Synthesis of Tröger's base bis(α-aminophosphonate) derivatives

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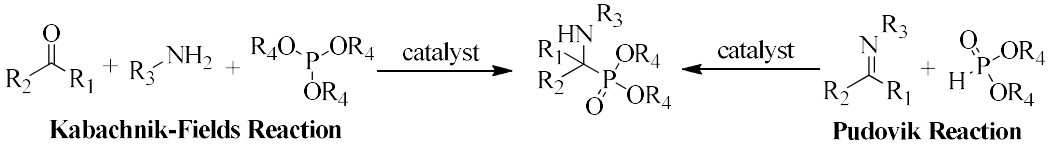
DOI: http://dx.doi.org/10.3998/ark.5550190.p009.563

Abstract
A straightforward and efficient introduction of α-aminophosphonate moiety on Tröger's base is described for the first time. A two step preparation route involving, the formation of imines from the coupling of Tröger's base di-aldehyde with various amines followed by conversion of the imines to bis(α-aminophosphonates) using triethyl phosphite and chlorotrimethylsilane (TMSCl). The products were obtained in enhanced yields in comparison with one-pot Kabachnik-Fields approach.

Keywords: Tröger's base, bis(α-aminophosphonate), amines, triethyl phosphite, TMSCl.

Introduction

α-Aminophosphonic acids and their phosphonate derivatives are of immense interest in synthetic organic chemistry due to their multiple activities as enzyme inhibitors, peptide mimics, antibiotics, herbicides, plant growth regulators, and haptens of catalytic antibodies.[1,2] Various methodologies have been reported in the literature for the preparation of α-aminophosphonates (Scheme 1). However, a one-pot protocol i.e. reaction of amine, aldehyde with trialkyl phosphite (Kabachnik-Fields reaction) represents a convenient route for the synthesis of α-amino phosphonates.[3,4] The other approach is Pudovik reaction where the imines are reacted with dialkylphosphites in the presence of a base or Lewis acid catalyst.[5] Literature is littered with plenty of information on the diverse catalysts[6,8] that accomplish these protocols as well as novel green protocols based on microwave,[9] ultrasound,[10] use of ionic liquids[11,12] etc.



Scheme 1. General protocols for the synthesis of α-aminophosphonates.

The search for an ideal molecule with a well defined structural framework to incorporate bis(*α*-aminophosphonate) moieties led to selection of Tröger's base[13,14] (Figure 1) as the first choice. This V-shaped molecule offers applications not only as a unique building block in supramolecular chemistry[15] but also explored in medicinal chemistry.[16,18] Added to this, synthesis of aminophosphonates incorporating Tröger's base has not been accomplished yet. In view of this knowledge and the potential of these molecules for different applications, it was deemed interesting to construct Tröger's base bis(*α*-aminophosphonates) as a novel class molecules. At the outset, it was presumed that a one-pot protocol reported earlier by our group[19,20] can be extended for the construction of novel Tröger's base based bis(*α*-aminophosphonates). The synthesis of targeted bis(*α*-aminophosphonates) can be achieved employing either a Tröger's base dialdehyde or a Tröger's base diamine, an amine or aldehyde, respectively and a di/trialkyl phosphite in a one pot reaction. However, there is dearth of effective protocols for large scale synthesis of Tröger's base diamine. Tröger's base dialdehyde has therefore been chosen as the preferred synthon for the construction of bis(*α*-aminophosphonates).

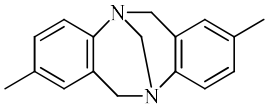
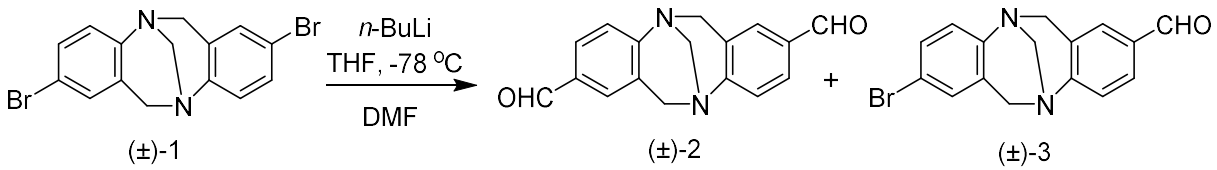


Figure 1. Tröger's base.

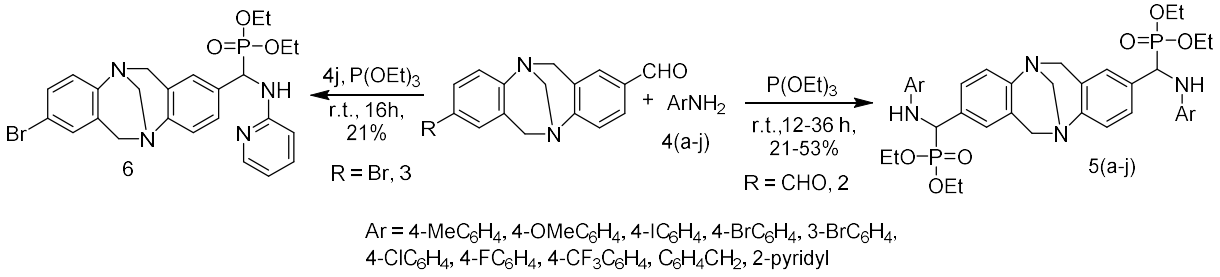
Results and Discussions

The Tröger's base dialdehyde **(±)-2** was prepared by the halogen-lithium exchange.[21] Thus, the Br-Li exchange reaction of dibromo Tröger's base **(±)-1** employing *n*-BuLi followed by treatment with DMF afforded the corresponding dialdehyde **(±)-2** along with the monoaldehyde **(±)-3** in 48% and 16% yields, respectively (Scheme 2).



Scheme 2. Synthesis of Trögers base aldehyde.

