N-Arylation of Protected Azamacrocycles

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Abstract: A rapid method for efficient palladium-catalyzed N-arylation of polynitrogenated macrocycles is presented. Its applicability for functionalization of protected azamacrocycles of various sizes with substituted aryl bromides of optional electronic properties is demonstrated. The compatibility of the protocol with common N-protecting schemes as well as the impact of electronic versus steric factors is discussed. Using a commercially available catalytic system and easily available alkoxide or phenoxide base, the method provides moderate to excellent yields of N-arylated azamacrocycles (45–96%).

Key words: azamacrocycles, N-arylation, C–N coupling, heterocycles, homogeneous catalysis

Owing to their peculiar complexation properties, azamacrocycles has become a coveted class of compounds for a variety of uses. In the past decade, their applicability as scaffolds for magnetic resonance imaging (MRI) contrast agents,[1] tagging systems for protein labeling,[2] and chemical probes for selective detection of transition metals[3] and anions[4] was demonstrated. They were also shown to be applicable, for example, in supramolecular chemistry,[5] biosensing,[6] enantioselective molecular recognition,[7] ion chromatography,[8] degradation of β-amyloids[9] as well as in the treatment of viral diseases.[10]

Among the available polynitrogenated skeletons cyclen, cyclam, and 1,4,7-triazacyclononane (TACN) are by far the most suitable for the above applications. The availability of straightforward synthetic routes for functionalization of one of the macrocyclic nitrogens is crucial for most uses, yet remains a major challenge. So far most syntheses have utilized N-alkylations.[11] Due to the lack of a robust and general synthetic approach for corresponding arylation of polyazamacrocycles, *N*-aryl derivatives have scarcely been reported. Nevertheless, the higher rigidity of *N*-aryl-substituted derivatives is expected to make them superior for numerous applications, such as for artificial receptors,[12] for paramagnetic tagging in NMR,[13] and for selective ionophors.[14] Whereas procedures for cross-coupling of mononitrogenated macrocycles have been successfully developed,[15] efficient N-arylation of polynitrogenated analogues has not yet been achieved. Common features of the few available preparation methods of N-arylated polyazamacrocycles[16] are long reaction times (days), narrow scope, and poor-to-moderate isolated yields. The particular sluggishness of the transformation is explainable by the fact that polyamines in general are recognized as one of the most reluctant substrates in Pd-catalyzed arylations.[16e–g] In addition, polyamines easily form stable transition-metal complexes.[1–3] Although useful in other contexts,[1–10] chelation of transition-metal ions prohibits N-arylation of unprotected polyazamacrocycles in preparatively useful yields.[16e–g]

Although microwave-assisted Pd-catalyzed cross couplings,[17] including general Buchwald–Hartwig reactions,[18] are known, so far no conditions suitable for the N-arylation of polyazamacrocyclic systems were yet established. Herein we report the first rapid, microwave-assisted Buchwald–Hartwig cross coupling protocol of polyazamacrocycles with aryl bromides. Its scope is demonstrated by efficient monofunctionalization of a range of partially protected polynitrogenated skeletons with substituted aryl bromides of varying electronic properties. The compatibility of the reaction conditions with common nitrogen protecting groups is explored.

Optimization studies were performed on tri(*N*-Boc)-cyclen **1**, the most common substrate in azamacrocycle chemistry.[16a] The nature of the catalyst, base, solvent, reaction temperature, and time were thoroughly optimized. Single mode microwave irradiation with careful temperature, pressure, and irradiation power monitoring was applied, making the procedure highly reproducible. The reaction rate of Pd-catalyzed aminations is determined by the reductive elimination step of the catalytic cycle[19] and thus bulky, electron-rich phosphines were expected to yield best conversions. Indeed, $Pd(OAc)_2$ catalyst along with $(t\text{-Bu})_3P$[16b] in a 5:8 ratio turned out superior for the cross coupling. Application of modern dialkylbiaryl phosphine ligands (RuPhos, DavePhos) did not improve conversions. Toluene was chemically compatible with the transformation, but unfavorable for microwave assisted reactions because of its low dipole moment. Originating from its similar chemical properties and excellent microwave absorbance, α,α,α-trifluorotoluene was found to be the most favorable solvent for the cross coupling. This solvent was originally introduced by Curran and coworker[20] for organic reactions and was later successfully applied in microwave-assisted Buchwald–Hartwig reactions.[21] It should be noted here that a 6:1 mixture of toluene–*tert*-butyl alcohol gave comparable microwave absorption and good overall yields, providing a cheap, easily accessible solvent alternative. The reaction temperature was varied between 60 and 180 °C, with 100 °C giving optimal enhancements. Careful optimization of the microwave-assisted protocol allowed shortening of the re-

