Tetrahedron 70 (2014) 5730–5738

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and tunable ion-recognition properties of novel macrocyclic triamides

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ARTICLE INFO

Article history:
Received 12 March 2014
Received in revised form 28 May 2014
Accepted 17 June 2014
Available online 20 June 2014

Keywords:
Macrocyclic triamides
Lithium hexamethyldisilazide (LiHMDS)
Anion and metal receptors

ABSTRACT

In this work, we report synthesis of rigid macrocyclic triamides and their tunable ion-recognition properties as selective anion and metal receptors. Diphenylacetylene-containing cyclic triamide **CTA-1b** and three cyclic triamides bearing functional methoxy and pyrimidine moieties were prepared by Lithium Hexamethyldisilazide (LiHMDS)-assisted cyclocondesation. **CTA-1b** displayed strong binding affinity to Cl^- and I^- anions, while **CTA-2b** exhibited a good binding affinity to the La^{3+} and Eu^{3+} cations. The selective recognition ability of ions has been tuned by incorporating pyrimidine and methoxy groups into the macrocyclic amides.

1. Introduction

Macrocyclic molecules have been attracting extensive attention in supramolecular chemistry owing to their unique conformational and cavity structures, their versatile ability to include various guests and their possibility of forming supramolecular assemblies in the past decades.[1–5] Of particular interest are cavity-containing molecules that bind ions with high affinity and selectivity, because ions play important chemical and biological roles in physiology, environmental disciplines, and food science.[6–8] As a consequence, tremendous efforts have been devoted to designing and synthesizing novel and functional macrocyclic host molecules, such as calixpyrroles,[9] cucurbiturils,[10] calixarenes,[11] heterocalixaromatics,[12] etc. Among these classes of macrocyclic molecules, macrocyclic amides should be highlighted as ion-recognition host owing to their direct hydrogen bonding interactions with ions.[13–17] However, commonly adopted stepwise manners cannot achieve satisfying yields of macrocyclic amides. In this regard, our previous study has shown that a cyclic triamide, namely **CTA-1a**, with a triangle-shaped cavity can be obtained in 62% yield via one-step cyclotrimerization reaction by treating an aminoester with 5 equiv of lithium hexamethyldisilazide (LiHMDS).[18] Thus, there is still a clear need to systematically study ion-recognition properties of this type of triangle cavity-containing macrocyclic amides. In addition, the expansion of the facile LiHMDS-assisted trimeric cyclization approach to functional aminoester remains to be further confirmed.

In this article, we report on synthesis and ion-recognition properties based on new macrocyclic amides with triangle cavity. Herein, a series of new cyclic triamides were prepared by facile cyclocondensation of the corresponding aminoesters promoted with LiHMDS. The structures of new cyclic triamides, named **CTA-1b**, **CTA-2**, and **CTA-3**, were shown in Fig. 1. It is particularly intriguing to investigate their tunable ion-recognition properties by functional moieties in the cyclic triamide. When incorporating pyrimidine and methoxy groups, **CTA-2** was found to serve as a cation receptor while **CTA-1** displayed strong binding affinity to Cl^- and I^- anions.

2. Results and discussion

2.1. Synthesis

The requisite aminoester **AE-1b** was prepared by Sonogashira reaction, as shown in Scheme 1A. The synthetic routes of **AE-2** bearing both the pyrimidine and methoxy units were outlined in Scheme 1B. The pyrimidine-containing derivatives, *N*-alkyl-2-iodo-5-aminopyrimidine (**10**) were prepared from 2-chloro-5-nitropyrimidine (**7**). Methyl 4-ethynyl-3,5-dimethoxybenzoate (**6**) was synthesized by iodination of 3,5-dihydroxybenzoic acid,

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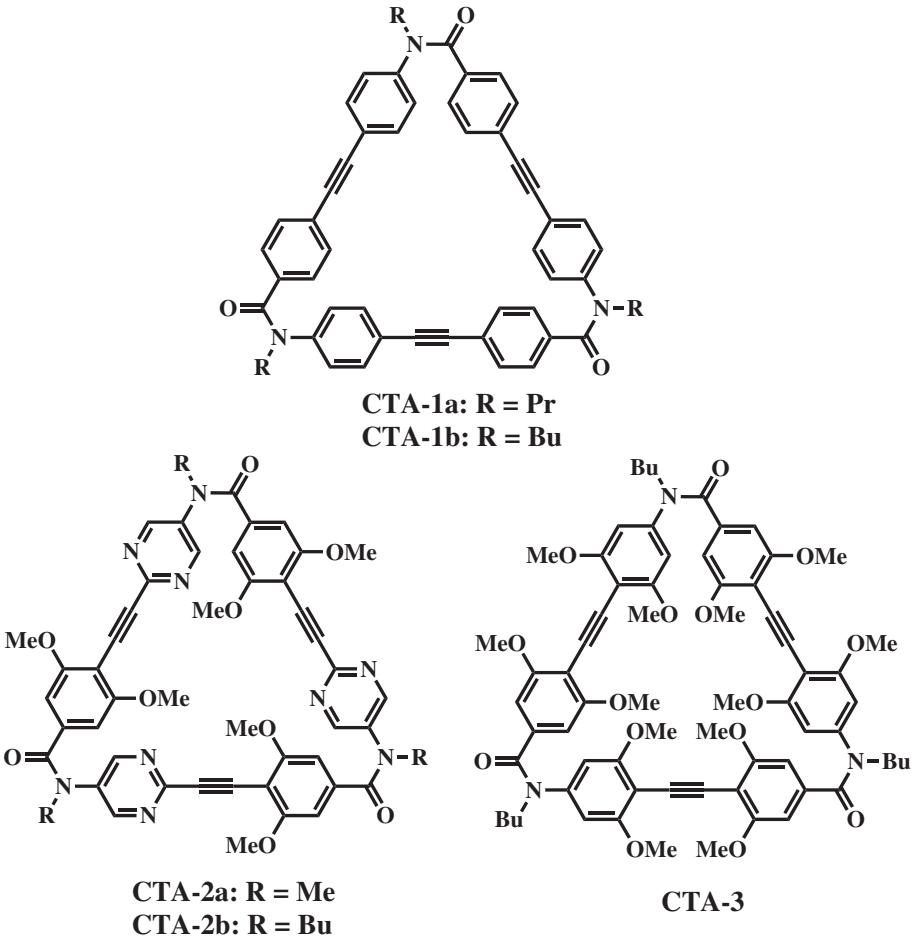


