N-Arylation of 1,4,7,10-Tetraazacyclododecanes

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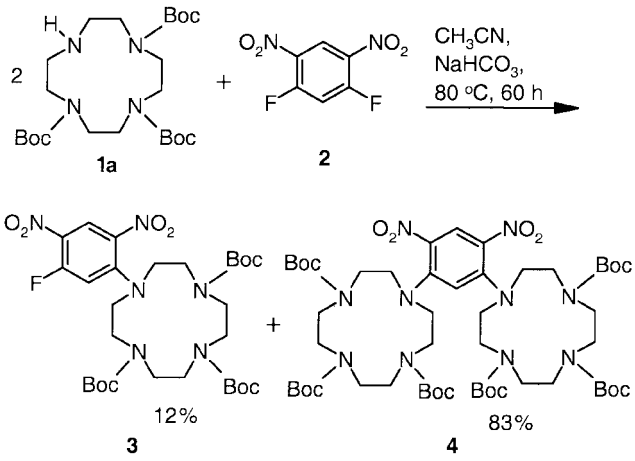
Abstract: Palladium-catalyzed N-arylation reactions provide acces to *N*-aryl-substituted and *N*-aryl-bridged 1,4,7,10-tetraazacyclododecanes. Yields of arylation products are low with simple haloarenes, whereas reactions with pyridine derivatives give substituted cyclens in moderate to satisfactory yields.

Keywords: azamacrocycle, palladium, *N*-arylation

Azamacrocycles, such as triazacyclononane, tetraazacyclododecane (cyclen) or tetraazacyclotetradecane (cyclam), have found many applications as ionophors for transition metal binding.[1–7] In addition, their Lewis-acidic metal complexes have been used as binding sites for Lewis-basic ligands in artificial receptors.[8–12] A variety of substituted cyclens has been already reported. The main route for functionalization starts from the commercially available parent azamacrocycle and uses alkylation or acylation reactions[13,14] of one or more nitrogen atoms to introduce additional functionality. However, these reactions lead to ligands with limited preorganization or reduced binding ability. *N*-Aryl-substituted and *N*-aryl-bridged cyclens could be of advantage in the design of selective ionophors or artificial receptors, but so far only the synthesis of very few compounds of this kind has been reported,[15] and a general synthetic approach is lacking. We have therefore adapted recently developed palladium-catalyzed N-arylation procedures[16,17] towards the functionalization of cyclens and report our findings in this paper.

Classical N-arylation procedures use the reaction of primary or secondary amines with halogenated arenes. Forcing reaction conditions are necessary with deactivated arenes, whereas suitable electron poor arenes react smoothly. The functionalization of threefold Boc-protected cyclen **1a**[18] by reaction with the Sanger reagent, 2,4-dinitrofluorobenzene, has been reported by Kimura et al.[19] We have applied the S_NAr reaction of an activated arene to the synthesis of arene-bridged biscyclen **4**, which is available by reaction of **1a** with 1,3-difluoro-4,6-dinitrobenzene (**2**) in good yield. However, subsequent variations of substituents and of the structure of the arene call for a synthetic method, which is not restricted by the electronic nature of the arene reactant.

Buchwald,[17,20–23] Hartwig[16,24] and others[25] have developed palladium-catalyzed procedures for N-arylation reactions under mild conditions with primary and secondary amines and haloarenes, which are not particularly electron poor. The work has been comprehensively reviewed. In two papers the results of palladium-catalyzed N-arylation of larger azamacrocycles and mixed *O*, *N*-macrocycles have been reported.[26,27] Our first attempts to transfer the methodology to the small azamacrocycle **1** by arylation of Cbz-protected compound **1b** with iodobenzene (entry 1, Table 1) under standard conditions using a palladium(0) source and BINAP as a ligand gave no conversion. Exchange of the protecting groups to Boc protection, as in **1a**, gave a low 8% isolated yield of arylation product **6a** (entry 2), which corresponds to 21% if corrected by unreacted starting materials. Neither longer reaction times (entry 3), subsequent addition of palladium catalyst, stoichiometric amounts of ligand, THF as solvent (entry 4) nor a palladium(II) salt as catalyst precursor (entry 5) improved yield and conversion. The use of bromobenzene as an arene coupling partner and DPPF as a ligand were advantageous (entries 6–8). Yields of the product reached 63%, as adjusted by recovered starting material, but reaction conversions remained unsatisfactory. The use of bromobenzene as solvent (entry 9, compare with 10), increased amounts of palladium source or catalyst (entry 11) or the addition of 18-crown-6, which allowed reactions with other substrates even at room temperature,[28] did not improve the conversion or coupling yields (entries 12–14) in this reaction. For comparison, **5b** was reacted with diethylamine (entry 28) giving the substitution product *N*,*N*-diethylaniline in nearly quantitative yield. The molecular model of **1a** (Figure 1) provides a possible expla-



Scheme 1 Synthesis of aryl-bridged biscyclen by twofold S_NAr reaction

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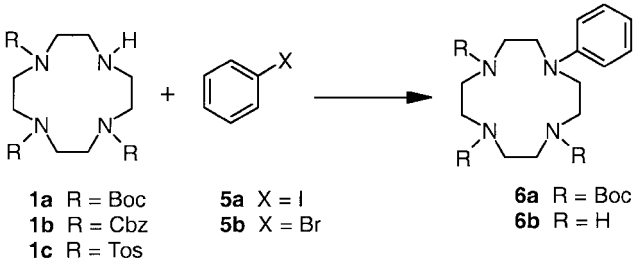
nation as to why the functionalization of the secondary amino group is so difficult. In the depicted lowest energy conformer, determined from force field calculation,[29] the secondary amino moiety is buried inside the molecule leading to considerable steric hindrance in the substitution reaction.