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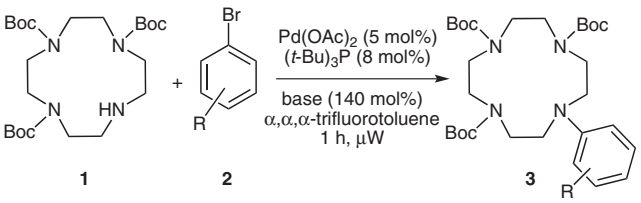
action times from the hitherto reported 24–60 hours[16] to 1 hour without any need for application of an increased amount of palladium catalyst. Longer reaction times or higher temperatures did not lead to higher yields, but in increased extent of side reactions, such as the Ullmann homocoupling of the aromatic moiety.[22] In line with previous studies,[23] microwave heating is not a necessity for the progress of the reaction; it can also be carried out with conventional heating. However, providing firm control of reaction time, temperature and pressure,[23] heating by microwave irradiation was preferred in this study. Numerous bases commonly used in Pd-catalyzed aminations were tried: DBU, MTBD,[24] Cs_2CO_3, K_3PO_4, and KF.[25] They led either to slow reaction rates or no reaction at all. Excellent conversions were obtained using sodium *tert*-butoxide[16c–e] for aryl bromides with *para*-electron-donating substituents (Table 1, entries 1–3 and 5) and the electron-poor *p*-CF_3 substituted analogue (Table 1, entry 8). However, the reaction failed for reactants with electron-withdrawing substituents such as nitro, cyano, or ester, due to competing O-arylation of the base, transesterification and/or substrate decomposition. Similarly, the use of the sterically unhindered and less basic sodium phenoxide[26] resulted in O-arylation. Further optimization revealed that the bulky and thereby less nucleophilic sodium 2,4,6-tri-*tert*-butylphenolate[27a] base is favorable for conversion of electron-poor substrates (Table 1, entries 6 and 7). This soft base was also compatible with electron-rich reactants (Table 1, entries 3 and 4), and provided moderate yields for aryl bromides bearing substituents with various electronic properties in *meta* position (Table 1, entries 9, 10). This observation demonstrates the key role of the applied base for the reaction.[27] In our hands, sterically hindering *ortho* substituents were not compatible with the reaction conditions, and thus 2,4-bromodimethylbenzene and 2,6-bromodimethylbenzene yielded complex product mixtures with only traces of the N-arylated adducts,[28] independently of the choice of base. Utilization of dialkylbiaryl phosphine ligands (RuPhos, DavePhos, etc.), which are commonly applied in modern palladium-mediated cross-coupling protocols for the sterically hindered *ortho*- and *meta*-substituted reactants did not yield any noticeable improvement. Nevertheless, coupling of two heterocycles was successful with any of the above bases (Table 1, entries 11 and 12).

In an attempt to further explore the scope of the reaction, the optimized conditions were applied for straightforward N-arylation of a variety of azamacrocycles (Table 2). Hence, in addition to the N-arylation of cyclen, good overall yields were obtained for monofunctionalization of the six- (piperazine), the seven- (1,4-diazepane), the nine- (TACN), and the fourteen-membered (cyclam) polynitrogenated rings, of which the last is famous for being especially challenging in cross couplings.

The use of protecting groups is inevitable for the selective functionalization of polyazamacrocycles. Therefore, the compatibility of the optimized reaction conditions with common amine-protecting schemes was studied, the results being summarized in Table 3. N-Arylation of the Boc- (Table 1, entry 1) and the CBz-protected cyclenes (Table 3, entry 1) gave the monoarylated products in high yields, whereas that of the formyl-protected[29] (Table 3, entry 2) showed potency for preparative applications. As the trifluoroacetyl group was previously employed for amine-protection in Pd-catalyzed cross couplings,[30] its compatibility with the reaction conditions was assessed, however, due to its reactivity under basic conditions,[31] with limited success (Table 3, entry 3).

Attempts to react cyclenes bearing protecting groups attached via an sp^3-carbon gave only traces of the desired product (Table 3, entries 4–6). This observation reveals the impact of the nature of the protecting group for the outcome of metal-catalyzed cross-coupling reactions of polyazamacrocycles: Protecting groups that delocalize the nitrogen lone pair into an amide or carbamate allow the cross-coupling to proceed, whereas those preserving their amine character do not facilitate the reaction, presumably through inhibition of the catalyst by strong metal complexation. This suggestion is supported by the recent application of a protected cyclen as palladium(II)

Table 1 Buchwald–Hartwig Coupling of *N*-Tri-Boc Cyclen with Functionalized Aryl Bromides

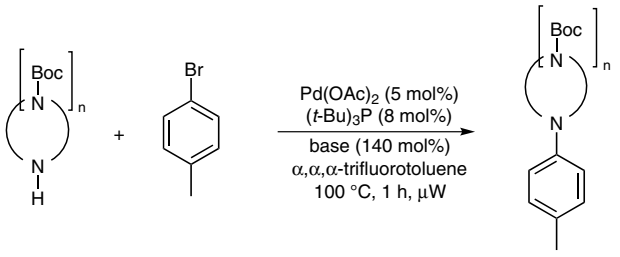


1 2 3

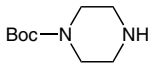
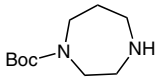
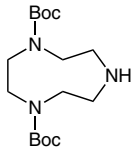
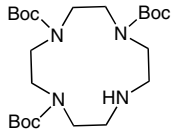
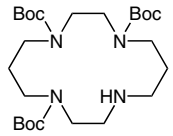
Entry	R[a]	Base[b]	Temp (°C)	Yield (%)[c]
1	*p*-Me	A	100	85
2	*p*-OMe	A	120	83
3	*p*-NMe_2	A	120	72
4	*p*-NMe_2	B	120	75
5	*p*-SMe	A	120	82
6	*p*-CO_2Me	B	100	80
7	*p*-CHO	B	100	70
8	*p*-CF_3	A	80	84
9	*m*-OMe	B	100	45
10	*m*-CO_2Me	B	100	40
11	2-pyridyl	A	100	40
12	6-(2-methylquinolyl)	B	100	60

[a] Relative positions; *p* denotes relative *para*, whereas *m* relative *meta* position of bromine and the R substituent.
[b] Base A: sodium *tert*-butoxide; base B: sodium 2,4,6-tri-*tert*-butylphenoxide.
[c] Isolated yield, following chromatographic purification.