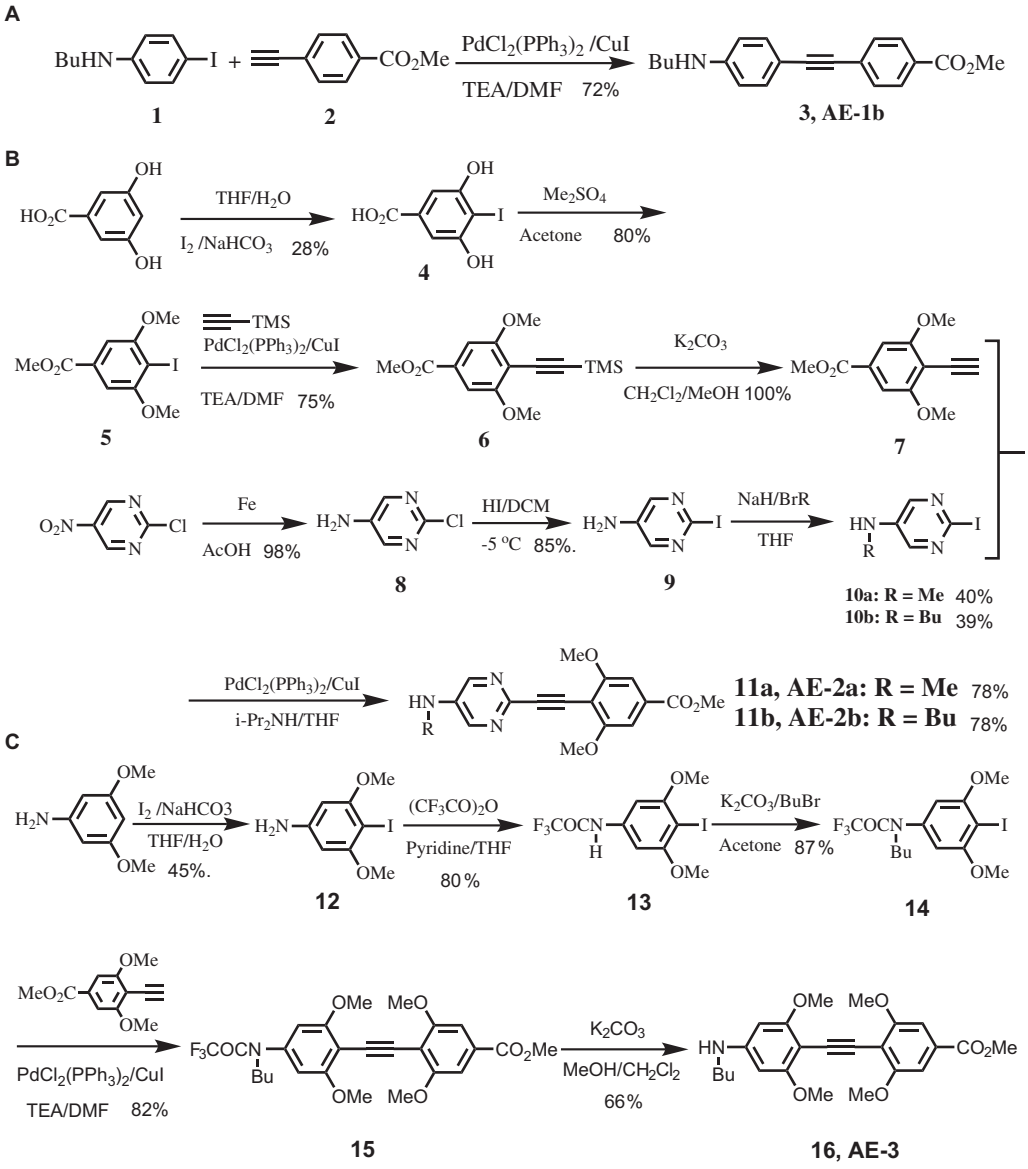
Fig. 1. Molecular structures of **CTA-1**, **CTA-2**, and **CTA-3**.