At the outset, a model Kabachnik-Fields reaction of Tröger's base dialdehyde **(±)-2**, 4-fluoro aniline and $P(OEt)_3$ was performed without any catalyst, under solvent-free conditions at ambient temperature, in accordance with our earlier reported procedure (Scheme 3). The reaction was completed in 12 h. The product was obtained in 53% yield and confirmed as **5g** by ^1H, ^{13}C NMR, IR and mass spectral analysis. In order to optimize the reaction conditions, the synthesis of **5g** has been carried out under a variety of conditions. Attempts to improve the yield by raising the reaction temperature or use of a solvent (MeOH) or increasing the concentration of triethyl phosphite/amine proved futile. As a last resort in improvising the yields, the reaction was performed in presence of a mild acid catalyst, TMSCl.[22,23] However the yield of product was reduced considerably (to 16%). This probably is due to the fact that TMSCl has been deactivated or decomposed either by presence of amine and/or water generated *in situ* during imine formation, or due to hydrolysis of imine by HCl generated *in situ*, both being detrimental to the progress of the reaction. Therefore, Kabachnik-Fields reaction carried out under neat reaction conditions has been found to be the best protocol. To establish the generality of reaction, various anilines having electron donating and electron withdrawing groups such as CH_3, OCH_3, Br, Cl, I, F, CF_3, NO_2, CN, and 2-aminopyridine were subjected to this protocol. The reactions were completed in about 24-36 h and products were obtained in 21-34% yield along with 24-15% of unreacted imines. Electron deficient substrates such as 4-nitro and 4-cyano anilines did not react at all with Tröger's base dialdehyde **(±)-2** and the starting materials were recovered (up to 93%) after workup. Reaction of mono-aldehyde **(±)-3** with 2-aminopyridine and triethyl phosphite gave corresponding mono-α-aminophosphonate **6** only in 21% yield (Scheme 3). This led to a conclusion that the poor yields in the reaction were not due to the steric crowding as in formation of mono-α-aminophosphonate **6** crowding does not exist. Probably, the Kabachnik-Fields protocol has inherent limitations in generating Tröger's base-α-aminophosphonates.



Scheme 3. One-pot synthesis (Kabachnik-Fields approach) of α-aminophosphonates.

In order to overcome the limitations noticed in the one-pot Kabachnik-Fields reaction, which requires longer reaction times and suffers from poor yields even under catalytic conditions, there is a need for an efficient and convenient method for construction of such significant scaffolds. A credible alternative would be Pudovik reaction where phosphites have been directly reacted with pre-synthesized imines in the presence of a catalyst. In this route, which is a two-step protocol

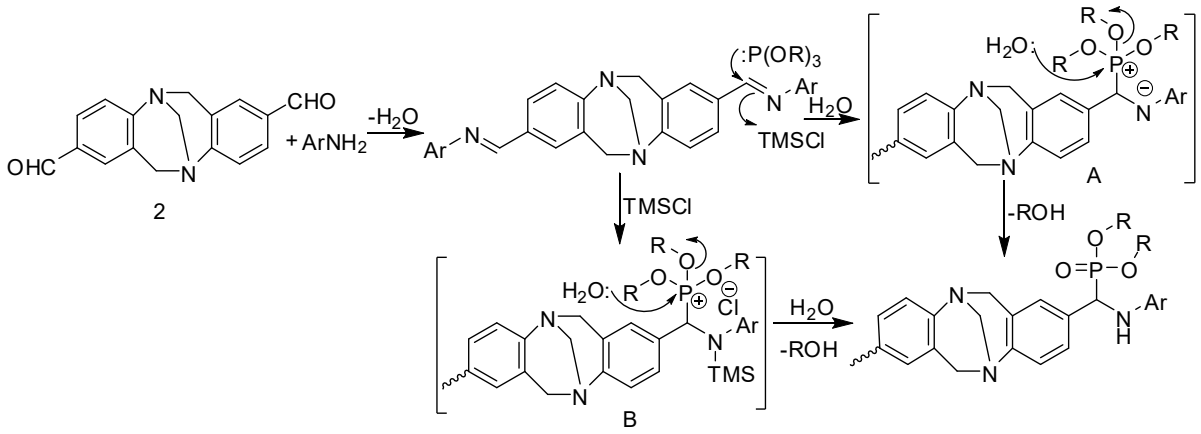
involving imine formation and isolation followed by Pudovik reaction, since there is no water to deactivate the catalyst by hydrolysis, it would be possible to check the role of catalyst in driving the reaction to completion.

Imines **7(a-j)** were prepared by the reaction of Tröger's base dialdehyde **(±)-2** with various amines **4(a-j)** in MeOH at room temperature (Table 1). The products were separated by simple filtration and were pure enough for all practical purposes. The products were obtained in good yields (76%-95%) and were confirmed by ^{1}H NMR and mass spectral analyses. Having Tröger's base aldimines **7(a-j)** in hand, synthesis of bis(*α*-aminophosphonates) was attempted by reacting imine **7a** with $P(OEt)_3$ in presence of TMSCl in MeOH at ambient temperature, as a model reaction (Table 1, Entry 1). The reaction was completed in 30 min (as monitored by TLC) and the product was obtained in 82% yield after purification. Further, to establish the generality of reaction, various imines having electron donating and electron withdrawing groups such as CH_3, OCH_3, Br, Cl, I, F, CF_3, and 2-aminopyridine were subjected to the above reaction protocol (Table 1). All the reactions were proceeded in 15-30 min and the products **5(a-j)** were obtained in good yields after purification by column chromatography. This method was tolerant to change in alkyl phosphites too, investigated by replacing the $P(OEt)_3$ with $P(OMe)_3$. The reaction of **7g** with trimethyl phosphite proceeded smoothly and the product **8** was obtained in 67% yield in the presence of TMSCl (Table 1, Entry 11).

The structures of compounds were identified by elemental analysis, IR, ^{1}H, ^{13}C NMR, and HRMS spectral data. Taking compound **5a** as an example, the absorption band at 3401 cm^{-1} (s) in its IR spectrum corresponds to an N-H stretch, the absorption bands at 1237 cm^{-1} (s) and 1029 cm^{-1} (s) correspond to P=O and P-O-C stretching, respectively.

