; Parker, J. K.; Mottram, D. S. *J. Agric. Food Chem.* **2007**, *55*, 4087; (g) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489.
10. (a) Zhang, X.; Sui, Z. *Tetrahedron* **2006**, *47*, 5953; (b) Rodrigues, A.; Ferreira, P. M. T.; Monteiro, L. S. *Tetrahedron* **2004**, *60*, 8489; (c) Kleyer, D. L.; Koch, T. H. *J. Org. Chem.* **1982**, *47*, 3145; (d) Kleyer, D. L.; Haltiwanger, R. C.; Koch, T. H. *J. Org. Chem.* **1983**, *48*, 147; (e) Aparicio, D.; Attanasi, O. A.; Filippone, P.; Ignacio, R.; Lillini, S.; Mantellini, F.; Palacios, F.; de los Santos, J. M. *J. Org. Chem.* **2006**, *71*, 5897.
11. (a) Mousset, D.; Gillaizeau, I.; Sabatié, A.; Bouyssou, P.; Coudert, G. *J. Org. Chem.* **2006**, *71*, 5993; (b) Mousset, D.; Gillaizeau, I.; Hassan, J.; Lepifre, F.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **2005**, *46*, 3703; (c) Claveau, E.; Gillaizeau, I.; Blu, J.; Bruel, A.; Coudert, G. *J. Org. Chem.* **2007**, *72*, 4832.
12. (a) Cottineau, B.; Gillaizeau, I.; Farard, J.; Auclair, M.-L.; Coudert, G. *Synlett* **2007**, 1925 and references cited herein.
13. It is noteworthy that the bisvinylphosphate **3** is stable for several months at 4 °C under argon atmosphere.
14. Farran, D.; Parrot, I.; Martinez, J.; Dewynter, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7488.
15. Lo Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem.* **2003**, *68*, 6360 and references cited herein.
16. Lepifre, F.; Buon, C.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 6373.
17. Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.
18. Charbonnier, F.; Moyano, A.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2303; (b) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757.
19. Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 1849.
20. Addition of HMPA, which stabilizes the formed anion, was in most cases useful to improve the reaction yield.
21. (a) Utsukihara, T.; Nakamura, H.; Watanabe, M.; Horiuchi, C. A. *Tetrahedron Lett.* **2006**, *47*, 9352; (b) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257; (c) Elmaaty, T. A.; Castle, L. W. *Org. Lett.* **2005**, *7*, 5529.
22. (a) Teranishi, K. *Bioorg. Chem.* **2007**, *35*, 82; (b) Teranishi, K. *Luminescence* **2007**, *22*, 147; (c) Raghavan, R.; Dorshow, R. B.; Neuman, W. L.; Moore, D. A. PCT Int. Appl. WO 2006071759, 2006.
23. Oba, M.; Terauchi, T.; Owari, Y.; Imai, Y.; Motoyama, I.; Nishiyama, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1275.