Scheme 2 Palladium-catalyzed N-arylation of partially protected cyclen with haloarenes; for reagents and conditions, see Table 1

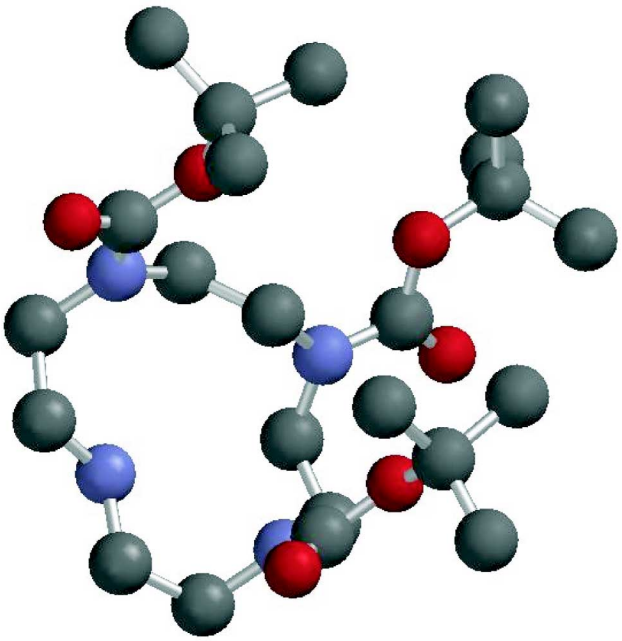
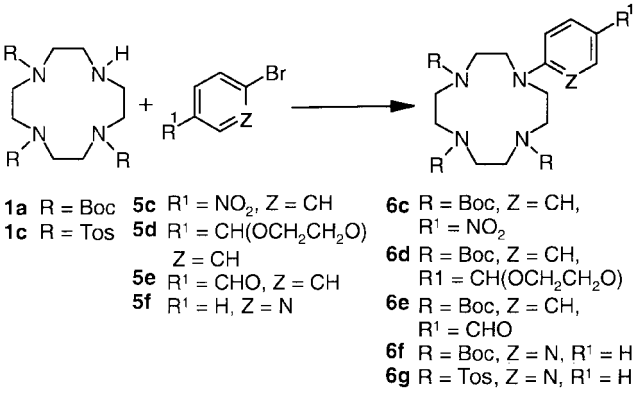
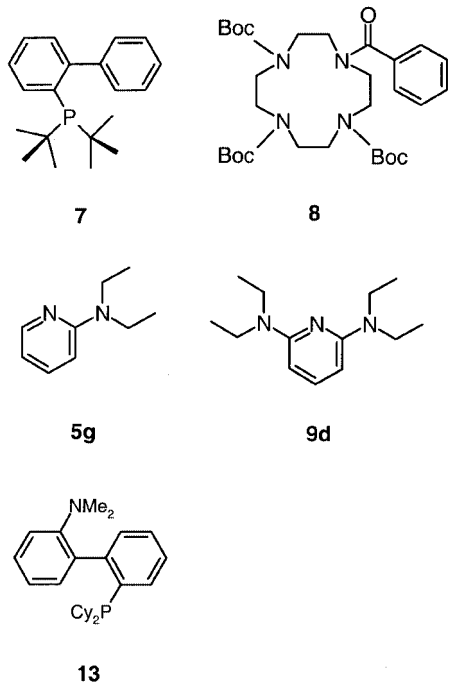


Figure Molecular model of the lowest energy conformer of **1a** as determined by force field methods

Several functionalized bromoarenes, such as **5c**, **5d** and **5e** were allowed to react with **1a** under various conditions (entries 15–21, Table 1 and Scheme 3) giving the corresponding coupling products in low yields. The use of **7**[30] or **13**[31] as a ligand, which was advantageous in recently reported reactions, did not improve yield and conversion significantly. In the reaction of **1a** with 4-bromobenzaldehyde (**5e**) (entries 19–21), compound **8** was isolated as the major product (Figure). We rationalize the formation of the acylation product **8** by a palladium mediated direct oxidative transformation of the aldehyde to the amide, followed by a reductive elimination of the arylhalide. Yoshida et al. reported such amide formation under similar coupling conditions.[32] The reaction was explained by the formation of the hemiaminal of aldehyde **5e** with amine **1a**, which reacts, after deprotonation with an arylpalladium species, to form an alkoxypalladium intermediate. The alkoxypalladium compound yields amide **8** and a hydridopalladium species, which generates, after reductive elimination, an aromatic hydrocarbon. The reaction of **1a** with 2-bromopyridine (**5f**) gave acceptable reaction conversions with better yields. The use of palladium(II) acetate as palladium source and triphenylphosphine as ligand turned out to be the best conditions for this reaction, which is in agreement with the findings of Witulski et al. in coupling reactions with larger *N,O*-macrocycles.[27] For comparison, **5f** was reacted with diethylamine giving the substitution product **5g** in nearly quantitative yield. This again illustrates that difficulties in the coupling reaction most likely arise from the structure of **1a**.



Scheme 3 Palladium-catalyzed N-arylation of partially protected cyclen with functionalized bromoarenes and bromopyridine; for reagents and conditions, see Table 1



Scheme 4

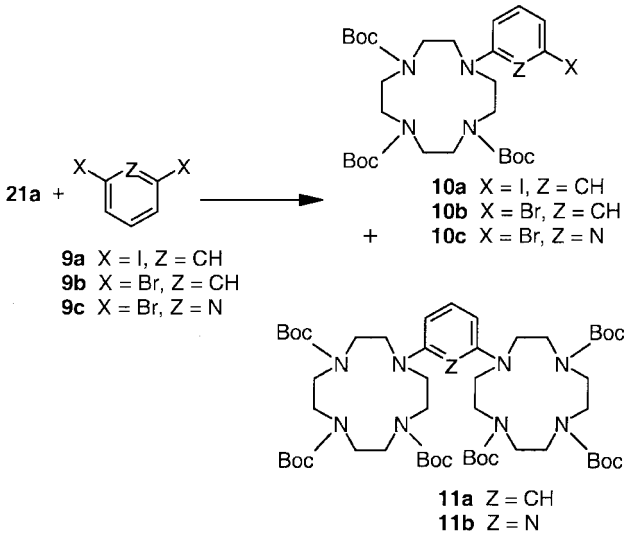
Table 1 Coupling Conditions and Yields for Palladium-catalyzed N-Arylation Reactions