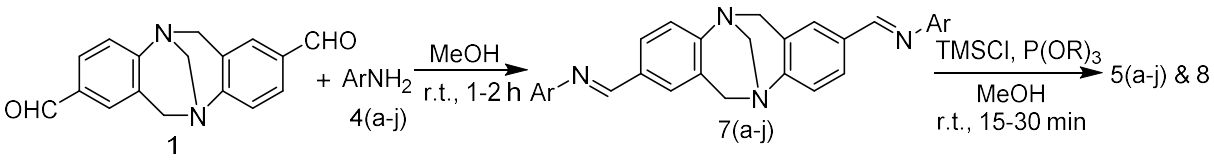
The Kabachnik-Fields protocol mechanism of the reaction (Scheme 4) involves the imine formation from Tröger's base aldehyde and an amine, followed by nucleophilic addition of trialkyl phosphite on imine to produce a phosphonium intermediate **A** (Kabachnik-Fields approach), which in the presence of water losses ethanol to give the desired bis(*α*-aminophosphonates).

In Pudovic approach (Scheme 4), the imine is activated in presence of TMSCl accelerating the nucleophilic attack of $P(OR)_3$ (accounting for the faster reaction rates). The nucleophilic attack which leads to the formation of the phosphonium intermediate **B** which on hydrolysis produces the desired bis(*α*-aminophosphonates).



Scheme 4. Plausible mechanism for the formation of Trögers base bis(*α*-aminophosphonates).

Table 1. Synthesis of bis(α-aminophosphonates) from aldimines (Pudovik approach)



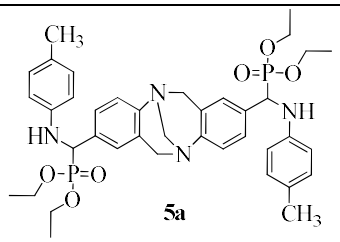
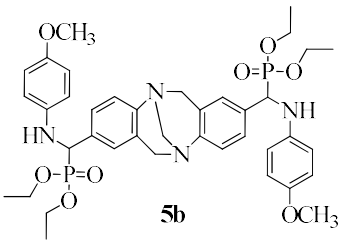
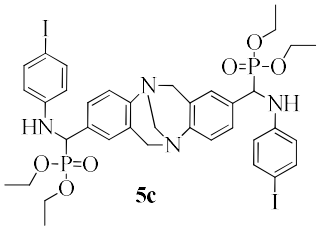
Entry	R	Ar	Product	Yield %[a] (one pot yield %[b])
1	Et	4-MeC_6H_4	 **5a**	82 (31)
2	Et	4-$OMeC_6H_4$	 **5b**	72 (21)
3	Et	4-IC_6H_4	 **5c**	80 (34)

Table 1 (continued)

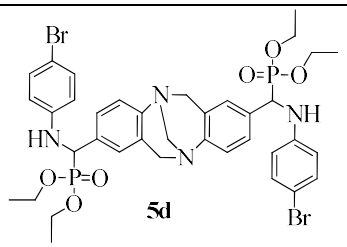
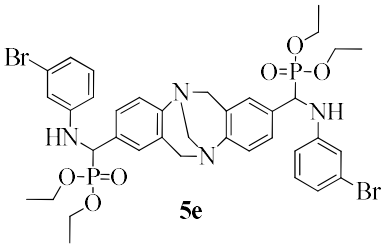
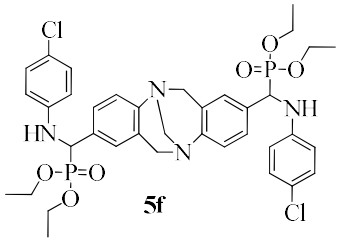
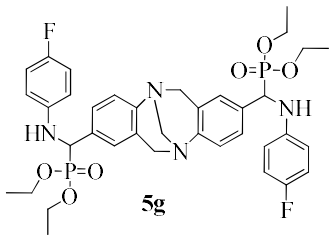
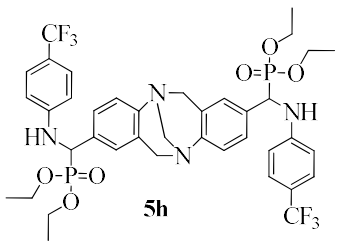
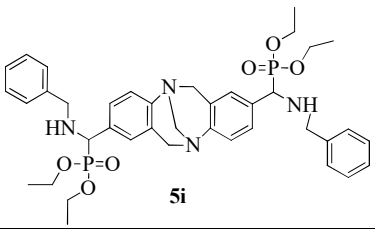
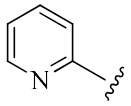
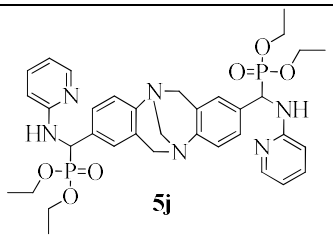
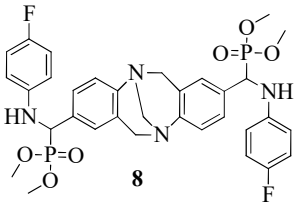
Entry	R	Ar	Product	Yield %a (one pot yield %b)
4	Et	4-BrC_6H_4	 **5d**	75 (28)
5	Et	3-BrC_6H_4	 **5e**	73 (32)
6	Et	4-ClC_6H_4	 **5f**	77 (29)
7	Et	4-FC_6H_4	 **5g**	82 (53)
8	Et	4-$CF_3C_6H_4$	 **5h**	73 (24)
9	Et	-$CH_2C_6H_4$	 **5i**	79 (31)

Table 1 (continued)

Entry	R	Ar	Product	Yield %a (one pot yield %b)
10	Et		 **5j**	72 (21)
11	Me	4-FC_6H_4	 **8**	67

[a] Reaction conditions: aldimine (1.0 mmol), trialkyl phosphite (2.2 mmol) and trimethylsilyl chloride (2.2 mmol), 5 ml of MeOH; [b] Reaction conditions (one pot): Tröger's base dialdehyde (1.0 mmol), aniline (2.1 mmol) and triethyl phosphite (2.2 mmol).

Conclusions

In conclusion, a series of novel Tröger's base bis(*α*-aminophosphonates) were synthesized by using Tröger's base dialdehyde as a versatile synthon. In a multicomponent one pot Kabachnik-Fields protocol, Tröger's base dialdehyde, substituted anilines and triethyl phosphite were reacted under solvent and catalyst free conditions. However, this method has limitations such as longer reaction times and low yields. Employing Pudovik method, phosphonates were synthesized in high yields and shorter reaction times from corresponding imines in the presence of TMSCl. The Pudovik approach provides a convenient method for the synthesis of Tröger's base bis(*α*-aminophosphonates) when compared to Kabachnik-Fields protocol.