Table 2 Pd-Catalyzed N-Arylation of Polyazamacrocycles with Functionalized Aryl Bromides

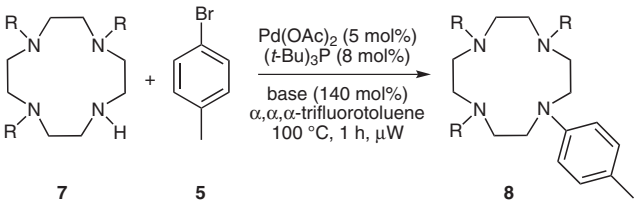


4 5 6

Entry	4	Base[a]	Yield (%)[b]
1		B	96
2		B	89
3		B	95
4		A	85
5		B	86

[a] Base A: sodium *tert*-butoxide; base B: sodium 2,4,6-tri-*tert*-butylphenolate.
[b] Isolated yield, following chromatographic purification.

Table 3 Screening of Protecting Groups Compatible with the Pd-Catalyzed Amination of Polyazamacrocycles



7 5 8

Entry	7	Base[a]	Yield (%)[b]
1	Cbz	A	86
2	CHO	B	60
3	$COCF_3$	B	mixture
4	CH_2CN	B	traces
5	allyl	A	traces
6	CH_2CO_2t-Bu	A	mixture

[a] Base A: sodium *tert*-butoxide; base B: sodium 2,4,6-tri-*tert*-butylphenoxide.
[b] Isolated yield, following chromatographic purification.

scavenger,[32] and by previous reports on difficulties (low yields) to perform arylation of nonprotected or alkylated polyazamacrocycles.[16e–g] The cross-coupling of the bulky tri-Boc (Table 1, entry 1) and tri-Cbz-protected (Table 3, entry 1) cyclenes did not give products in lower yield than the sterically less hindered, flexible triformyl protected one (Table 3, entry 2). This observation is significant in light of the previous suggestion that the bulkiness of nitrogen protecting groups may be the rate limiting factor for the N-arylation of cyclenes.[16a] The collected data demonstrate that conjugation of the free electron pairs of the azacyclic amines is a key element for smooth progress of the catalytic cycle.

Previous methods for Buchwald–Hartwig N-arylation of polyazamacrocycles[16] were neither robust, nor general and suffered from low conversions and long reaction times greatly limiting their applicability. Preceding attempts for selective N-arylation of unprotected polyazamacrocycles gave only low yields,[16e–g] originating from the excellent chelating ability of these macrocycles. The procedure disclosed here provides isolated yields acceptable for preparative work for N-arylation of azamacrocycles of optional size, within one hour. It is demonstrated to be applicable for couplings with a wide range of aryl bromides and its compatibility with common protecting schemes is explored. The use of protecting groups that delocalize those nitrogen lone pair, that are not intended to react in the cross coupling is shown necessary to achieve acceptable yields in N-arylation of polyazamacrocycles.

All reactions were carried out under inert atmosphere (argon or N_2). Solvents were purified according standard techniques[33] or purchased from Sigma Aldrich in Sure/Seal™ bottles and used as received. Cyclen and TACN were purchased from ABCR, cyclam was purchased from Sigma Aldrich; they were used without further purification. Chemicals involved in the Pd-mediated couplings were purified prior to use and stored in a glove box. Solid reagents were grinded and dried overnight in a vacuum desiccator (~1 mbar); liquid reagents were distilled using a Kugelrohr apparatus under argon atmosphere. *t*-BuONa was purchased from Sigma-Aldrich and sublimed in vacuo prior to use. $Pd(OAc)_2$ was purchased from ABCR and was used as a 0.05 M stock solution in anhyd toluene. $(t\text{-Bu})_3P$ was purchased from Sigma-Aldrich as 1 M stock solution in toluene and was diluted to 0.25 M stock solution. 1,4,7-Tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (**1**), 1,4,7-tris(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane, 1,4,7-tris(trifluoroacetyl)-1,4,7,10-tetraazacyclododecane, 1,4,7-tris(formyl)-1,4,7,10-tetraazacyclododecane, 1,4,7-tris(allyl)-1,4,7,10-tetraazacyclododecane, 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane, 1,4,8-tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraaazacyclotetradodecane, and 1,4-bis(*tert*-butoxycarbonyl)-1,4,7-triaazacyclononane were prepared following literature procedures.[34]

Reactions were monitored by LC-MS (ESI) and TLC was carried out on silica gel (Merck 60 F_{254}) or Al_2O_3 plates (Merck 60 F_{254}) us-

ing UV light, ninhydrin and/or Hannesian's reagent for staining. Column chromatography was performed using Merck silica gel (Grade 9385, 230–400 mesh) or Merck Al_2O_3 90 (Active neutral 70–230 mesh, Activity III). All products were characterized by ^1H, ^{13}C NMR, and HRMS. NMR spectra for the synthesized compounds are provided in the Supporting Information (S4–S39). ^1H NMR data are reported in δ units, parts per million (ppm), by referencing to the residual solvent signal ($CDCl_3$ 7.26 ppm, CD_2Cl_2 5.32 ppm, or 1,2-dichloroethane-d_4 6.00 ppm). ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.16 ppm), CD_2Cl_2 (53.84 ppm) or 1,2-dichloroethane-d_4 (73.8 ppm) and were obtained with ^1H broadband decoupling. The NMR data were processed with *MestreNova* (Mestrelab Research S.L.). Pd-mediated cross coupling reactions were carried out in a Biotage® Initiator microwave synthesizer using single mode microwave irradiation with temperature and pressure control. The reaction temperature was held constant throughout the irradiation.[23] LC-MS (ESI/UV) analyses were performed using a PerkinElmer PE Sciex API 150 EX mass spectrometer equipped with a Grace column (Genesis Light C8 4 μm, length 50 mm, ID 4.6 mm) and MeCN–H_2O (95:5) eluent containing 1% formic acid. The chromatograms were analyzed with Analyst 1.5.1 software. Melting points were obtained on a Büchi B-545 melting point apparatus. HRMS analyses were performed by Stenhagen Analys AB, Gothenburg, Sweden.