Entry	Starting Materials	Palladium Source 5 mol%[a]	Ligand 7.5–10 mol%[b]	Solvent	Reaction Temp (°C)	Reaction Time (h)	Isolated Yield (%)	Yield Corrected by Conversion (%)
1	**1b** + **5a**	Pd_2dba_3	BINAP	toluene	80	48	n.c.[c]	n.c.
2	**1a** + **5a**	Pd_2dba_3	BINAP	toluene	80	48	8	21
3	**1a** + **5a**	Pd_2dba_3	BINAP	toluene	80	96	8	21
4	**1a** + **5a**	Pd_2dba_3	BINAP	THF	66	120	4	10
5	**1a** + **5a**	$Pd(OAc)_2$	BINAP	toluene	80	120	4	26
6	**1a** + **5b**	Pd_2dba_3	BINAP	toluene	80	120	7	31
7	**1a** + **5b**	$Pd(OAc)_2$	DPPF	toluene	80	120	20	54
8	**1a** + **5b**	$Pd(OAc)_2$	DPPF	toluene	80	26	11	63
9	**1a** + **5b**	$Pd(OAc)_2$	DPPF	**5b**	80	27	12	41
10	**1a** + **5a**	$Pd(OAc)_2$	DPPF	toluene	80	120	17	51
11a	**1a** + **5b**	$Pd(OAc)_2$ 5 mol%	DPPF 15 mol%	toluene	80	120	18	48
11b	**1a + 5b**	$Pd(OAc)_2$ 10 mol%	DPPF 15 mol%	toluene	80	120	19	47
12	**1a** + **5b**	$Pd(OAc)_2$	DPPF	toluene + 18-crown-6[d]	80	36	10	24
13	**1a** + **5a**	Pd_2dba_3	BINAP	THF	20	120	n.c.	n.c.
14	**1a** + **5b**	$Pd(OAc)_2$	DPPF	toluene + 18-crown-6[d]	20	160	n.c.	n.c.
15	**1a** + **5c**	$Pd(OAc)_2$	PPh_3	toluene	80	30	15 (**6c**)	26 (**6c**
16	**1a** + **5c**	$Pd(OAc)_2$	DPPF	toluene	80	60	7 (**6c**)	20 (**6c**)
17	**1a** + **5c**	$Pd(OAc)_2$	**7**	toluene	80	86	16 (**6c**)	32 (**6c**)
18	**1a** + **5d**	$Pd(OAc)_2$	PPh_3	toluene	80	80	13 (**6d**)	20 (**6d**)
19	**1a** + **5e**	$Pd(OAc)_2$	PPh_3	toluene	80	96	5 (**6e**) 25 (**8**)	9 (**6e**) 45 (**8**)
20	**1a** + **5e**	$Pd(OAc)_2$	PPh_3	toluene	80	39	6 (**6e**) 40 (**8**)	10 (**6e**) 67 (**8**)
21	**1a** + **5e**	$Pd(OAc)_2$	DPPF	toluene	80	96	4 (**6e**) 15 (**8**)	8 (**6e**) 39 (**8**)
22	**1a** + **5f**	$Pd(OAc)_2$	PPh_3	toluene	80	65	55 (**6f**)	89 (**6f**)
23	**1a** + **5f**	$Pd(OAc)_2$	**7**	toluene	80	96	30 (**6f**)	40 (**6f**)
24	**1c** + **5f**	$Pd(OAc)_2$	PPh_3	toluene	80	144	46 (**6g**)	60 (**6g**)
25	**1a + 5f**	Pd_2dba_3	**13**	toluene	80	115	11 (**6f**)	35 (**6f**)
26	**1a + 5f**	$Pd(OAc)_2$	**13**	toluene	80	115	22 (**6f**)	43 (**6f**)
27	$HNEt_2$ + **5b**	$Pd(OAc)_2$	DPPF	toluene	80	44	92 (**5h**)	92 (**5h**)
28	$HNEt_2$ + **5f**	$Pd(OAc)_2$	PPh_3	toluene	80	8	98 (**5g**)	98 (**5g**)

[a] The value corresponds to the amount of palladium added to the reaction mixture.
[b] 10 mol% for monodentate ligands and 7.5 mol% for bidentate ligands unless otherwise stated.
[c] No conversion.
[d] 1.4 Equiv of 18-crown-6 were added.

Table 2 Coupling Conditions and Yields of Aryl- and Heteroaryl-bridged Cyclens Prepared

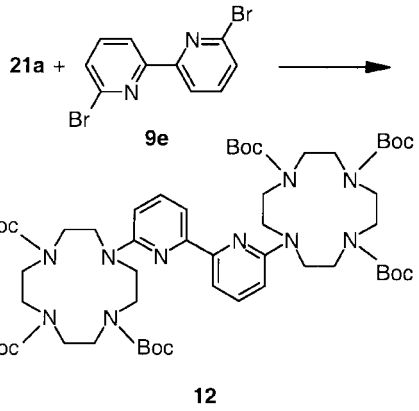
Entry	Starting Materials	Palladium Source 5 mol%	Ligand 7.5–10 mol%	Solvent	Reaction Temp (°C)	Reaction Time (h)	Isolated Yield	Yield Corrected by Conversion
1	**1a** + **9a**	$Pd(OAc)_2$	DPPF	toluene	80	40	3 (**6a**) 1 (**11a**)	7 (**6a**) 1 (**11a**)
2	**1a** + **9a**	$Pd(OAc)_2$	DPPF	toluene	80	120	4 (**6a**) 2 (**11a**)	5 (**6a**) 2 (**11a**)
3	**1a** + **9a**	Pd_2dba_3	BINAP	toluene	80	86	5 (**6a**) 2 (**11a**)	9 (**6a**) 3 (**11a**)
4	**1a** + **9b**	$Pd(OAc)_2$	DPPF	toluene	80	40	8 (**6a**) 2 (**11a**)	12 (**6a**) 5 (**11a**)
5	**1a** + **9c**	$Pd(OAc)_2$	PPh_3	toluene	80	62	54 (**11b**) 7 (**12**)	68 (**11b**) 7 (**12**)
6	**1a** + **9c**	$Pd(OAc)_2$	PPh_3	toluene Cs_2CO_3	80	72	43 (**10c**) 11 (**11b**)	77 (**10c**) 20 (**11b**)
7	$HNEt_2$ + **9c**	$Pd(OAc)_2$	PPh_3	toluene	80	29	86 (**9d**)	86 (**9d**)
8	**1a** + **9e**	$Pd(OAc)_2$	PPh_3	toluene	80	38	72 (**12**)	78 (**12**)



Scheme 5 Synthesis of arene-bridged bis-cyclens by palladium-catalyzed N-arylation; for reagents and conditions, see Table 2

Twofold coupling reactions of **1a** with **9a** and **9b** gave, as expected from the reactions with **5a** and **5b**, aryl-bridged cyclen **11a** in only very small amounts (entries 1–4, Table 2 and Scheme 4). With the more reactive 2,6-dibromopyridine (**9c**) moderate, but preparative useful yields of heteroaryl-bridged cyclen **11b** could be isolated (entries 5, 6). Interestingly compound **12** was isolated from this reaction as a minor product. Its formation most likely proceeds via palladium-catalyzed aryl-aryl coupling of **10c**.[33] This, reaction is successfully competing with the second N-aryl coupling step leading to **11b**, but it can be suppressed by the use of Cs_2CO_3 as a weaker base (entry 6). A selective synthesis of compound **12** is possible by coupling of **1a** with **9e** giving **12** in 78% yield (Scheme 5).