Experimental Section

General. All the starting materials were from the best known commercial sources and used as received. Organic layers were dried over anhydrous Na_2SO_4. Thin layer chromatography (TLC) was performed on Merck F_{254} precoated silica gel plates. Visualisation was accomplished with UV light and/or iodine. Column chromatography was performed on silica gel (60×120 mesh) on a glass column. Melting points were determined in open capillaries and are uncorrected. IR spectra were

recorded on a FTIR spectrometer as KBr pellets or neat, ^{1}H and ^{13}C NMR spectra for analytical purpose were recorded in $CDCl_3$ on a Bruker instrument at 300 MHz, Avance instrument at 500 MHz and 75 MHz, respectively; chemical shifts are expressed in δ-scale downfield from TMS as an internal standard. Mass data (ESI) were recorded by quadruple mass spectrometry. HRMS data were obtained with the ESI ionization sources.

Synthesis of 6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-dicarbaldehyde ((±)-2). To a stirred solution of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine **(±)-1** (9.50 g, 25 mmol) in THF (100 mL), 1.6 M *n*-BuLi (37 mL, 59.5 mmol) was added dropwise over 20 min at -78 °C. After 10 min, electrophile DMF (5.8 mL, 74.5 mmol) was added swiftly and the reaction mixture was allowed to reach room temperature over approximately 30 min. The reaction was continued for additional 30 min before water (200 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 250 mL). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo and the crude product was purified by column chromatography with 40% of EtOAc in hexane as the eluent gave Tröger's base dialdehyde **(±)-2** in 48% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 9.84 (s, 2H), 7.70 (dd, *J* 8.2 Hz, 1.5 Hz, 2H), 7.50-7.46 (m, 2H), 7.28 (d, *J* 8.2 Hz, 2H), 4.81 (d, *J* 16.5 Hz, 2H), 4.36-4.29 (m, 4H). Along with Tröger's base dialdehyde **(±)-2**, mono substituted Tröger's base **(±)-3** also afforded in 16% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.79 (s, 1H), 7.65 (dd, *J* 8.3 Hz, 1.5 Hz, 2H), 7.45-7.40 (m, 2H), 7.27-7.18 (m, 2H), 4.77 (d, *J* 16.6 Hz, 2H), 4.33-4.20 (m, 4H).

General procedure for the synthesis of imines 7(a-j). To the suspension of Tröger's base dialdehyde (1 mmol) in 5 ml of MeOH, aniline (2.5 mmol) was added and stirred at room temperature for 1-2 h. After completion of the reaction (monitored by TLC), filtered off the solid formed, and excess aniline was removed by washing the solid thoroughly with MeOH. Imines thus filtered were pure and obtained in 76-95% yields.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-methylaniline) (7a). White solid, yield 95%, mp 146-147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.32 (s, 2H), 7.65 (dd, *J* 1.5 Hz, 8.3 Hz, 2H), 7.54-7.50 (m, 2H), 7.22 (d, *J* 8.3 Hz, 2H), 7.16 (d, *J* 8.1 Hz, 4H), 7.07 (d, *J* 8.3 Hz, 4H), 4.78 (d, *J* 16.6 Hz, 2H), 4.37 (s, 2H), 4.31 (d, *J* 16.8 Hz, 2H), 2.35 (s, 6H); MS (ESI) *m/z* (%): 457 ([M + H], 100); HRMS (ESI): calcd for $C_{31}H_{29}N_4$ 457.23867, found 457.23947.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-methoxyaniline) (7b). White solid, yield 89%, mp 220-221 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.33 (s, 2H), 7.68-7.60 (m, 2H), 7.54-7.50 (m, 2H), 7.22 (d, *J* 8.3 Hz, 2H), 7.16 (d, *J* 9.1 Hz, 4H), 6.90 (d, *J* 9.1 Hz, 4H), 4.78 (d, *J* 16.6 Hz, 2H), 4.37 (s, 2H), 4.33 (d, *J* 17.4 Hz, 2H), 3.81 (s, 6H); MS (ESI) *m/z* (%): 489 ([M + H], 100). HRMS (ESI) calcd for $C_{31}H_{29}O_2N_4$ 489.22850, found 489.22911.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-iodoaniline) (7c). White solid, yield 86%, mp 244-245 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.26 (s, 2H), 7.69-7.62 (m, 6H), 7.53-7.49 (m, 2H), 7.23 (d, *J* 8.3 Hz, 2H), 6.89 (d, *J* 8.3 Hz,