Note: Due to the flexibility of the cyclenes, most reported NMR spectra contain multiplets belonging to more than one conformer. The presence of conformers was confirmed using variable temperature NMR of selected examples (see Supporting Information, Figures S23, S38, and S39).

1,4,7-Tris(cyanomethyl)-1,4,7,10-tetraazacyclododecane (Table 3, entry 4)

A flame-dried and N_2-purged round-bottomed flask was charged with cyclen (250 mg, 1.45 mmol) and Et_3N (627 μL, 4.50 mmol). The mixture was dissolved in anhyd CH_2Cl_2 (14 mL) and the flask was immersed in an ice/salt bath (–15 °C). A solution of bromoacetonitrile (307 μL, 4.43 mmol) in anhyd CH_2Cl_2 (16 mL) was added using a syringe pump (0.3 mL/min). Upon completion of the addition, the reaction mixture was allowed to warm slowly to r.t. and was stirred overnight. Phosphate buffer (pH 7, 30 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases where dried (Na_2SO_4), filtered, and the organic solvent was removed in vacuo. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH, 4:1) to provide the title compound as a colorless foam (147 mg, 35%).

^1H NMR (400 MHz, CD_2Cl_2–CD_3CN): δ = 9.42 (br s, 2 H), 7.43 (br s, 1 H), 3.68 (s, 4 H), 3.60 (s, 2 H), 3.11–2.51 (m, 16 H).

^{13}C NMR (101 MHz, CD_2Cl_2–CD_3CN): δ = 115.9, 114.0, 50.6, 50.1, 48.4, 45.9, 44.4.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{23}N_7$: 290.2088 $[M + H]^+$; found: 290.2093.

Sodium 2,4,6-Tri-*tert*-butylphenolate[27a]

A flame-dried and argon-purged round-bottomed flask was charged with 2,4,6-tri-*tert*-butylphenol (2 g, 7.62 mmol) and anhyd THF (40 mL). Fine-cut pieces of Na (175 mg, 7.62 mmol) and a small crystal of I_2 was added. A reflux condenser was fitted to the neck of the flask and the system was slowly brought to reflux and kept refluxing overnight. The reaction mixture was cooled to r.t. and the solvent was removed in vacuo (using a rotary evaporator placed inside a glove box). The resulting white precipitate was filtered, washed with small amounts of anhyd THF, and further dried overnight under vacuum (~1 mbar) at 100 °C yielding a greenish solid (1.62 g, 75%). ^1H NMR spectra showed the presence of the alkoxide without coordinated THF molecules, in contrast to the previous report.

^1H NMR (400 MHz, CD_2Cl_2): δ = 7.10 (s, 2 H), 1.45 (s, 18 H), 1.25 (s, 9 H).

Microwave-Assisted Pd-Mediated Couplings; General Procedure

All reactions described here can be carried out under dry conditions on a standard laboratory bench. Motivated by our easy access to a glove box and its superiority for work under dry conditions, the reaction mixtures in this study were prepared inside a glove box. Hence, a flame-dried and N_2-purged Biotage® microwave vial was charged with the alkoxide (*t*-BuONa or sodium 2,4,6-tri-*tert*-butylphenolate, 140 mol%). $Pd(OAc)_2$ (5 mol% from a 0.05 M stock solution in toluene) and $(t\text{-Bu})_3P$ (8 mol% from a 0.25 M stock solution in toluene) were added and the mixture was stirred for 5 min. A solution of the amine (100 mol%) and the aromatic bromide (105 mol%) in α,α,α-trifluorotoluene (0.1 M) was transferred via a syringe to the microwave vial, which was capped, removed from the glove box, and irradiated in the microwave reactor until completion of the reaction. The reaction mixture was diluted with toluene (10 mL), filtered over a plug of Celite, and the solvents were removed in vacuo. The crude products were purified by column chromatography.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(4-methylphenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 1)

Following the general procedure, a mixture of 1,4,7-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (**1**; 102 mg, 0.216 mmol), 4-bromotoluene (39 mg, 0.226 mmol), *t*-BuONa (30 mg, 0.302 mmol), $Pd(OAc)_2$ (214 μL, 1.07×10^{-2} mmol), and $(t\text{-Bu})_3P$ (69 μL, 1.72×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 80:1 to 60:1) to provide the title compound as a colorless solid (104 mg, 85%); mp 156–158 °C.