methylation, followed by Sonogashira reaction. The Sonogashira reaction of **10** with **6** led to the *N*-methyl- and *N*-butyl-substituted aminoesters **AE-2a** and **AE-2b**, respectively. The aminoester, methyl 4-((4-(butylamino)-2,6-dimethoxyphenyl) ethynyl)-3,5-dimethoxybenzoate (**AE-3**) with four methoxy group was prepared stepwise from methyl 4-((4-(*N*-butyl-2,2,2-trifluoroacetamido)-2,6-dimethoxyphenyl)ethynyl)-3,5-dimethoxybenzoate (**15**). Compound **14** was obtained from 3,5-dimethoxyaniline (**11**) via iodination, protection, Sonogashira reaction, and deprotection (Scheme 1C). In this procedure, it should be noted that the protection of the amino group with an electron-withdrawing trifluoroacetyl group is necessary to activate aromatic iodine for efficient Sonogashira reaction to give **15** in 82% yield. The incorporation of electron-withdrawing group at both sides is an efficient method to eliminate the negative effect of electron-donating group, allowing successful Sonogashira reaction to obtain **15**.

As shown in Scheme 2, the rigid macrocyclic triamides of **CTA-1b**, **CTA-2a**, **CTA-2b**, and **CTA-3** were prepared by cyclocondensation of different aminoester monomers **AE-1b**, **AE-2a**, **AE-2b**, and **AE-3**, respectively, with LiHMDS at room temperature.

The products of one-step cyclotrimerization reaction were measured by gel-permeation chromatography (GPC). All the GPC profiles were normalized before result discussion. The molecular weight information obtained from GPC curves was provided in Table 1. As shown in Fig. 2a, **AE-1b** was almost consumed with 1.2 equiv of LiHMDS to afford **CTA-1b** in 50% yield after isolation with preparative HPLC using $CHCl_3$ as eluent. This facile method to prepare cyclic triamides in good yield may be attributed to the cis-preferred conformation in *N*-alkylated aromatic amides.[19] The aminoester **AE-2a** (0.3 mmol) was dissolved in dried THF (15 mL) under argon before LiHMDS (1 M in THF, 1.2 equiv) was quickly injected via a syringe. The mixture was stirred at room temperature for 2 h, followed by quenching with aqueous NH_4Cl. The analysis of the mixture showed a sharp peak accompanied with a broad polymer peak. The crude product was then purified to give the cyclic triamide **CTA-2b** with a promising isolation yield of 52%, suggesting a facile one-step preparation for the macrocyclic amides obtained. The GPC profiles indicated that the aminoester was consumed within 1 h at room temperature. When a large amount of LiHMDS (5 equiv) was employed, the yield of macrocyclic amide **CTA-2b** decreased (Fig. 2b, line 1).

Too much base possibly caused the decomposition of **CTA-2b** containing functional groups, which is different from our previous work using 5 equiv of LiHMDS.[18] Under similar conditions, **CTA-3**, a cyclic triamide with 12 methoxy groups, was also synthesized. It was found that considerable monomer remained in the reaction mixture, which might be originated from the deactivation of LiHMDS caused by the Li^+ binding in crown-ether-like 12 methoxy groups located at **CTA-3**. This hypothesis was confirmed further with the similar results by increasing the amount of LiHMDS from 1.2 to 2 equiv (Fig. 2c, line 4). To avoid the deactivation, LiHMDS was subsequently added dropwise over 0.5–1 h. The GPC profile (Fig. 2c, line 5) indicated that **AE-3** was almost consumed to produce the cyclic triamide **CTA-3** in 20% yield. The lower yield of **CTA-3**, compared to that of **CTA-2**, was attributed to the combined effects of both deactivation of LiHMDS caused by the cation binding and the stereo-hindrance of the 12 methoxy groups.



Scheme 1. Synthesis routes of **AE-1b**, **AE-2a**, **AE-2b**, and **AE-3**.