2H), 4.78 (d, *J* 16.6 Hz, 2H), 4.36 (s, 2H), 4.30 (d, *J* 17.4 Hz, 2H); MS (ESI) *m/z* (%) 681 ([M + H], 100); HRMS (ESI) calcd for $C_{29}H_{23}N_4I_2$ 681.00066, found 681.00137.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-bromoaniline) (7d). White solid, yield 85%, mp 269-270 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.27 (s, 2H), 7.65 (dd, *J* 1.3, 8.1 Hz, 2H), 7.53-7.49 (m, 2H), 7.46 (d, *J* 8.7 Hz, 4H), 7.23 (d, *J* 8.3 Hz, 2H), 7.01 (d, *J* 8.7 Hz, 2H), 4.78 (d, *J* 16.6 Hz, 2H), 4.36 (s, 2H), 4.31 (d, *J* 16.8 Hz, 2H); MS (ESI) *m/z* (%) 585 ([M + H], 100); HRMS (ESI) calcd for $C_{29}H_{23}N_4Br_2$ 585.02840, found 585.02888.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(3-bromoaniline) (7e). White solid, yield 87%, mp 162-163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.27 (s, 2H), 7.67 (d, *J* 7.7 Hz, 2H), 7.55-7.49 (m, 2H), 7.35-7.18 (m, 8H), 7.07 (d, *J* 7.7 Hz, 2H), 4.79 (d, *J* 16.6 Hz, 2H), 4.37 (s, 2H), 4.32 (d, *J* 17.0 Hz, 2H); MS (ESI) *m/z* (%) 584 ([M + H], 100); HRMS (ESI) calcd for $C_{29}H_{23}N_4Br_2$ 585.02840, found 585.02921.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-chloroaniline) (7f). White solid, yield 88%, mp 160-161°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.28 (s, 2H), 7.75-7.63 (m, 2H), 7.55-7.45 (m, 2H), 7.36-7.21 (m, 4H), 7.14-7.04 (m, 4H), 6.60 (d, *J* 8.7 Hz, 2H), 4.80 (dd, *J* 4.5, 16.6 Hz, 2H), 4.42-4.26 (m, 4H); MS (ESI) *m/z* (%) 497 ([M + H], 100); HRMS (ESI) calcd for $C_{29}H_{23}N_4Cl_2$ 497.12943, found 497.13007.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-fluoroaniline) (7g). White solid, yield 87%, mp 183-184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.29 (s, 2H), 7.66 (dd, *J* 1.3, 8.1 Hz, 2H), 7.52 (d, *J* 1.1 Hz, 2H), 7.23 (d, *J* 8.1 Hz, 2H), 7.17-6.99 (m, 8H), 4.79 (d, *J* 16.6 Hz, 2H), 4.37 (s, 2H), 4.32 (d, *J* 16.6 Hz, 2H); MS (ESI) *m/z* (%): 465 ([M + H], 100); HRMS (ESI): calcd for $C_{29}H_{23}N_4F_2$ 465.18853, found 465.18792.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(4-(trifluoromethyl)aniline) (7h). White solid, yield 81%, mp 222-223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.28 (s, 2H), 7.69 (d, *J* 8.1 Hz, 2H), 7.61 (d, *J* 8.3 Hz, 4H), 7.56-7.52 (m, 2H), 7.30-7.23 (m, 4H), 7.18 (d, J 8.3 Hz, 2H), 4.81 (d, *J* 16.6 Hz, 2H), 4.39 (s, 2H), 4.33 (d, *J* 17.4 Hz, 2H); MS (ESI) *m/z* (%) 565 ([M + H], 100); HRMS (ESI) calcd for $C_{31}H_{23}N_4F_6$ 565.18214, found 565.18215.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(1-phenylmethanamine) (7i). White solid, yield 92%, mp 247-248 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.24 (s, 2H), 7.53 (dd, *J* 1.6, 8.4 Hz, 2H), 7.39 (d, *J* 1.1 Hz, 2H), 7.33-7.21 (m, 10H), 7.15 (d, *J* 8.4 Hz, 2H), 4.74 (s, 4H), 4.71 (d, *J* 16.6 Hz, 2H), 4.32 (s, 2H), 4.23 (d, *J* 16.6 Hz, 2H); MS (ESI) *m/z* (%) 457 ([M + H], 100); HRMS (ESI) calcd for $C_{31}H_{29}N_4$ 457.23867, found 457.23942.

(±)-((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(methanylylidene))-bis(pyridin-2-amine) (7j). White solid, yield 76%, mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.02 (s, 2H), 8.46 (d, *J* 3.6 Hz, 2H), 8.06 (d, *J* 4.1 Hz, 1H), 7.80-7.60 (m, 5H), 7.42 (t, *J* 7.2 Hz, 1H), 7.30-7.21 (m, 4H), 7.15 (t, *J* 6.6 Hz, 1H), 6.63 (t, *J* 6.0 Hz, 1H), 6.49 (d, *J* 8.3 Hz, 1H),

4.80 (d, *J* 16.4 Hz, 2H), 4.47-4.26 (m, 4H); MS (ESI) *m/z* (%) 430 ([M + H], 100); HRMS (ESI) calcd for $C_{27}H_{23}N_6$ 431.19787 found 431.19776.

General procedure for the synthesis of Tröger's base bis(*α*-aminophosphonates) [5(a-j)]:

Method A (Kabachnik-Fields approach). A mixture of Tröger's base dialdehyde **(±)-2** (1.0 mmol), an aniline (2.1 mmol) and triethyl phosphite (2.2 mmol) was stirred at room temperature for the appropriate reaction time (12-36 h). After completion of the reaction (monitored by TLC), EtOAc was added to the reaction mixture. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the resulting crude material was purified by silica gel column chromatography using EtOAc as eluent to afford the Tröger's base bis(*α*-aminophosphonates) **5(a-j)**. Compound **6** obtained from the corresponding mono-aldehyde.

(±)-Diethyl((8-bromo-6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocin-2-yl)(pyridin-2-ylamino)methyl)phosphonates (6). Light brown foam; yield 87% (one pot yield: 21%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.05 (dd, *J* 1.1 Hz, 1H), 7.35 (td, *J* 1.8 Hz, 1H), 7.30 (dt, *J* 1.8 Hz, 1H), 7.23 (dd, *J* 2.3 Hz, 1H), 7.07 (d, *J* 8.4 Hz, 1H), 7.06-7.04 (m, 1H), 7.01 (d, *J* 2.1 Hz, 1H), 6.98 (dd, *J* 8.5 Hz, 1H), 6.57 (qd, *J* 0.86 Hz, 5.0 Hz, 1H), 6.40 (d, *J* 8.4 Hz, 1H), 4,64 (dd, *J* 16.6 Hz, 2H), 4.26 (qd, *J* 0.8 Hz, 9.3 Hz, 2H), 4.15-3.98 (m, 4H), 3.92-3.54 (m, 1H), 1.68 (bs, 1H), 1.19 (t, *J* 7.2 Hz, 3H), 0.92 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 156.8, 156.7, 147.8, 147.3, 146.9, 137.4, 137.4, 131.9, 131.8, 130.3, 129.9, 129.5, 127.5, 127.2, 127.2, 127.1, 127.0, 126.8, 126.7, 126.7, 126.4, 124.9, 116.4, 113.8, 108.6, 108.4, 66.7, 63.1 (d, *J* 6.6 Hz), 58.6 (d, *J* 3.3 Hz), 58.3, 52.8 (d, *J* 12.6 Hz), 50.8 (d, *J* 13.2 Hz), 16.2 (d, *J* 4.9 Hz), 15.9 (d, *J* 5.5 Hz), 15.8 (d, *J* 6.0 Hz); IR (KBr, cm^{-1}) 3444, 2982, 1603, 1479, 1227, 1023, 962, 763; MS (ESI) *m/z* (%) 543 ([M + H], 100); HRMS (ESI) calcd for $C_{25}H_{29}N_4O_3PBr$ 543.11552, found 543.11434.