^1H NMR (400 MHz, CD_2Cl_2): δ = 7.04 (AA′XX′, 2 H), 6.67 (AA′XX′, 2 H), 3.63–3.03 (3 br m, 16 H), 2.24 (s, 3 H), 1.46 (s, 18 H), 1.42 (s, 9 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.6, 156.0, 147.8, 130.1, 128.3, 116.4, 79.9, 79.6, 51.1, 50.3, 49.7, 28.74, 28.67, 20.4.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{51}N_4O_6$: 563.3803 $[M + H]^+$; found: 563.3809.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(4-methoxyphenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 2)

Following the general procedure, a mixture of **1** (100 mg, 0.211 mmol), 4-bromoanisole (41 mg, 0.222 mmol), *t*-BuONa (28 mg, 0.296 mmol), $Pd(OAc)_2$ (210 μL, 1.05×10^{-2} mmol), and $(t\text{-Bu})_3P$ (68 μL, 1.69×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 120 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 60:1 to 40:1) to provide the title compound as a slightly orange solid (101 mg, 83%); mp: a dark gel formed at 78 °C.

^1H NMR (400 MHz, CD_2Cl_2): δ = 6.82 (AA′XX′, 2H), 6.78 (AA′XX′, 2 H), 3.74 (s, 3 H), 3.33 (br m, 16 H), 1.47 (s, 18 H), 1.43 (s, 9 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.5, 155.9, 153.8, 144.1, 119.0, 115.0, 79.9, 79.5, 55.9, 49.9, 49.3, 28.7, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{51}N_4O_7$: 579.3752 $[M + H]^+$; found: 579.3752.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(4-dimethylaminophenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 3)

Following the general procedure, a mixture of **1** (103 mg, 0.218 mmol), 4-bromodimethylaniline (46 mg, 0.229 mmol), *t*-BuONa (29 mg, 0.305 mmol), $Pd(OAc)_2$ (216 μL, 1.08×10^{-2} mmol), and $(t\text{-Bu})_3P$ (70 μL, 1.74×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 120 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 50:1) to provide the title compound as a slightly brown solid (93 mg, 72%); mp: a thick, black gel formed at 82 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.88 (AA′XX′, 2 H), 6.73 (AA′XX′, 2 H), 3.34 (s, 8 H), 3.28 (s, 8 H), 2.86 (s, 6 H), 1.47 (s, 18 H), 1.44 (s, 9 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.3, 155.8, 145.6, 141.5, 120.1, 114.6, 79.9, 79.4, 50.7, 49.6, 41.7, 28.7, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{54}N_5O_6$: 592.4069 $[M + H]^+$; found: 592.4074.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(4-dimethylaminophenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 4)

Following the general procedure, a mixture of **1** (101 mg, 0.214 mmol), 4-bromodimethylaniline (45 mg, 0.224 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (85 mg, 0.299 mmol), $Pd(OAc)_2$ (212 μL, 1.06×10^{-2} mmol), and (*t*-Bu)$_3$P (68 μL, 1.70×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 120 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 50:1) to provide the title compound as a slightly brown solid (94 mg, 75%); mp: a thick, black gel formed at 82 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.88 (AA′XX′, 2 H), 6.73 (AA′XX′, 2 H), 3.34 (s, 8 H), 3.28 (s, 8 H), 2.86 (s, 6 H), 1.47 (s, 18 H), 1.44 (s, 9 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.3, 155.8, 145.6, 141.5, 120.1, 114.6, 79.9, 79.4, 50.7, 49.6, 49.0, 41.7, 28.7, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{54}N_5O_6$: 592.4069 $[M + H]^+$; found: 592.4074.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(4-methylthiophenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 5)

Following the general procedure, a mixture of **1** (100 mg, 0.211 mmol), 4-bromothioanisole (45 mg, 0.222 mmol), *t*-BuONa (28 mg, 0.296 mmol), $Pd(OAc)_2$ (210 μL, 1.05×10^{-2} mmol), and (*t*-Bu)$_3$P (68 μL, 1.69×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 120 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 60:1 to 40:1) to provide the title compound as a slightly yellow solid (104 mg, 82%); mp: a thick, dark gel formed at 73 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.23 (AA′XX′, 2 H), 6.68 (AA′XX′, 2 H), 3.47 (m, 4 H), 3.36 (m, 8 H), 3.24 (br m, 4 H), 2.40 (s, 3 H), 1.45 (s, 18 H), 1.43 (s, 9 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.5, 148.1, 130.9, 125.6, 115.8, 80.0, 79.8, 50.5, 49.6, 28.7, 28.6, 18.7.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{51}N_4O_6S$: 595.3524 $[M + H]^+$; found: 595.3529.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-[4-(methoxycarbonyl)phenyl]-1,4,7,10-tetraazacyclododecane (Table 1, entry 6)

Following the general procedure, a mixture of **1** (104 mg, 0.220 mmol), methyl 4-bromobenzoate (50 mg, 0.231 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (88 mg, 0.308 mmol), $Pd(OAc)_2$ (220 μL, 1.10×10^{-2} mmol), and (*t*-Bu)$_3$P (70 μL, 1.76×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH, 50:1 to 40:1) to provide the title compound as a white foam (107 mg, 80%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.85 (AA′XX′, 2 H), 6.66 (AA′XX′, 2 H), 3.81 (s, 3 H), 3.61 (br s, 4 H), 3.42 (br s, 8 H), 3.32 (br s, 4 H), 1.44 (s, 9 H), 1.42 (s, 18 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 167.4, 157.1, 156.6, 152.3, 131.6, 118.1, 111.9, 80.2, 51.7, 50.6, 49.6, 28.6, 28.5.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{52}N_4O_8$: 607.3701 $[M + H]^+$; found: 607.3707.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-[(4-formyl)phenyl]-1,4,7,10-tetraazacyclododecane (Table 1, entry 7)