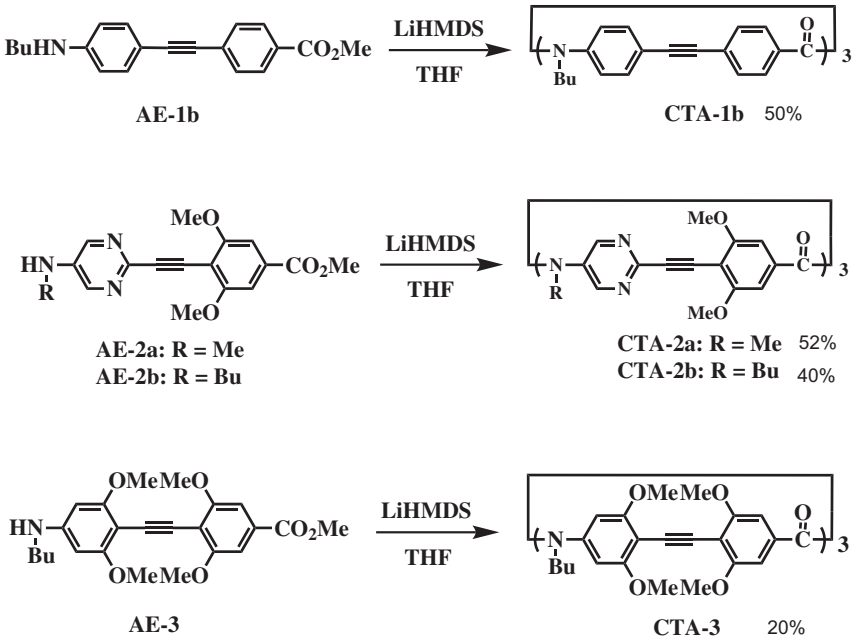
2.2. Ion-recognition properties

The anion-recognition properties of **CTA-1b**, with the unique triangle cavity as we described above, was first revealed by ^{1}H NMR spectroscopy, in which 1 equiv of **CTA-1b** was quantitatively titrated with up to 5 equiv of tetrabutylammonium chloride (TBACl) or tetrabutylammonium iodide (TBAI) in $CDCl_3$ at room temperature. As it can be seen from the ^{1}H NMR spectra of **CTA-1b** in Fig. 3, all protons on the aromatic rings were shifted toward the upfield with the addition of TBACl or TBAI to **CTA-1b**. When 5 equiv of TBACl was added, the signal of the aromatic protons on the carbon adjacent to the amino group was shifted by 0.10 ppm, which clearly indicated binding of the anion inside the central cavity. A peak shift could exhibit a strong binding nature between the host and guest.[17] In the case of titration with 5.0 equiv of TBAI, the shift of the signal was 0.06 ppm.

The recognition properties of **CTA-1b** toward Cl^- were supported by energy minimization calculation using MM2 force field as illustrated in Fig. 4. The geometry optimization revealed that **CTA-1b** exhibits equilateral triangle conformation with the aromatic rings slightly inclined from the perpendicular plane to the triangle. The diameter of the macrocycle cavity is about 7.5 Å, which is large enough to hold the anions such as Cl^- (d=3.34 Å) and I^- (d=4.12 Å). The driving force for **CTA-1b** to bind anions can be attributed to the weak C—H···Cl or C—H···I hydrogen bonding as additional binding sites within a host cavity.[20] It should be noted that **CTA-1b**—Cl^-/—I^- binding complexes were induced by an relatively weak symmetrical non-coplanar hydrogen bonding inclined to the cavity plane, whose shift of the signal (about 0.10 ppm) was lower than that of strong coplanar binding complexes with hydrogen bonding.[21–24]

CTA-2b was also studied for binding halide anions such as Cl^-, Br^- and I^-, but little change was observed by ^{1}H NMR titration (see Fig. 5). This low responsibility can be attributed to that the six-electron-rich methoxy groups symmetrically stretched out on both sides of the cavity plane, and the charge repulsion between electron-rich methoxy groups and halide anions prevents the binding interaction.

When **CTA-1b** was employed to bind the cations such as La^{3+} and Eu^{3+}, the recognition cannot be seen under the same experimental conditions, implying a weak binding affinity of **CTA-1b** to



Scheme 2. Synthesis routes of **CTA-1b**, **CTA-2a**, **CTA-2b**, and **CTA-3**.

Table 1
The molecular weight information of the new cyclic amides

Macrocycles	Yield (%)	M_n (GPC)	M_w (GPC)	PDI (M_n/M_w)	Mass MALDI-TOF
CTA-1b	50	978	1012	1.03	827.15
CTA-2a	52	747	780	1.04	887.10
CTA-2b	40	1046	1096	1.05	1013.12
CTA-3	20	1154	1184	1.03	1187.11

those cations (see Fig. 6). However, **CTA-2b** with the functional moieties of pyrimidine and methoxy group showed opposite binding behaviours compared to **CTA-1b**.

When 1 equiv of $(CF_3SO_3)_3La$ was added to **CTA-2b** in DMSO-d_6, both sets of the aryl protons signals (proton 1 and 2, proton 3 and 4, Fig. 7) were observed to split into double peaks. When 3 equiv of La^{3+} was added, the peak split into triple peaks, suggesting the coexistence of 1:1 and 1:2 complexes in the system. Note that when 10 equiv of La^{3+} was added, the triple peaks combined to single signals again with a little chemical shift compared to the neat **CTA-2b**, indicating that one host molecule of **CTA-2b** binds two guest cations to afford a 1:2 complex. The recognition properties using

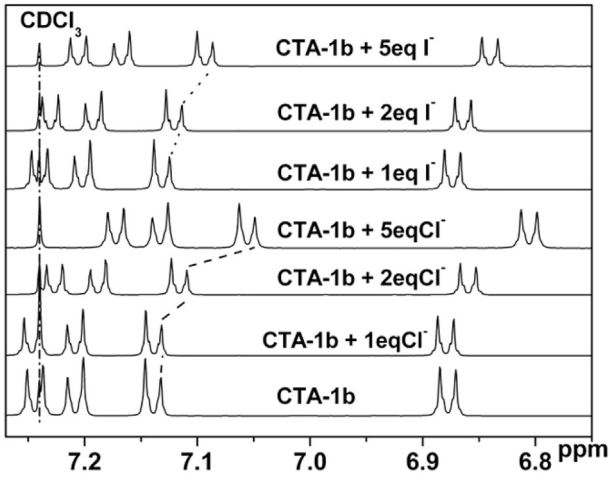


Fig. 3. ^{1}H NMR spectra (aromatic region) of **CTA-1b** upon titration with TBACl and TBAI ($CDCl_3$, 298 K).