Method B (Pudovik approach). To the suspension of an aldimines **7(a-j)** (1.0 mmol) in 5 ml of MeOH, trialkyl phosphite (2.2 mmol) and trimethylsilyl chloride (2.2 mmol) were added at room temperature and stirred for the appropriate reaction time (15-30 min). After completion of the reaction (monitored by TLC), MeOH was removed under reduced pressure. An oily compound was formed. Water was added to the reaction mixture and extracted with EtOAc. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the resulting crude material was purified by silica gel column chromatography using EtOAc as eluent to afford the Tröger's base bis(*α*-aminophosphonates) **5(a-j)**.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis((*p*-tolylamino)methylene))bis(phosphonate) (5a). Light brown foam; yield 82% (one pot yield: 31%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.25-7.18 (m, 2H), 7.10-7.04 (m, 2H), 6.99-6.95 (m, 2H), 6.91-6.84 (m, 4H), 6.49-6.43 (m, 4H), 4.66 (d, *J* 16.9 Hz, 2H), 4.63-4.54 (m, 4H), 4.28-3.41 (m, 10H), 2.17 (s, 3H), 2.15 (s, 3H), 1.71 (bs, 2H), 1.25-1.10 (m, 6H), 0.82-0.73 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.5, 143.8, 143.7, 131.4, 131.3, 131.2, 129.5, 127.7, 127.4, 127.3, 126.7, 126.6, 125.9, 125.1, 124.9, 113.6, 66.5, 63.4, 63.1 (d, *J* 7.1 Hz), 58.4, 56.5, 54.5, 20.1, 16.1, 15.8 (d, *J* 5.5 Hz), 15.5 (d, *J* 5.5 Hz); IR (KBr, cm^{-1}) 3401, 2953, 2922, 1607, 1518,

1237, 1029, 964, 754; MS (ESI) *m/z* (%) 755 ([M + Na], 100); HRMS (ESI) calcd for $C_{39}H_{51}N_4P_2O_6$ 733.32783, found 733.32687.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-methoxyphenyl)amino)methylene))bis(phosphonate) (5b). Light brown foam; yield 72% (one pot yield: 21%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.28-7.18 (m, 2H), 7.10-7.04 (m, 2H), 6.99-6.95 (m, 2H), 6.91-6.84 (m, 4H), 6.49-6.43 (m, 4H), 4.70-4.50 (m, 4H), 4.27-4.22 (m, 2H), 4.17-3.90 (m, 4H), 3.84-3.58 (m, 10H), 3.46-3.28 (m, 2H), 1.30-1.09 (m, 6H), 0.99-0.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 152.5, 147.6, 147.5, 140.1, 127.9, 127.8, 126.7, 126.6, 126.0, 125.9, 125.3, 125.2, 114.9, 114.6, 66.6, 63.1 (d, *J* 6.6 Hz), 58.5 (d, *J* 6.6 Hz), 55.5, 29.6, 16.2 (d, *J* 6.6 Hz), 15.8 (d, *J* 6.6 Hz), 15.6 (d, *J* 6.6 Hz); IR (KBr, cm^{-1}) : 3386, 2926, 2856, 1604, 1512, 1238, 1026, 965, 754; MS (ESI) *m/z* (%) 787 ([M + Na], 100); HRMS (ESI) calcd for $C_{39}H_{51}N_4O_8P_2$ 765.31766, found 765.31412.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-iodophenyl)amino)methylene))bis(phosphonate) (5c). Light brown foam; yield 80% (one pot yield: 34%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.31 (d, *J* 8.3 Hz, 4H), 7.20 (t, *J* 8.1 Hz, 2H), 7.07 (t, *J* 7.9 Hz, 2H), 6.94 (s, 2H), 6.32 (d, *J* 6.9 Hz, 4H), 4.86-4.46 (m, 6H), 4.25 (s, 2H), 4.20-3.92 (m, 4H), 3.82-3.62 (m, 2H), 3.58-3.27 (m, 2H), 1.86 (bs, 2H), 1.36-1.10 (m, 6H), 0.86-0.70 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.9, 145.9, 145.6, 137.7, 13.9, 130.9, 130.8, 130.7, 127.9, 127.9, 126.8, 126.6, 126.5, 125.9, 125.3, 125.2, 115.9, 115.8, 66.6 (d, *J* 4.5 Hz), 63.4 (d, *J* 7.3 Hz), 63.2 (d, *J* 7.3 Hz), 58.6, 58.5 (d, *J* 6.4 Hz), 55.8 (d, *J* 7.3 Hz), 54.6 (d, *J* 6.4 Hz), 16.3 (d, *J* 6.4 Hz), 15.9 (d, *J* 5.4 Hz), 15.7 (d, *J* 5.4 Hz); IR (KBr, cm^{-1}) 3296, 2983, 1593, 1482, 1231, 1022, 966, 757; MS (ESI) *m/z* (%) 979 ([M + Na], 100); HRMS (ESI) calcd for $C_{37}H_{44}N_4O_6P_2I_2Na$ 979.07177, found 979.07260.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-bromophenyl)amino)methylene))bis(phosphonate) (5d). Light brown foam; yield 75% (one pot yield: 28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.24-7.03 (m, 8H), 6.98-6.92 (m, 2H), 6.45-6.38 (m, 4H), 4.87-4.50 (m, 6H), 4.28-3.28 (m, 10H), 1.30-1.11 (m, 6H), 0.99-0.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.9, 145.2, 145.1, 131.8, 130.9, 130.8, 127.9, 126.8, 126.8, 125.9, 125.4, 125.3, 125.2, 115.3, 115.2, 110.1, 110.0, 66.7, 63.4 (d, *J* 7.3 Hz), 63.2 (d, *J* 5.4 Hz), 58.5 (d, *J* 6.4 Hz), 55.9, 54.8, 16.3 (d, *J* 5.4 Hz), 15.9 (d, *J* 5.4 Hz), 15.7 (d, *J* 6.4 Hz); IR (KBr, cm^{-1}) 3298, 2984, 2904, 1593, 1491, 1233, 1023, 966, 754; MS (ESI) *m/z* (%) 885 ([M + Na], 100); HRMS (ESI) calcd for $C_{37}H_{45}N_4O_6P_2Br_2$ 861.11756, found 861.11777.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((3-bromophenyl)amino)methylene))bis(phosphonate) (5e). Light brown foam; yield 73% (one pot yield: 32%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.20 (t, *J* 8.85 Hz, 2H), 7.12-7.06 (m, 2H), 7.00-6.94 (m, 2H), 6.90 (dt, *J* 3.2 Hz, 2H), 6.80-6.75 (m, 2H), 6.72-6.68 (m, 2H), 6.46-6.39 (m, 2H), 4.85-4.50 (m, 6H), 4.27 (t, *J* 7.5 Hz, 2H), 4.19-3.93 (m, 4H), 3.86-3.63 (m, 2H), 3.56-3.25 (m, 2H), 1.70 (bs, 2H), 1.29-1.11 (m, 6H), 0.95-0.70 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.5, 147.4, 130.4, 127.8, 126.9, 126.9, 126.1, 126.0, 125.9, 125.9, 125.3, 125.2, 123.0, 121.2, 121.1, 116.5, 116.2, 116.2, 112.2, 112.0, 66.7, 63.5 (d, *J* 6.4 Hz), 63.4 (d, *J* 7.2 Hz), 63.2 (d, *J* 7.2