Following the general procedure, a mixture of **1** (105 mg, 0.222 mmol), 4-bromobenzaldehyde (43 mg, 0.233 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (88 mg, 0.310 mmol), $Pd(OAc)_2$ (222 μL, 1.11×10^{-2} mmol), and (*t*-Bu)$_3$P (71 μL, 1.77×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH, 50:1 to 40:1) to provide the title compound as a white foam (90 mg, 70%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.71 (s, 1 H), 7.70 (AA′XX′, 2 H), 6.73 (AA′XX′, 1 H), 3.64 (br s, 4 H), 3.44 (br s, 8 H), 3.33 (br m, 4 H), 1.45 (s, 9 H), 1.41 (s, 18 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 190.1, 157.4, 156.5, 153.2, 132.2, 126.2, 112.0, 80.4, 80.3, 54.0, 50.6, 50.5, 49.5, 28.6, 28.5.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{49}N_4O_7$: 577.3596 $[M + H]^+$; found: 577.3601.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(4-trifluoromethylphenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 8)

Following the general procedure, a mixture of **1** (102 mg, 0.216 mmol), 4-bromotrifluoromethylbenzene (51 mg, 0.226 mmol), *t*-BuONa (29 mg, 0.302 mmol), $Pd(OAc)_2$ (214 μL, 1.07×10^{-2} mmol), and (*t*-Bu)$_3$P (69 μL, 1.72×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 80 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 80:1 to 50:1) to provide the title compound as a slightly yellow foam (112 mg, 84%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.44 (AA′XX′, 2 H), 6.69 (AA′XX′, 2 H), 3.58 (t, *J* = 5.3 Hz, 4 H), 3.41 (d, *J* = 3.3 Hz, 8 H), 3.29 (s, 4 H), 1.45 (s, 9 H), 1.43 (s, 18 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.7, 156.1, 150.9, 126.3 (*J* = 3.8 Hz), 125.1 (*J* = 269.9 Hz), 117.8, 112.0, 79.8, 50.2, 49.0, 28.2, 28.1

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{48}F_3N_4O_6$: 617.3520 $[M + H]^+$; found: 617.3526.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(3-methoxyphenyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 9)

Following the general procedure, a mixture of **1** (89 mg, 0.188 mmol), 3-bromoanisole (37 mg, 0.198 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (75 mg, 0.264 mmol), $Pd(OAc)_2$ (188 μL, 9.40×10^{-3} mmol), and (*t*-Bu)$_3$P (60 μL, 1.50×10^{-2} mmol) in α,α,α-trifluorotoluene (1.6 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 5:1) to provide the title compound as a colorless foam (50 mg, 45%). To confirm the presence of rotamers variable temperature NMR (VT-NMR) was run and the spectra are provided in the Supporting Information.

^{1}H NMR (500 MHz, CD_2ClCD_2Cl, 30 °C): δ = 7.12 (t, *J* = 8.2 Hz, 1 H), 6.34 (td, *J* = 8.2, 2.1 Hz, 2 H), 6.28 (t, *J* = 2.1 Hz, 1 H), 3.76 (s, 3 H), 3.56–3.42 (m, 4 H), 3.42–3.32 (m, 8 H), 3.25 (br m, 4 H), 1.46 (s, 18 H), 1.44 (s, 9 H).

^{13}C NMR (126 MHz, CD_2ClCD_2Cl): δ = 159.6, 156.5, 154.8, 154.5, 150.8, 129.4, 108.7, 101.7, 101.1, 79.3, 78.9, 78.6, 57.7, 54.6, 51.9, 50.53, 50.46, 49.9, 27.7, 27.6.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{51}N_4O_7$: 579.3752 $[M + H]^+$; found: 579.3758.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-[3-(methoxycarbonyl)phenyl]-1,4,7,10-tetraazacyclododecane (Table 1, entry 10)

Following the general procedure, a mixture of **1** (94 mg, 0.199 mmol), methyl-3-bromomethylbenzoate (45 mg, 0.209 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (80 mg, 0.278 mmol), $Pd(OAc)_2$ (198 μL, 9.90×10^{-3} mmol), and (*t*-Bu)$_3$P (64 μL, 1.59×10^{-2} mmol) in α,α,α-trifluorotoluene (1.7 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 5:1) to provide the title compound as a colorless foam (49 mg, 40%).

^{1}H NMR (500 MHz, CD_2ClCD_2Cl, 65 °C): δ = 7.45 (d, *J* = 7.6 Hz, 1 H), 7.39 (s, 1 H), 7.32 (dd, *J* = 7.9 Hz, 1 H), 6.94 (dd, *J* = 8.2, 1.9 Hz, 1 H), 3.91 (s, 3 H), 3.56 (t, *J* = 8.2, 4.6 Hz, 4 H), 3.44 (m, 8 H), 3.31 (br m, 4 H), 1.48 (m, 27 H).

^{13}C NMR (126 MHz, CD_2ClCD_2Cl, 105 °C): δ = 167.1, 156.05, 155.97, 149.1, 131.1, 129.1, 119.15, 119.0, 114.7, 79.8, 79.6, 53.2, 51.6, 50.2, 49.8, 49.1, 29.4, 28.4, 28.37.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{51}N_4O_8$: 607.3701 $[M + H]^+$; found: 607.3707.