The reaction of **9c** with diethylamine (entry 7) under standard conditions gave *N*,*N*-diethylaniline in good yield, which illustrates the general feasibility of the reaction.



Scheme 6

Even though many optimized procedures for palladium catalyzed N-aryl bond formation have been reported, the functionalization of **1a** by these methods turned out to be very difficult. Steric hindrance caused by the protecting groups presumably limits the accessibility of the reacting secondary amine in the small macrocycle. Yields of arylation products and reaction conversion are generally very low and in some cases unsatisfactory. The best results were obtained with triphenylphosphine as monodentate ligand and $Pd(OAc)_2$ in toluene, which supports the earlier reported results with *N*,*O*-azacrownethers.[27] Although we could not find coupling conditions for **1a** with simple haloarenes that give satisfactory yields, the determined conditions provide at least access to aryl-substituted cyclens in small amounts. Such compounds have recently

received considerable interest for applications as chemosensors,[34] and *N*-aryl coupling is by far the most convenient method for their preparation. Much better results were obtained in the S_NAr reaction of **1a** with **2** and the palladium-catalyzed coupling reactions of **1a** with pyridine derivatives **5f** and **9c** yielding arene- and heteroarene-substituted cyclens under optimized conditions in moderate to satisfactory amounts. Our results show that the success of palladium-catalyzed N-arylation of protected azamacrocycles is structure dependent and requires further optimization for reactions with the sterically demanding amine **1a**. However, although the method is still limited it provides access to some derivatives of so far unknown arene-bridged cyclens, which are of interest for use as ionophors in chemosensors or artificial receptors in molecular recognition.

All reactions were carried out in oven-dried glassware under a N_2 atm using standard Schlenk-technique unless otherwise stated. Elemental analyses were performed at Microanalytical Laboratories, University of Regensburg. Toluene was distilled under N_2 from molten Na. THF was distilled under N_2 from molten K. The crown ether 18C6 and all aryl halides were purchased from commercial sources and were used without further purification. Sodium *t*-butoxide and caesium carbonate were purchased from Aldrich Chemical Co., stored under N_2, and weighed out in the air. The protected azamacrocycles were prepared as previously described in literature.[15,35,36] PPh_3 was purchased form Merck Co. and was purified by crystallization form EtOH and dried in high vacuum. Palladium acetate, $Pd_2(dba)_3$ and other phosphine ligands were purchased from Strem Chemical Co. and used without further purification. Preparative flash column chromatography (CC) was performed using Merck Flash Silica Gel (70–230 mesh). Yields refer to isolated yields and conversion corrected yields (based on isolated and unreacted starting material) of compounds estimated to be ≥95% by ^1H NMR and elemental analysis or high resolution mass-spectroscopy (for new compounds). All products were characterized from ^1H NMR, ^{13}C NMR, IR, UV/Vis and mass spectra. NMR spectra were recorded at 250 and 400 MHz (^1H) and at 63 and 100 MHz (^{13}C) in $CDCl_3$ solutions. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (–) for CH_2 or for quaternary carbons (C_{quat}). Mps were taken on a hot-plate microscope apparatus and are uncorrected. Petroleum ether (PE) with a boiling range of 60–70 °C was used.

Palladium-catalyzed Synthesis of *N*-Aryl-azamacrocycles; General Procedure A

A Schlenk tube was charged with 5 mol% of a palladium source (0.025 mmol for tris(dibenzylideneacetone)dipalladium(0); 0.050 mmol for palladium acetate), a phosphine ligand (0.10 mmol in case of monodentate ligands; 0.075 mmol in case of bidentate ligands), sodium *t*-butoxide (1.4 mmol) and toluene (2 mL). To this mixture the protected azamacrocycle (0.11 mmol) and the aryl halide (0.10 mmol) was added, the tube was sealed, the reaction mixture was degassed by three freeze, pump, thaw cycles and heated to 80 °C. The mixture was stirred for 26–120 h, cooled to r.t., diluted with CH_2Cl_2 (40 mL), filtered through Celite, and concentrated in vacuum. The crude product was purified by CC on silica gel (PE–EtOAc, 4:1). After isolation of the product, the eluent was changed to PE–EtOAc (2:3) to recover unreacted starting material. Yields are given as isolated yield and corrected by conversion (cbc).

Palladium-catalyzed Synthesis of *N′N*-Aryl-bisazamacrocycles; General Procedure B

Into a Schlenk tube were added the protected azamacrocycle (2 mmol), the aryl halide (1 mmol) and sodium *t*-butoxide or caesium carbonate (2.8 mmol) as base. To this mixture a phosphine ligand (0.20 mmol in case of monodentate ligands; 0.15 mmol in case of bidentate ligands) and a palladium source (0.05 mmol for tris(dibenzylideneacetone)dipalladium(0); 0.10 for palladium acetate) were added. The solid materials were suspended in toluene (4–5 mL). The tube was sealed, the mixture was degassed by three freeze, pump, thaw cycles and heated to 80 °C. The reaction mixture was stirred for 40–120 h, cooled to r.t., diluted with CH_2Cl_2 (50 mL), filtered through Celite, and concentrated in vacuum. The crude product was purified by CC on silica gel (PE–EtOAc, 4:1). After isolation of the product, the eluent was changed to PE–EtOAc (2:3) to recover unreacted azamacrocycle. Yields are given as isolated yield and corrected by conversion (cbc).