Hz), 58.6, 58.5 (d, *J* 5.4 Hz), 55.8 (d, *J* 10.9 Hz), 54.5 (d, *J* 11.8 Hz), 16.2 (d, *J* 6.4 Hz), 15.9 (d, *J* 5.4 Hz), 15.6 (d, *J* 6.4 Hz); IR (KBr, cm^{-1}) 3283, 2950, 2850, 1594, 1232, 1032, 763; MS (ESI) *m/z* (%) 885 ([M + H], 100); HRMS (ESI) calcd for $C_{37}H_{45}N_4O_6P_2Br_2$ 861.11756, found 861.11777.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-chlorophenyl)amino)methylene))bis(phosphonate) (5f). Light brown foam; yield 77% (one pot yield: 29%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.21-7.16 (m, 2H), 7.10-6.93 (m, 8H), 6.47-6.43 (m, 4H), 4.73-4.49 (m, 6H), 4.27-4.23 (m, 2H), 4.13-4.01 (m, 4H), 3.80-3.49 (m, 4H), 1.61 (bs, 2H), 1.24-1.16 (m, 6H), 0.82-0.76 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.7, 147.7, 144.8, 144.6, 130.9, 130.8, 128.9, 127.9, 127.8, 126.8, 126.7, 126.6, 126.6, 125.9, 125.3, 125.1, 122.9, 122.8, 114.7, 114.7, 66.6, 63.3 (d, *J* 9.9 Hz), 63.1, 58.5 (d, *J* 9.9 Hz), 56.4, 54.4, 16.2, 15.8 (d, *J* 5.5 Hz), 15.6 (d, *J* 5.5 Hz); IR (KBr, cm^{-1}) 3302, 2983, 2926, 1598, 1493, 1232, 1023, 968, 755; MS (ESI) *m/z* (%) 795 ([M + Na], 100); HRMS (ESI) calcd for $C_{37}H_{44}N_4O_6P_2Cl_2Na$ 795.20053, found 795.19954.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-fluorophenyl)amino)methylene))bis(phosphonate) (5g). White solid; yield 82% (one pot yield: 53%); Mp 216-217 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.25-7.16 (m, 2H), 7.07 (t, *J* 8.1 Hz, 2H), 6.99-6.94 (m, 2H), 6.76 (t, *J* 8.7 Hz, 4H), 6.50-6.42 (m, 4H), 4.67 (d, *J* 16.6 Hz, 2H) 4.62-4.46 (m, 4H), 4.28-4.23 (m, 2H), 4.18-3.97 (m, 4H), 3.82-3.71 (m, 2H), 3.60-3.44 (m, 2H), 1.81 (bs, 2H), 1.27-1.14 (m, 6H), 0.85-0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 157.6, 154.5, 147.8, 142.5, 142.3, 131.1, 131.1, 131.0, 127.8, 126.8, 126.7, 126.0, 125.9, 125.9, 125.3, 125.2, 125.1, 115.7, 115.5, 114.6, 114.5, 114.4, 66.6, 63.2 (d, *J* 8.8 Hz), 63.0, 58.5 (d, *J* 8.8 Hz), 56.9, 54.9, 16.2 (d, *J* 6.6 Hz), 15.6 (d, *J* 6.6 Hz); IR (KBr, cm^{-1}) 3287, 2981, 2905, 1611, 1508, 1234, 1020, 957, 756; MS (ESI) *m/z* (%) 763 ([M + Na], 100) HRMS (ESI) calcd for $C_{37}H_{44}N_4O_6P_2F_2Na$ 763.25964, found 763.25928.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-(trifluoromethyl)phenyl)amino)methylene))bis(phosphonate) (5h). Light brown foam; yield 73% (one pot yield: 24%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:7.32-7.18 (m, 6H), 7.13-7.07 (m, 2H), 7.00-6.97 (dt, *J* 7.8, 2.3 Hz, 2H), 6.56 (dd, *J* 2.9 Hz, 8.6 Hz, 4H), 4.71-4.57 (m, 4H), 4.30-3.92 (m, 8H), 3.88-3.64 (m, 2H), 3.54-3.43 (m, 2H), 1.70 (bs, 2H), 1.30-1.11 (m, 6H), 0.97-0.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 148.9, 148.8, 147.9, 130.8, 130.7, 130.6, 130.5, 128.0, 127.9, 127.8, 126.8, 126.7, 126.4, 125.9, 125.7, 125.4, 125.2, 123.5, 112.8, 112.7, 119.9, 119.7, 66.6 (d, *J* 6.36 Hz), 63.4 (d, *J* 7.27 Hz), 63.1 (d, *J* 7.3 Hz), 58.6, 58.5 (d, *J* 6.4 Hz), 55.5 (t, *J* 5.4 Hz), 54.3 (t, *J* 5.4 Hz), 16.2 (d, *J* 6.4 Hz), 15.8 (d, *J* 5.4 Hz), 15.6 (d, *J* 6.4 Hz), 15.5 (d, *J* 5.4 Hz); IR (KBr, cm^{-1}): 3292, 2925, 2854, 1615, 1492, 1325, 1233, 1024, 968, 756; MS (ESI) *m/z* (%) 863 ([M + Na], 100); HRMS (ESI) calcd for $C_{39}H_{44}N_4O_6P_2F_6Na$ 863.25325, found 863.25256.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis((benzylamino)methylene))bis(phosphonate) (5i). Light brown foam; yield 79% (one pot yield: 31%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.30-7.11 (m, 14H), 6.99-6.95 (m, 2H), 4.71 (dd, *J* 4.42, 16.6 Hz, 2H), 4.32 (s, 2H), 4.22-3.45 (m, 16H), 2.88 (bs, 2H), 1.27-1.16 (m, 6H), 1.08-