1,4,7-Tris(*tert*-butoxycarbonyl)-10-(2-pyridinyl)-1,4,7,10-tetraazacyclododecane (Table 1, entry 11)

Following the general procedure, a mixture of **1** (102 mg, 0.216 mmol), 2-bromopyridine (36 mg, 0.226 mmol), *t*-BuONa (29 mg, 0.302 mmol), $Pd(OAc)_2$ (214 μL, 1.07×10^{-2} mmol), and $(t\text{-Bu})_3P$ (69 μL, 1.72×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 2:1 to 1:1) to provide the title compound as a slightly brown foam (48 mg, 40%). The analytical data were in agreement with the literature.[16a]

1,4,7-Tris(*tert*-butoxycarbonyl)-10-[6-(2-methylquinolidinyl)]-1,4,7,10-tetraazacyclododecane (Table 1, entry 12)

Following the general procedure, a mixture of **1** (105 mg, 0.222 mmol), 6-bromo-2-methylquinoline (52 mg, 0.233 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (88 mg, 0.311 mmol), $Pd(OAc)_2$ (222 μL, 1.11×10^{-2} mmol), and $(t\text{-Bu})_3P$ (71 μL, 1.77×10^{-2} mmol) in α,α,α-trifluorotoluene (1.8 mL) was heated to 120 °C for 1 h. The crude product was purified by preparative HPLC (ACE 5 C18-PFP, 250 × 20 mm, isocratic H_2O–MeOH, 20:80, 17 mL/min) to provide the title compound as a colorless foam (82 mg, 60%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.86 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 9.3 Hz, 1 H), 7.23 (dd, *J* = 9.3, 2.8 Hz, 1 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 2.8 Hz, 1 H), 3.60 (br s, 4 H), 3.51–3.33 (m, 8 H), 3.22 (br m, 4 H), 2.62 (s, 3 H), 1.47 (s, 17 H), 1.43 (s, 10 H).

^{13}C NMR (151 MHz, CD_2Cl_2): δ = 156.6, 156.2, 155.7, 147.0, 143.0, 134.7, 130.0, 127.9, 122.5, 121.6, 108.1, 80.1, 79.8, 78.2, 51.0, 50.6, 28.6, 25.0.

HRMS (ESI): *m*/*z* calcd for $C_{33}H_{52}N_5O_6$: 614.3912 $[M + H]^+$; found: 614.3918.

***N*-(*tert*-Butoxycarbonyl)-*N*'-(4-methylphenyl)piperazine (Table 2, entry 1)**

Following the general procedure, a mixture of *N*-(*tert*-butoxycarbonyl)piperazine (50 mg, 0.268 mmol), 4-bromotoluene (48 mg, 0.282 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (107 mg, 0.376 mmol), $Pd(OAc)_2$ (268 μL, 1.34×10^{-2} mmol), and $(t\text{-Bu})_3P$ (86 μL, 2.14×10^{-2} mmol) in α,α,α-trifluorotoluene (2.3 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 50:1 to 10:1) to provide the title compound as a white solid (71 mg, 96%); mp 103–106 °C (Lit.[35] mp 105 °C).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.06 (AA′XX′, 2 H), 6.82 (AA′XX′, 2 H), 3.58-3.49 (m, 4 H), 3.08–3.00 (m, 4 H), 2.25 (s, 3 H), 1.45 (s, 9 H).

The analytical data were in agreement with those reported in the literature.[35]

***N*-1-(*tert*-Butoxycarbonyl)-4-(4-methylphenyl)-1,4-diazepane (Table 2, entry 2)**

Following the general procedure, a mixture of 1-Boc-homopiperazine (52 mg, 0.260 mmol), 4-bromotoluene (47 mg, 0.272 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (103 mg, 0.363 mmol), $Pd(OAc)_2$ (258 μL, 1.29×10^{-2} mmol) and $(t\text{-Bu})_3P$ (83 μL, 2.07×10^{-2} mmol) in α,α,α-trifluorotoluene (2.3 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 50:1 to 10:1) to provide the title compound as a hygroscopic white solid (67 mg, 89%); mp: not determined (Lit.[36] mp: not reported).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.00 (AA′XX′, 2 H), 6.61 (AA′XX′, 2 H), 3.51 (m, 6 H), 3.26 (t, *J* = 5.9 Hz, 1 H), 3.18 (t, *J* = 5.9 Hz, 1 H), 2.21 (s, 3 H), 1.94 (m, 2 H), 1.41 (s, 5 H), 1.33 (s, 4 H).

The analytical data were in agreement with those reported in the literature.[36]

1,4-Bis(*tert*-butoxycarbonyl)-7-(4-methylphenyl)-1,4,7-triazacyclononane (Table 2, entry 3)

Following the general procedure, a mixture of 1,4-bis(*tert*-butoxycarbonyl)-1,4,7-triaazacyclononane (103 mg, 0.313 mmol), 4-bromotoluene (56 mg, 0.328 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (124 mg, 0.438 mmol), $Pd(OAc)_2$ (312 μL, 1.56×10^{-2} mmol) and $(t\text{-Bu})_3P$ (100 μL, 2.50×10^{-2} mmol) in α,α,α-trifluorotoluene (2.7 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 10:1) to provide the title compound as a white solid (125 mg, 95%); mp 113–116 °C.

^{1}H NMR (400 MHz, CD_2Cl_2, rotamers): δ = 7.02–6.97 (m, 2 H), 6.63–6.58 (m, 2 H), 3.57–3.45 (m, 4 H), 3.45–3.31 (m, 8 H), 1.47 (s, 9 H), 1.39 (s, 5 H), 1.36 (s, 4 H).