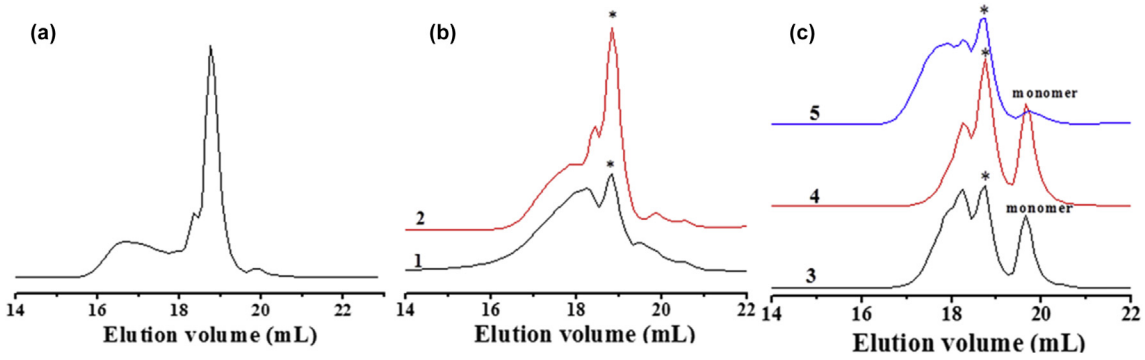


Fig. 2. Representative GPC profiles for the preparation of cyclic triamides from different aminoesters. (a) **CTA-1b**; (b) **CTA-2b**; (c) **CTA-3**. Line 1: 5 equiv LiHMDS; line 2: 1.2 equiv LiHMDS; line 3: 5 equiv LiHMDS; line 4: 2 equiv LiHMDS; line 5: 1.2 equiv LiHMDS was dropped. Peaks of cyclic triamides.

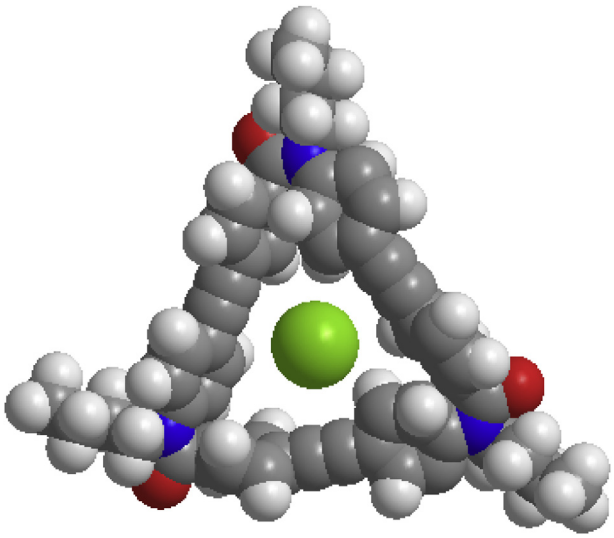


Fig. 4. Lowest energy conformation of **CTA-1** with MM2 field force. Cl^- anion was held inside the cavity.

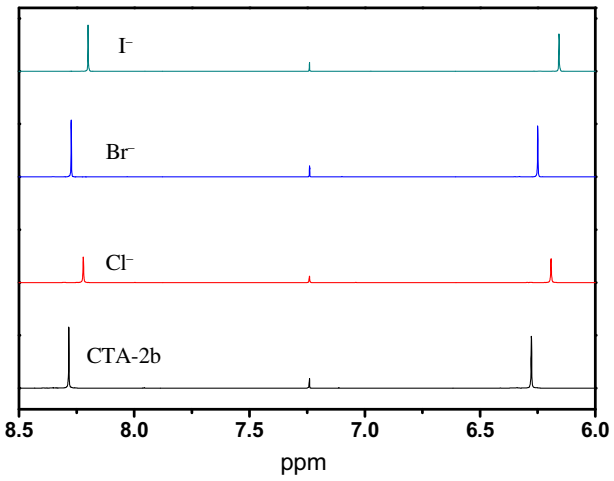


Fig. 5. ^1H NMR spectra of **CTA-2b** upon titration with 5 equiv TBACl, TBABr, and TBAI ($CDCl_3$, 298 K).

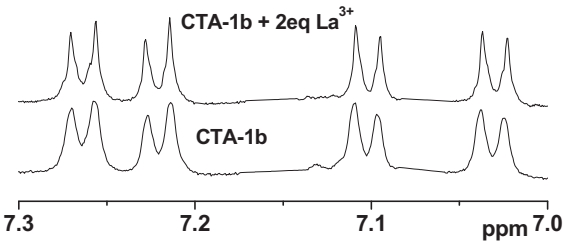


Fig. 6. ^1H NMR spectra (aromatic region) of **CTA-1b** upon titration with La^{3+} (DMSO-d_6, 298 K).

$(CH_3CO_2)_3Eu$ salts as a guest showed similar results. The signal splitting as a result of binding cations can be explained by the fact that **CTA-2b** has symmetric structures with reorganized ligand binding elements of pyrimidine and methoxy group.