1,3-Bis(1,4,7-tris[*t*-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-2,4-dinitrobenzene (4)

A mixture of 1,3-difluoro-4,6-dinitrobenzene (**2**, 0.26 g, 1.27 mmol) and 1,4,7-tris(*t*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (**1**, 1.20 g, 2.54 mmol) was dissolved in CH_3CN (30 mL). The solution was stirred in the presence of $NaHCO_3$ (0.45 g, 5.33 mmol) at 80 °C under N_2 for 60 h, insoluble inorganic salts were filtered off, the solvent was removed in vacuo, and the residue was subjected to CC on silica gel (PE–EtOAc, 1:1).

Yield: 1.17 g (83%); yellow solid.

R_f = 0.22 (PE–EtOAc, 1:1).

Mp 105 °C.

UV (MeCN): λ_{max}, nm (log ε) = 229 (4.206), 365 (4.239).

IR (KBr): 2974, 2932, 1703, 1561, 1366, 1164 cm^{-1}.

^1H NMR (250 MHz): δ = 1.41 (s, 36 H), 1.44 (s, 18 H), 3.39–3.55 (m, 32 H), 6.59 (s, 1 H), 8.44 (s, 1 H).

^{13}C NMR (63 MHz): δ = 28.4 (+), 28.5 (+), 47.6 (–), 49.5 (–), 50.5 (–), 51.4 (–), 80.3 (C_{quat}), 80.4 (C_{quat}), 106.9 (+), 129.0 (+), 130.9 (C_{quat}), 149.1 (C_{quat}), 156.4 (C_{quat}), 156.6 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 1109 (100, MH^+), 1009 (18, MH^+–BOC).

Anal. Calcd for $C_{52}H_{88}N_{10}O_{16}$: C, 56.30; H, 8.00; N, 12.63. Found: C, 55.85; H, 7.94; N, 11.98.

1-Fluoro-3-(1,4,7-tris[*t*-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-2,4-dinitrobenzene (3)

Compound **3** was isolated as a by-product in the reaction of **1** with **2.**

Yield: 0.10 g (12%); yellow solid.

R_f = 0.48 (PE–EtOAc, 1:1).

Mp 86 °C.

UV (MeCN): λ_{max}, nm (log ε) = 228 (4.045), 368 (4.179).

IR (KBr): 2976, 2931, 1698, 1580, 1367, 1161 cm^{-1}.

^1H NMR (250 MHz): δ = 1.46 (s, 9 H), 1.48 (s, 18 H), 3.42–3.50 (m, 16 H), 6.86 (d, 1 H, ^3J = 13.9 Hz). 8.55 (d, 1 H, ^4J = 7.9 Hz).

^{13}C NMR (63 MHz): δ = 28.5 (+), 28.5 (+), 47.7 (–), 49.6 (–), 50.5 (–), 52.4 (–), 80.6 (C_{quat}), 81.0 (C_{quat}), 105.8 (+, d, $^2J_{C,F}$ = 26.6 Hz), 126.4 (C_{quat}, d, $^4J_{C,F}$ = 8.9 Hz), 126.8 (C_{quat}), 133.7 (+), 148.8 (C_{quat}, d, $^3J_{C,F}$ = 11.8 Hz), 156.2 (C_{quat}), 157.0 (C_{quat}), 158.3 (C_{quat}, d, $^1J_{C,F}$ = 269.0 Hz).

MS (ESI, 70 eV): *m/z* (%) = 657 (95, MH^+), 557 (100, MH^+–BOC).

HRMS: *m/z* calcd for $C_{29}H_{45}FN_6O_{10}$ $[MH]^+$: 657.3259. Found: 657.3259 ± 1.5 ppm.

2-Diethylaminopyridine (5g)
A mixture of palladium acetate (14.2 mg, 2 mol%), DPPF (52.2 mg, 3 mol%), sodium *t*-butoxide (395 mg, 4.1 mmol), 2-bromopyridine (**5f**) (500 mg, 3.2 mmol) and diethylamine (254 mg, 3.5 mmol) were placed into a Schlenk tube and suspended in toluene (2 mL). The mixture was degassed and heated for 8 h at 80 °C, cooled to r.t., diluted with CH_2Cl_2 (20 mL), and filtered through Celite. The filtrate was concentrated in vacuum and purified by CC (PE–EtOAc, 9:1) to yield 464 mg (98%) **5g** as a colourless liquid.

R_f = 0.64 (PE–EtOAc, 6:1).

^{1}H NMR (250 MHz): δ = 1.18 (t, 6 H, ^3J = 7.1 Hz), 3.51 (q, 4 H, ^3J = 7.1 Hz), 6.43–6.49 (m, 2 H), 7.36–7.43 (m, 1 H), 8.14 (dd, 1 H, ^3J = 5.9 Hz, ^4J = 1.9 Hz).

^{13}C NMR (63 MHz): δ = 12.9 (+), 42.4 (–), 105.5 (+), 110.8 (+), 137.0 (+), 148.1 (+), 157.5 (C_{quat}).

2,6-Bis(diethylamino)pyridine (9d)
A mixture of palladium acetate (13.5 mg, 1.3 mol%), DPPF (51.4 mg, 2 mol%), sodium *t*-butoxide (528 mg, 5.5 mmol), 2,6-dibromopyridine (**9c**, 500 mg, 2.1 mmol) and diethylamine (338 mg, 4.64 mmol) were placed into a Schlenk tube and suspended in toluene (3 mL). The mixture was degassed and heated for 29 h at 80 °C, cooled to r.t., taken up in CH_2Cl_2 (20 mL), and filtered through Celite. The filtrate was concentrated in vacuum and purified by CC (PE–EtOAc, 19:1) to yield 402 mg (86%) of **9d** as a colorless liquid.

R_f = 0.72 (PE–EtOAc, 6:1).

^{1}H NMR (250 MHz): δ = 1.16 (t, 12 H, ^3J = 7.0 Hz), 3.46 (q, 8 H, ^3J = 7.0 Hz), 5.71 (d, 2 H, ^3J = 8 Hz), 7.19–7.28 (m, 1 H).

***N*,*N*-Diethylaminoaniline (5h)**
A mixture of palladium acetate (35.6 mg, 5 mol%), DPPF (132 mg, 7.5 mol%), sodium *t*-butoxide (397 mg, 4.1 mmol), **5b** (500 mg, 3.2 mmol) and diethylamine (255 mg, 3.5 mmol) was added in a Schlenk tube and suspended with toluene (3 mL). The reaction mixture was degassed and heated for 64 h at 80 °C, diluted with CH_2Cl_2 (20 mL), and filtered through Celite. The filtrate was concentrated in vacuum and purified by CC (PE–EtOAc, 19:1) to yield 434 mg (92%) of **5h**.