^{13}C NMR (101 MHz, CD_2Cl_2, rotamers): δ = 156.03, 155.97, 155.8, 146.6, 146.2, 130.1, 130.0, 126.1, 125.9, 125.7, 113.2, 113.0, 112.9, 79.9, 79.8, 79.8, 53.25, 53.18, 53.0, 51.9, 51.0, 50.0, 49.9, 49.8, 49.6, 40.9, 48.6, 28.7, 28.6, 28.52, 28.46, 20.3.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{38}N_3O_4$: 420.2857 $[M + H]^+$; found: 420.2862.

1,4,8-Tris(*tert*-butoxycarbonyl)-11-(4-methylphenyl)-1,4,8,11-tetraazacyclotetradodecane (Table 2, entry 5)

Following the general procedure, a mixture of 1,4,8-tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraaazacyclotetradodecane (55 mg, 0.110 mmol), 4-bromotoluene (20 mg, 0.115 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (44 mg, 0.154 mmol), $Pd(OAc)_2$ (110 μL, 5.40×10^{-3} mmol), and $(t\text{-Bu})_3P$ (35 μL, 8.70×10^{-3} mmol) in α,α,α-trifluorotoluene (1 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, hexane–EtOAc, 3:1) to provide the title compound as a white foam (56 mg, 86%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.99 (AA′XX′, 2 H), 6.68 (AA′XX′, 2 H), 3.48–3.15 (m, 16 H), 2.22 (s, 3 H), 1.90–1.71 (m, 4 H), 1.48 (s, 9 H), 1.46 (s, 9 H), 1.43 (s, 9 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.0, 155.9, 147.3, 130.0, 126.5, 113.7, 79.9, 79.8, 79.7, 51.6, 49.9, 48.9, 47.4, 46.7, 30.1, 28.61, 28.60, 28.57, 20.3.

HRMS (ESI): *m*/*z* calcd for $C_{32}H_{55}N_4O_6$: 591.4116 $[M + H]^+$; found: 591.4122.

1,4,7-Tris(benzyloxycarbonyl)-10-(4-methylphenyl)-1,4,7,10-tetraazacyclododecane (Table 3, entry 1)

Following the general procedure, a mixture of 1,4,7-tris(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (102 mg, 0.177 mmol), 4-bromotoluene (32 mg, 0.186 mmol), *t*-BuONa (24 mg, 0.248 mmol), $Pd(OAc)_2$ (176 μL, 8.80×10^{-3} mmol), and $(t\text{-Bu})_3P$ (57 μL, 1.41×10^{-2} mmol) in α,α,α-trifluorotoluene (1.6 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–*i*-PrOH, 60:1) to provide the title compound as a white foam (102 mg, 86%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.48–7.19 (m, 15 H), 7.05 (AA′XX′, 2 H), 6.69 (AA′XX′, 2H), 5.13 (s, 4 H), 5.01 (s, 2 H), 3.33 (br s, 16 H), 2.27 (s, 3 H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 157.0, 156.4, 147.7, 137.5, 137.3, 130.2, 128.8, 128.7, 128.5, 128.4, 128.2, 128.0, 117.9, 67.3, 67.1, 50.6, 49.9, 49.4, 20.5.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{45}N_4O_6$: 665.3334 $[M + H]^+$; found: 665.3339.

1,4,7-Tris(formyl)-10-(4-methylphenyl)-1,4,7,10-tetraazacyclododecane (Table 3, entry 2)

Following the general procedure, a mixture of 1,4,7-tris(formyl)-1,4,7,10-tetraazacyclododecane (106 mg, 0.414 mmol), 4-bromotoluene (74 mg, 0.434 mmol), sodium 2,4,6-tri-*tert*-butylphenolate (165 mg, 0.578 mmol), $Pd(OAc)_2$ (412 μL, 2.06×10^{-2} mmol) and $(t\text{-Bu})_3P$ (132 μL, 3.30×10^{-2} mmol) in α,α,α-trifluorotoluene–1,4-dioxane (1:1, 3.5 mL) was heated to 100 °C for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH, 1:40) to provide the title compound as a white foam (86 mg, 60%). The presence of rotamers in the acquired NMR spectra was confirmed by VT-NMR. The spectra at various temperatures are provided in the Supporting Information.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.17–7.78 (several singlets, 3 H), 7.22–7.12 (m, 2 H), 7.01–6.96 (m, 1.2 H), 6.95–6.92 (m, 0.6 H), 6.88 (d, *J* = 8.4 Hz, 0.2 H), 3.80–3.74 (m, 0.4 H), 3.72–3.57 (m, 4.3 H), 3.58–3.51 (m, 1.3 H), 3.48–3.19 (m, 10 H).

^{13}C NMR (126 MHz, CD_2ClCD_2Cl): δ = 165.0, 164.6, 164.4, 164.3, 164.2, 164.1, 164.0, 163.90, 163.86, 163.8, 163.54, 163.52, 147.5, 147.2, 147.1, 134.2, 134.0, 133.2, 130.7, 130.65, 130.4, 123.0, 122.7, 122.2, 121.4, 59.5, 57.4, 56.3, 55.4, 55.3, 54.4, 53.0, 52.1, 51.4, 50.3, 49.5, 48.4, 48.2, 48.0, 47.6, 47.5, 47.1, 47.0, 46.0, 45.8, 45.4, 45.0, 44.8, 44.6, 44.3, 43.9, 43.7, 43.4, 43.2, 43.1, 20.8, 20.74, 20.72, 20.70.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{27}N_4O_3$: 347.2078 $[M + H]^+$; found: 347.2083.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^{1}H and ^{13}C NMR spectra.

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