One La^{3+} can be coordinated by one set of ligands consisting of three N atoms and three methoxy groups in **CTA-2b** around one side of the cavity plane (Fig. 8a). Consequently, the **CTA-2b**/La^{3+}=1:1 complex has different chemical environment around the

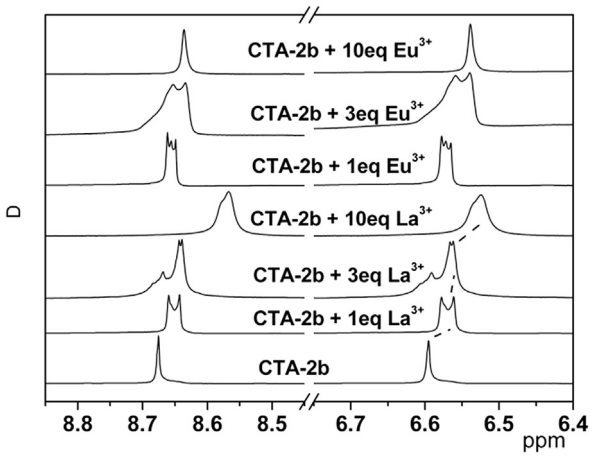


Fig. 7. ^1H NMR spectra (aromatic region) of **CTA-2b** upon titration with $(CF_3SO_3)_3La$ and $(CH_3CO_2)_3Eu$ (DMSO-d_6, 298 K).

two sides of the cavity. The proton pairs of 1 and 2, and 3 and 4 were subsequently separated into double peaks. When both sides bind two cations, the proton pairs of 1 and 2, and 3 and 4 display the same chemical shifts arising from the symmetrical charge distributions (Fig. 8b).

It is also noted that the methoxy signals exhibited the same splitting behaviour when quantitative equivalent of La^{3+} was added (Fig. 9). Clearly, the proton splitting changes fit well into the 1:1 and 1:2 complex as well as the both coexistent complexes when different equivalent of cations were added. **CTA-3** was also titrated with La^{3+}, but insoluble product was obtained.

3. Conclusion

In summary, diphenylacetylene-containing cyclic triamide **CTA-1b**, and three cyclic triamides bearing functional methoxy groups or pyrimidine moieties were first prepared by a facile one-step LiHMDS-assisted cyclocondensation in a mild reaction condition. **CTA-1** displayed strong binding affinity to Cl^- and I^- anions, while weak responsibility to La^{3+} and Eu^{3+} cations. By incorporating functional moieties into the cyclic triamide, **CTA-2** was transferred into a cation receptor. Thus, tuning the ion-recognition ability of macrocyclic amides has been successfully fulfilled, which provides an easy and effective strategy to design new ion receptors. Further investigation about the ion recognition of these cyclic triamides is under progress.

4. Experimental section

4.1. General information

Commercially available THF (Kanto) (stabilizer-free) was used as dry solvent. LiHMDS (1.0 M solution in THF, Aldrich), $Pd(PPh_3)_4$, triethylamine, isopropylamine, trifluoroacetic anhydride, *n*-butylbromide, and methylbromide were purchased from TCI and used as received. CuI and chloroform were provided by Kanto. Compounds **1**,[25] compounds **2**,[26] 2-chloro-5-nitropyrimidine[27] were synthesized according to the reported methods, respectively. ^1H and ^{13}C NMR spectra were measured on JEOL ECA-600 spectrometers in $CDCl_3$ or DMSO-d_6. The M_n and M_w/M_n of oligomer were measured with a TOSOH HLC-8120 gel-permeation chromatography (GPC) unit (eluent: tetrahydrofuran (THF), calibration: polystyrene standards) using two TSK-gel columns (2×Multipore HXL-M). The molecular weights of intermediates were determined on a gas chromatograph mass spectrometer (GC–MS) with a Shimadzu GC–MS-QP5050A.

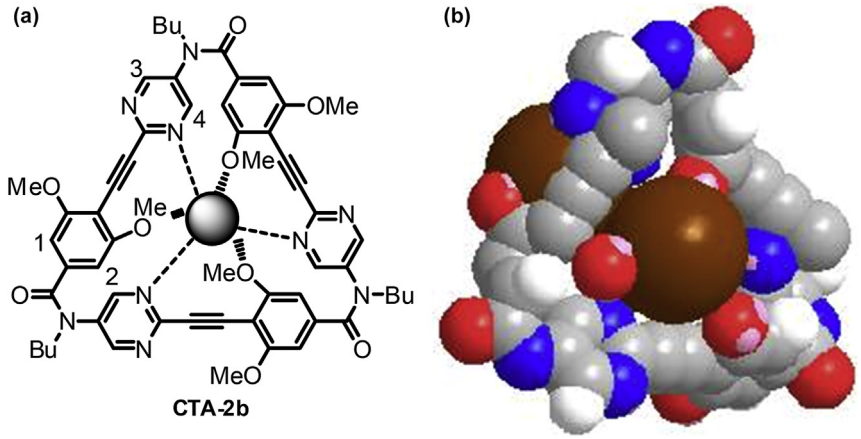


Fig. 8. Binding structure of **CTA-2b** to La^{3+}. (a) One La^{3+} was bound; the position of protons 1, 2, 3, and 4 at the aromatic region wase also labelled. (b) Two La^{3+} were bound with MM2 field force. Butyl and methyl were omitted for clarity.