0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.6, 139.2, 131.2, 131.1, 128.2, 128.2, 127.7, 127.5, 126.9, 125.1, 125.0, 66.7, 62.9 (d, *J* 6.0 Hz), 62.6 (d, *J* 6.0 Hz), 60.1 (d, *J* 6.0 Hz), 58.5 (d, *J* 6.0 Hz), 58.0 (d, *J* 8.8 Hz), 51.3 (d, *J* 3.8 Hz), 51.1 (d, *J* 3.3 Hz), 16.3 (d, *J* 5.5 Hz), 16.0 (d, *J* 4.4 Hz); IR (KBr, cm^{-1}) 3290, 1592, 1487, 1231, 1024, 764; MS (ESI) *m/z* (%) 755 ([M + Na], 100); HRMS (ESI) calcd for $C_{39}H_{51}N_4O_6P_2$ 733.32783, found 733.32884.

(±)-Tetraethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis((pyridin-2-ylamino)methylene))bis(phosphonate) (5j). Light brown foam; yield 72% (one pot yield: 21%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.05-7.98 (m, 2H), 7.36-7.22 (m, 4H), 7.12-6.97 (m, 4H), 6.53 (t, *J* 5.3 Hz, 2H), 6.37 (t, *J* 8.3 Hz, 2H), 4.64 (dd, *J* 7.5 Hz, 16.6 Hz, 2H), 4.25 (s, 2H), 4.16-3.36 (m, 12H), 2.26 (bs, 2H), 1.27-0.72 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 156.8, 156.7, 147.8, 147.5, 137.3, 131.8, 131.7, 131.5, 127.7, 127.1, 126.8, 126.7, 126.3, 126.1, 126.0, 125.0, 113.7, 108.6, 108.6, 108.3, 66.7, 63.3, 63.0 (t, *J* 6.0 Hz), 58.7 (d, *J* 3.3 Hz), 52.9, 50.9, 16.2 (t, *J* 4.4 Hz), 15.9 (d, *J* 4.4 Hz), 15.6 (d, *J* 6.0 Hz); IR (KBr, cm^{-1}) 3407, 2982, 1606, 1482, 1230, 1023, 966, 773; MS (ESI) *m/z* (%) 707([M + H], 100); HRMS (ESI) calcd for $C_{35}H_{45}N_6O_6P_2$ 707.28703, found 707.28720.

Tetramethyl((6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocine-2,8-diyl)bis(((4-fluorophenyl)amino)methylene))bis(phosphonate) (8). Light brown foam; yield 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.21 (t, *J* 7.9 Hz, 2H), 7.09 (t, *J* 6.0 Hz, 2H), 6.99-6.92 (m, 2H), 6.78 (t, *J* 7.9 Hz, 4H), 6.53-6.42 (m, 4H), 4.77-4.42 (m, 4H), 4.25 (s, 2H), 4.19-4.05 (m, 2H), 3.82-3.61 (m, 8H), 3.42-3.28 (m, 4H); MS (ESI) *m/z* (%) 685 ([M + H], 100); HRMS (ESI) calcd for $C_{33}H_{37}N_4O_6N_4F_2P_2$ 685.21509, found 685.21592.

(±)-Diethyl((8-bromo-6,12-dihydro-5,11-methanodibenzo[*b,f*][1,5]diazocin-2-yl)(pyridin-2-ylamino)methyl)phosphonates (6). Light brown foam; yield 87% (one pot yield: 21%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.05 (dd, *J* 1.1 Hz, 1H), 7.35 (td, *J* 1.8 Hz, 1H), 7.30 (dt, *J* 1.8 Hz, 1H), 7.23 (dd, *J* 2.3 Hz, 1H), 7.07 (d, *J* 8.4 Hz, 1H), 7.06-7.04 (m, 1H), 7.01 (d, *J* 2.1 Hz, 1H), 6.98 (dd, *J* 8.5 Hz, 1H), 6.57 (qd, *J* 0.86 Hz, 5.0 Hz, 1H), 6.40 (d, *J* 8.4 Hz, 1H), 4,64 (dd, *J* 16.6 Hz, 2H), 4.26 (qd, *J* 0.8 Hz, 9.3 Hz, 2H), 4.15-3.98 (m, 4H), 3.92-3.54 (m, 1H), 1.68 (bs, 1H), 1.19 (t, *J* 7.2 Hz, 3H), 0.92 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 156.8, 156.7, 147.8, 147.3, 146.9, 137.4, 137.4, 131.9, 131.8, 130.3, 129.9, 129.5, 127.5, 127.2, 127.2, 127.1, 127.0, 126.8, 126.7, 126.7, 126.4, 124.9, 116.4, 113.8, 108.6, 108.4, 66.7, 63.1 (d, *J* 6.6 Hz), 58.6 (d, *J* 3.3 Hz), 58.3, 52.8 (d, *J* 12.6 Hz), 50.8 (d, *J* 13.2 Hz), 16.2 (d, *J* 4.9 Hz), 15.9 (d, *J* 5.5 Hz), 15.8 (d, *J* 6.0 Hz); IR (KBr, cm^{-1}) 3444, 2982, 1603, 1479, 1227, 1023, 962, 763; MS (ESI) *m/z* (%) 543 ([M + H], 100); HRMS (ESI) calcd for $C_{25}H_{29}N_4O_3PBr$ 543.11552, found 543.11434.

Acknowledgments

MBR and GRP acknowledge the fellowship support from the CSIR, New Delhi. We thank CSIR-IICT for the facilities.

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