R_f = 0.81 (PE–EtOAc, 10:1).

^{1}H NMR (250 MHz): δ = 1.15 (t, 6 H, ^3J = 7.0 Hz), 3.34 (q, 4 H, ^3J = 7.0 Hz), 6.61–6.71 (m, 3 H), 7.15–7.22 (m, 2 H).

1-Phenyl-4,7,10-tris(*t*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (6a)
Azamacrocycle **1a** (300 mg, 0.64 mmol) and aryl halide **5b** were reacted according to the general procedure A using $Pd(OAc)_2$ and DPPF as a catalyst. The reaction mixture was heated to 80 °C for 120 h. Compound **6a** [71 mg (20%, 54%^{cbc})] was isolated as a white solid.

R_f = 0.61 (PE–EtOAc, 1:1).

Mp 62 °C.

UV (MeCN): λ_{max}, nm (log ε) = 218 (3.955), 256 (4.078), 292 (3.453).

IR (KBr): 2977, 2931, 1692, 1167, 776, 753 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.46 (s, 9 H), 1.48 (s, 18 H), 3.37–3.51 (m, 16 H), 6.72–6.79 (m, 3 H), 7.22 (dd, 2 H, ^3J = 7.4 Hz, ^4J = 1.0 Hz).

^{13}C NMR (100 MHz): δ = 28.4 (+), 28.5 (+), 49.9 (–), 50.1 (–), 51.9, 79.9 (C_{quat}), 129.2 (+), 137.4 (C_{quat}), 156.4 (C_{quat}).

MS (EI, 70 eV): *m/z* (%) = 548 (94, M^+), 57 (100).

HRMS: *m/z* calcd. for $C_{29}H_{48}N_4O_6$ $[M]^+$: 548.3573. Found: 548.3576 ± 0.4 ppm.

1-(4-Nitrobenezene)-4,7,10-tris(*t*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (6c)
Azamacrocycle **1a** (500 mg, 1.06 mmol) and aryl halide **5c** were allowed to react according to the general procedure A using $Pd(OAc)_2$ and PPh_3 as a catalyst. The reaction mixture was heated to 80 °C for 30 h. Compound **6c** was isolated as a yellow solid; yield: 98 mg (15%, 26%^{cbc}).

R_f = 0.37 (PE–EtOAc, 1:1).

Mp 108 °C.

UV (MeCN): λ_{max}, nm (log ε) = 232 (4.053), 396 (4.432).

IR (KBr): 2976, 2933, 1695, 1597, 1319, 778 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.38 (s, 18 H), 1.45 (s, 9 H), 3.36–3.45 (m, 12 H), 3.44 (br s, 4 H), 6.61 (d, 2 H, ^3J = 9.4 Hz), 8.08 (d, 2 H, ^4J = 9.4 Hz).

^{13}C NMR (100 MHz): δ = 28.44 (+), 28.5 (+), 49.0 (–), 50.0 (–), 50.2 (–), 53.2 (–), 110.7 (+), 126.3 (+), 137.4 (C_{quat}), 152.7 (C_{quat}), 156.2 (C_{quat}), 157.3 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 594 (48, MH^+), 578 (100).

HRMS: *m/z* calcd. for $C_{29}H_{47}N_5O_8$ $[M]^+$: 593.3424. Found: 593.3428 ± 0.4 ppm.

1-(4-[1,3]Dioxalan-2-yl-phenyl)-1,4,7,10-tetraazacyclododecane (6d)
Azamacrocycle **1a** (400 mg, 0.85 mmol) and aryl halide **5d** were reacted according to the general procedure A using $Pd(OAc)_2$ and PPh_3 as a catalyst. The reaction mixture was heated to 80 °C for 80 h. Compound **6d** was isolated as a pale yellow solid; yield: 71 mg (13%, 20%^{cbc}).

R_f = 0.42 (PE–EtOAc, 1:1).

Mp 78 °C.

UV (MeCN): λ_{max}, nm (log ε) = 263 (4.405), 338 (3.854).

IR (KBr): 2978, 2933, 1694, 1169, 777 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.45 (s, 18 H), 1.47 (s, 9 H), 3.24–3.52 (m, 16 H), 3.98–4.03 (m, 2 H), 4.13–4.17 (m, 2 H), 5.71 (s, 1 H), 6.71 (d, 2 H, ^3J = 8.6 Hz), 7.33 (d, 2 H, ^3J = 8.6 Hz).

^{13}C NMR (100 MHz): δ = 28.5 (+), 28.6 (+), 49.2 (–), 50.2 (–), 50.8 (–), 53.1 (–), 65.2 (–), 79.7 (C_{quat}), 80.0 (C_{quat}), 104.0 (+), 114,5 (+), 127.0 (C_{quat}), 127.7 (+), 150.1 (C_{quat}), 156.3 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 623 (82, MH^+), 591 (100).

HRMS: *m/z* calcd. for $C_{32}H_{52}N_4O_8$ $[MH]^+$: 621.3863. Found: 621.3869 ± 1.7 ppm.

1-(*N*-Phenylcarbonyl)-4,7,10-tris(*t*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (8) and 4-(1,4,7,10-Tetraazacyclododec-1-yl)-benzaldehyde (6e)
Azamacrocycle **1a** (300 mg, 0.64 mmol) and aryl halide **5e** were reacted at 80 °C for 39 h according to the general procedure A using $Pd(OAc)_2$ and PPh_3 as a catalyst.

Compound 6e
Isolated as minor product; yield: 22 mg (6%, 10% ^{cbc}); pale yellow solid.

R_f = 0.53 (PE–EtOAc, 1:1).

Mp 63 °C.

UV (MeCN): λ_{max}, nm (log ε) = 342 (3.075).

IR (KBr): 2977, 2963, 1694, 1164, 832 cm^{-1}.

^{1}H NMR (250 MHz): δ = 1.42 (s, 9 H), 1.47 (s, 18 H), 3.37–3.86 (m, 16 H), 6.71 (d, 2 H, ^3J = 8.9 Hz), 7.72 (d, 2 H, ^3J = 8.9 Hz), 9.74 (s, 1 H).