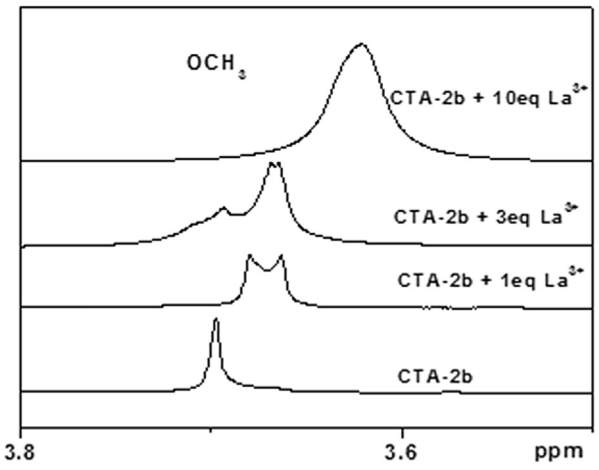


Fig. 9. ^{1}H NMR spectra (methoxy) of **CTA-2b** upon titration with $(CF_3SO_3)_3La$ (DMSO-d_6, 298 K).

MALDI-TOF mass spectra were recorded on a Shimadzu/Krotos Axima CFR in the linear mode using a laser (λ=337 nm). Sample solutions of macrocycles (1 mg), with dithranol (30 mg) as a matrix, were prepared in chloroform (5.5 mL). Column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh, Merck) with specified solvents. IR spectra were recorded on a JASCO FT/IR-410. Isolation of macrocycles was carried out with a Japan Analytical Industry LC-908 Recycling Preparative HPLC (eluent: chloroform) using two TSK-gel columns (2×G 2000HHR).

4.2. Synthesis

*4.2.1. Synthesis of methyl 4-((4-(butylamino)phenyl)ethynyl)benzoate (**3**).* A mixture of **1** (1.100 g, 4.0 mmol), **2** (0.641 g, 4.0 mmol), $PdCl_2(PPh_3)_2$ (0.140 g, 0.2 mmol), CuI (0.076 g, 0.4 mmol), and PPh_3 (0.105 g, 0.4 mmol) was degassed and back replaced by argon, followed by injection of dried DMF (40 mL) and triethylamine (TEA, 1.5 mL). The mixture was stirred at room temperature for 3 h before it was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$ (30 mL×3). The organic layer was washed with brine for 2 times and the combined organic solvents were dried over anhydrous $MgSO_4$ before the solvents were removed in vacuum. The residue was purified by column chromatography (silica gel using 1:10 of EA/hexane as eluent) to give a yellow solid of **3**. Yield: 0.885 g, 72%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.95–7.97 (d, J=8.2 Hz, 2H), 7.50–7.52 (d, J=8.2 Hz, 2H), 7.32–7.35 (d, J=8.2 Hz, 2H), 6.51–6.54 (d, J=8.2 Hz, 2H), 3.90 (s, 3H), 3.85 (br s, 1H), 3.10–3.13 (t, J=7.2 Hz, 2H), 1.57–1.62 (quint, J=7.2 Hz, 2H), 1.40–1.43 (sext, J=7.2 Hz, 2H), 0.93–0.96 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 166.7, 148.8, 133.1, 131.0, 129.4, 129.0, 128.5, 112.2, 110.1, 94.1, 86.7, 52.1, 43.2, 31.5, 20.2, 13.8. FTIR (KBr, cm^{-1}): 3388, 2931, 2861, 2206, 1697, 1595, 1435, 1279, 1112, 829, 772, 695. MS (EI, m/z): calcd: 307.2; found: 307 (M^+).

*4.2.2. Synthesis of 3,5-dihydroxy-4-iodobenzoic acid (**4**).* 3,5-Dihydroxybenzoate (5.045 g, 30 mmol) was dissolved in THF and H_2O (70 mL:70 mL) at 0 °C, to which iodine (8.009 g, 31.5 mmol) and $NaHCO_3$ (2.660 g, 31.5 mmol) were added in four portions, respectively, in 4 h. The mixture was stirred for 1 day at room temperature. The mixture of iodine (3.20 g, 12.6 mmol) and $NaHCO_3$ (1.064 g, 12.6 mmol) was added and stirred for another 2 days at room temperature. The mixture was diluted with ether and stirred with K_2SO_3 before the red colour disappeared and then extracted with ether (50 mL×3). After evaporation, the residue was recrystallized from methanol to afford **4** as a yellow crystal. Yield: 2.000 g, 28%. ^{1}H NMR (600 MHz, DMSO-d_6): 10.51 (br s, 2H), 6.93 (s, 2H), 3.79 (s, 6H). ^{13}C NMR (150 MHz, DMSO-d_6): 166.0, 158.3, 130.6, 105.8, 81.8, 52.2. MS (EI, m/z): calcd: 279.9; found: 280 (M^+).

*4.2.3. Synthesis of methyl 4-iodo-3,5-dimethoxybenzoate (**5**).* The mixture of **4** (5.600 g, 19.0 mmol), K_2CO_3 (8.540 g, 61.8 mmol), and acetone (50 mL) was heated at reflux for 4 h. After cooling to room temperature, it was quenched with water and extracted with ether. The organic phase was washed with brine and dried over $MgSO_4$. After removing all the solvents, the residue was recrystallized from methanol to give **5** as white needles. Yield: 4.900 g, 80%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.14 (br s, 2H), 3.90–3.93 (m, 9H). ^{13}C NMR (600 MHz, DMSO-d_6): 166.6, 159.4, 131.8, 104.7, 84.2, 56.8, 52.4. MS (EI, m/z): calcd: 322.0; found: 322 (M^+).