^{13}C NMR (100 MHz): δ = 28.4 (+), 29.0 (+), 49.2 (–), 50.2 (–), 53.0 (–), 80.4 (C_{quat}), 111.6 (+), 122.5 (C_{quat}), 125.9 (C_{quat}), 132.1 (+), 156.3 (C_{quat}), 190.3 (+).

MS (ESI, 70 eV): *m/z* (%) = 577 (53, MH^+), 599 (100, $M+Na^+$).

HRMS: *m/z* calcd. for $C_{30}H_{48}N_4O_7$ $[M]^+$: 576.3523. Found: 576.3516 ± 0.6 ppm.

Compound 8

Isolated as the major product; yield: 151 mg (40%, 67%^{cbc}); white solid.

R_f = 0.39 (PE–EtOAc, 1:1).

Mp 71 °C.

UV (MeCN): λ_{max}, nm (log ε) = 338 (3.162).

IR (KBr): 2978, 2934, 1696, 1641, 1166, 733 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.30 (s, 9 H), 1.47 (s, 9 H), 1.50 (s, 9 H), 3.31–3.63 (m, 16 H), 7.34–7.41 (m, 5 H).

^{13}C NMR (100 MHz): δ = 28.3 (+), 28.4 (+), 48.1 (–), 49.0 (–), 49.3 (–), 49.7 (–), 49.9 (–), 50.3 (–), 50.7 (–), 51.3 (–), 80.0 (C_{quat}), 80.3 (C_{quat}), 80.4 (C_{quat}), 126.3 (+), 128.5 (+), 129.3 (+), 136.6 (C_{quat}), 155.5 (C_{quat}), 156.8 (C_{quat}), 157.0 (C_{quat}), 172.4 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 577 (25, MH^+), 599 (100, $M+Na^+$).

HRMS: *m/z* calcd. for $C_{30}H_{48}N_4O_7$ $[M]^+$: 576.3523. Found: 576.3513 ± 0.4 ppm.

1-(2-Pyridinyl)-4,7,10-tris(*t*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (6f)

Azamacrocycle **1a** (400 mg, 0.85 mmol) and bromopyridine **5f** were reacted at 80 °C for 65 h according to the general procedure A using $Pd(OAc)_2$ and PPh_3 as a catalyst. Compound **6f** was isolated as white solid; yield: 257 mg (55%, 89%^{cbc}).

R_f = 0.48 (PE–EtOAc, 1:1).

Mp 58 °C.

UV (MeCN): λ_{max}, nm (log ε) = 252 (4.179), 308 (3.514).

IR (KBr): 2977, 2933, 1693, 1168, 776 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.45 (s, 27 H), 3.21 (br s, 4 H), 3.42–3.51 (m, 8 H), 3.67 (br s, 4 H), 6.53–6.59 (m, 2 H), 7.36–7.43 (m, 1 H), 8.13 (dd, 1 H, ^3J = 4.9 Hz, ^4J = 1.2 Hz).

^{13}C NMR (100 MHz): δ = 28.4 (+), 28.5 (+), 50.6 (–), 51.8 (–), 79.9 (C_{quat}), 107.8 (+), 112.5 (+), 137.1 (+), 147.7 (+), 156.5 (C_{quat}), 159.3 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 550 (100, MH^+).

Anal. Calcd for $C_{28}H_{47}N_5O_6$: C, 61.18; H, 8.62; N, 12.74. Found: C, 61.11; H, 8.59; N, 12.01.

1-Pyridine-4,7,10-tritosyl-1,4,7,10-tetraazacyclododecane (6g)

Azamacrocycle **1c** (100 mg, 0.16 mmol) and bromopyridine **5f** were allowed to react according to the general procedure A at 80 °C for 144 h using $Pd(OAc)_2$ and PPh_3 as a catalyst. Compound **6g** was isolated as white solid; yield: 52 mg (46%, 60%^{cbc}).

R_f = 0.31 (PE–EtOAc, 1:1).

Mp 117 °C.

UV (MeCN): λ_{max}, nm (log ε) = 231 (4.688), 308 (3.631).

IR (KBr): 2928, 2861, 1340, 1161, 693, 550 cm^{-1}

^{1}H NMR (400 MHz): δ = 2.43 (s, 6 H), 2.45 (s, 3H), 3.18 (br s, 4 H), 3.40–3.47 (m, 8 H), 4.00 (br s, 4 H), 6.57 (dd, 1 H, ^3J = 6.8 Hz, ^4J = 1.6 Hz), 6.84 (d, 1 H, ^3J = 8.6 Hz), 7.32 (d, 6 H, ^3J = 8.2 Hz), 7.47–7.53 (m, 1 H), 7.67 (dd, 6 H, ^3J = 8.2 Hz, ^4J = 1.7 Hz), 8.09 (dd, 1 H, ^3J = 4.9 Hz, ^4J = 1.4 Hz).

^{13}C NMR (100 MHz): δ = 21.5 (+), 21.6 (+), 51.4 (–), 51.7 (–), 51.8 (–), 52.3 (–), 107.6 (+), 112.5 (+), 127.7 (+), 128.0 (+), 129.8 (+), 129.9 (+), 133.2 (C_{quat}), 133.9 (C_{quat}), 137.7 (+), 143.9 (C_{quat}), 144.1 (C_{quat}), 147.4 (+), 158.3 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 712 (100, MH^+).

HRMS: *m/z* calcd. for $C_{34}H_{41}N_5O_6S_3$ $[M]^+$: 711.2218. Found: 711.2214 ± 0.6 ppm.

1,3-Bis(1,4,7-tris[*t*-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-benzene (11a)

Protected azamacrocycle **1a** (2 equiv, 700mg, 1.48 mmol) and aryl halide **9b** were reacted according to the general procedure A at 80 °C for 40 h with sodium *t*-butoxide as base and $Pd(OAc)_2$/DPPF as a catalyst. The major product was the dehydrohalogenation compound **6a**; yield: 32 mg (8%, 12%^{cbc}); R_f = 0.61 (PE–EtOAc, 1:1). Compound **11a** was isolated as colorless, viscous oil; yield: 15 mg (2%, 5%^{cbc}).

R_f = 0.47 (PE–EtOAc, 1:1).

UV (MeCN): λ_{max}, nm (log ε) = 258 (3.879), 283 (3.458).

IR (KBr): ν = 2976, 2931, 1695, 1165, 782 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.45 (s, 36 H), 1.47 (s, 18 H), 3.38–3.45 (m, 32 H), 6.03 (s, 1 H), 6.17 (d, 2 H, ^3J = 8.1 Hz), 7.07 (t, 1 H, ^3J = 8.2 Hz).

^{13}C NMR (100 MHz): δ = 28.4 (+), 28.5 (+), 28.6 (+), 50.2 (–), 50.7 (–), 79.9 (C_{quat}), 80.0 (C_{quat}), 129.3 (+), 130.0 (+), 137.4 (C_{quat}), 156.3 (C_{quat}).

MS (EI, 70 eV): *m/z* (%) = 1018 (100, M^+), 57 (72).

The *m/z* of the molecular ion is too high to obtain HRMS with our instrumentation. However, the calculated and measured isotope intensity patterns of the M^+ peak are identical (1018 / 100%; 1019 / 62%; 1020 / 22%; 1022 / 10%).

1,3-Bis(1,4,7-tris[*t*-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-pyridine (11b)

Protected azamacrocycle **1a** (2 equiv, 1 g, 2.12 mmol) and bromopyridine **9c** were reacted according to the general procedure B at 80 °C for 62 h with sodium *t*-butoxide as base and $Pd(OAc)_2$ and PPh_3 as a catalyst. Compound **12** was isolated as a side product; yield: 81 mg (7%, 8%^{cbc}), white solid; R_f = 0.19 (PE–EtOAc, 7:3). Compound **11b** was isolated as the major product; yield: 587 mg (54%, 68%^{cbc}); white solid.

R_f = 0.47 (PE–EtOAc, 1:1).

Mp 107 °C.

UV (MeCN): λ_{max}, nm (log ε) = 225 (4.383), 260 (4.031), 320 (4.078).

IR (KBr): 2978, 2934, 1695, 1167, 777 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.45 (s, 54 H), 3.27–3.59 (m, 32 H), 5.92 (d, 2 H, ^3J = 8.1 Hz), 7.23 (t, 1 H, ^3J = 8.1 Hz).

^{13}C NMR (100 MHz): δ = 28.5 (+), 28.6 (+), 49.2 (–), 50.2 (–), 51.8 (–), 79.8 (C_{quat}), 96.1 (+), 138.6 (+), 156.4 (C_{quat}), 158.3 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 1020 (100, MH^+), 1042 (37, $M+Na^+$).

Anal. Calcd for $C_{51}H_{89}N_9O_{12}$: C, 60.04; H, 8.79; N, 12.35. Found: C, 59.83; H, 8.79; N, 11.86.

1-(3-Bromo-2-pyridinyl)-4,7,10-tris(*t*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (10c)

Following the general procedure B, protected azamacrocycle **1a** (2 equiv, 500 mg, 1.06 mmol) and bromopyridine **9c** were reacted at 80 °C for 72 h with caesium carbonate as base and $Pd(OAc)_2$ and PPh_3 as a catalyst. Compound **11b** was isolated as a minor product; yield: 61 mg (11%, 20%^{cbc}), white solid; R_f = 0.47 (PE–EtOAc,

1:1). Compound **10c** was isolated as the major product; yield: 145 mg (43%, 77%[cbc]); white solid.

R_f = 0.64 (PE–EtOAc, 1:1).

Mp 74 °C.

UV (MeCN): λ_{max}, nm (log ∈) = 258 (4.203), 315 (3.736).

IR (KBr): 2978, 2932, 1695, 1169, 776 cm^{-1}.

^{1}H NMR (250 MHz): δ = 1.41 (s, 18 H), 1.43 (s, 9 H), 3.24–3.62 (m, 16 H), 6.44 (d, 1 H, ^3J = 8.3 Hz), 6.67 (d, 1 H, ^3J = 7.4 Hz), 7.19 (dd, 1 H, ^3J = 8.3 Hz, ^3J = 7.3 Hz).

^{13}C NMR (63 MHz): δ = 28.4 (+), 28.5 (+), 49.9 (–), 50.3 (–), 51.9 (–), 80.0 (C_{quat}), 105.1 (+), 115.1 (+), 139.1 (+), 140.0 (C_{quat}), 156.5 (C_{quat}), 158.8 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 630 (100, MH^+, ^{81}Br), 628 (94, MH^+, ^{79}Br), 550 (80, M^+–Br).

Anal. Calcd for $C_{28}H_{46}N_5O_6Br$: C, 53.71; H, 7.38; N, 11.14. Found: C, 53.69; H, 7.30; N, 10.80.

1,3-Bis(1,4,7-tris[*t*-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-bipyridine (12)

According to the general procedure B, **1a** (2 equiv, 500 mg, 1.06 mmol) and dibromobipyridine **9e** were reacted at 80 °C for 38 h with sodium *t*-butoxide as base and $Pd(OAc)_2$ and PPh_3 as a catalyst. Compound **12** was isolated as a white solid; yield: 419 mg (72%, 78%[cbc]).

R_f = 0.19 (PE–EtOAc, 7:3).

Mp 109 °C.

UV (MeCN): λ_{max}, nm (log ε) = 222 (4.726), 267 (4.536), 352 (4.306).

IR (KBr): 2978, 2933, 1695, 1578, 1169, 782 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.45 (s, 54 H), 3.22–3.74 (m, 32 H), 6.59 (d, 2 H, ^3J = 8.2 Hz), 7.52 (t, 2 H, ^3J = 7.8 Hz), 7.65 (d, 2 H, ^3J = 7.3 Hz).

^{13}C NMR (100 MHz): δ = 28.5 (+), 28.6 (+), 50.3 (–), 50.7 (–), 52.2 (–), 79.8 (C_{quat}), 79.9 (C_{quat}), 107.6 (+), 109.6 (+), 137.9 (+), 154.5 (C_{quat}), 156.5 (C_{quat}), 158.6 (C_{quat}).

MS (ESI, 70 eV): *m/z* (%) = 1097 (100, MH^+), 1119 (15, $M+Na^+$).

Anal. Calcd for $C_{56}H_{92}N_{10}O_{12}$: C, 61.29; H, 8.45; N, 12.76. Found: C, 61.63; H, 8.53; N, 12.18.

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