*4.2.4. Synthesis of methyl 3,5-dimethoxy-4-((trimethylsilyl)ethynyl) benzoate (**6**).* A 30 mL flask was charged with compound **5** (322.1 mg, 1.0 mmol), PPh_3 (26.2 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and bis(triphenylphosphine)palladium(II) dichloride (36.0 mg, 0.05 mmol). The mixture was degassed and backfilled with argon, to which TEA (5 mL) and DMF (10 mL) were added by injection. Then the mixture was sealed with a rubber septum and stirred at room temperature for 5 min before trimethylsilylacetylene (0.3 mL, 2.0 mmol) was added by injection. The mixture was stirred at 60 °C for 20 h, then quenched with NH_4Cl and extracted with ether (20 mL×3). The organic layer was washed with brine for 2 times. The combined organic layer was dried over anhydrous $MgSO_4$

before evaporation. The residue was purified by column chromatography on silica gel using 1:8 EA/hexane as eluent to give a white solid of **6**. Yield: 0.220 g, 75%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.18 (br, s, 2H), 3.90–3.91 (m, 9H), 1.36–1.39 (t, J=7.2 Hz, 3H), 0.27–0.28 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): 163.3, 160.6, 159,0, 133.8, 123.7, 62.2, 14.2. MS (EI, m/z): calcd: 292.1; found: 292 (M^+).

*4.2.5. Synthesis of methyl 4-ethynyl-3,5-dimethoxybenzoate (**7**).* A mixture of **6** (0.220 g, 0.8 mmol), K_2CO_3 (0.518 g, 3.8 mmol), dried methanol (10 mL), and dichloromethane (10 mL) was stirred at room temperature for 2 h, which was then quenched with water and extracted with ether (20 mL×3). The organic layer was washed with brine and dried over $MgSO_4$ before evaporation to give a brown solid of **7**. Yield: 0.165 g, 100%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.20 (s, 2H), 3.92 (s, 6H), 3.90 (s, 3H), 3.65 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): 166.4, 161.8, 131.5, 104.6, 104.5, 87.8, 75.7, 56.3, 52.5. FTIR (KBr, cm^{-1}): 3272, 2952, 1714, 1578, 1458, 1129, 1000, 766, 670. MS (EI, m/z): calcd: 220.0; found: 220 (M^+).

*4.2.6. Synthesis of 2-chloropyrimidin-5-amine (**8**).* A mixture of 2-chloro-5-nitropyrimidine (0.160 g, 1 mmol), iron powder (0.200 g, 3.6 mmol), dried ethanol (2.5 mL), and acetic acid (0.4 mL) was refluxed for 6 h, which was then diluted with ethyl acetate, and neutralized with aqueous $NaHCO_3$ before it was filtered with Celite. The filtrate was extracted with ethyl acetate (20 mL×3), washed with brine, and dried over $MgSO_4$. Evaporation of the solvents gives a yellow solid of **8**. Yield: 0.127 g, 98%. ^{1}H NMR (600 MHz, DMSO-d_6): 8.03 (s, 2H), 5.76 (br s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): 146.0, 144.2, 142.3. FTIR (KBr, cm^{-1}): 3394, 3332, 3212, 1649, 1585, 1545, 1412, 1163, 644. MS (EI, m/z): calcd: 129.0; found: 129 (M^+).

*4.2.7. Synthesis of 2-iodopyrimidin-5-amine (**9**).* A 20 mL flask was charged with **8** (0.648 g, 5.0 mmol) and cooled by salt ice bath to −5 °C, then HI (57%, 6.67 mL, 10 equiv) was added dropwise and stirred for 5 h at −5 °C. The mixture was quenched with water and neutralized carefully by 5 g $NaHCO_3$ to pH=7–8 followed by decolorized with K_2SO_3. The solution was extracted by ethyl acetate and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvents afforded a yellow crystal of **9**. Yield: 0.939 g, 85%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.93 (s, 2H), 5.72 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): 144.4, 143.1, 110.8. FTIR (KBr, cm^{-1}): 3368, 3300, 3185, 1629, 1571, 1536, 1402, 1123, 890, 735, 638. MS (EI, m/z): calcd: 220.9; found: 221 (M^+).

*4.2.8. Synthesis of N-methyl-2-iodo pyrimidin-5-amine (**10a**).* Compound **9** (2.300 g, 10.4 mmol) was dissolved in 25 mL dried THF and cooled to 0 °C, to which NaH (60% in paraffin liquid, 0.200 g, 5 mmol) was added in potions under nitrogen. The mixture was stirred at for 1 h, then warmed to room temperature for another 1 h before Bu_4NBr (0.161 g, 5 mmol) and MeBr (1.56 mL, 25 mmol) were added under nitrogen. The mixture was stirred overnight and then quenched with methanol and extracted with ethyl acetate. After removing the solvents, the residue was purified by column chromatography (silica gel using EA/hexane=1:3 then increased 2:1 as eluent) to give a yellow solid of **10a** (0.470 g, 40%). ^{1}H NMR (600 MHz, DMSO-d_6): 7.84 (s, 2H), 6.25 (br s, 1H), 2.67 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): 143.4, 142.5, 111.6, 28.7. FTIR (KBr, cm^{-1}): 3326, 2992, 1580, 1486, 1391, 1128, 627. MS (EI, m/z): calcd: 235.0; found: 235 (M^+).

*4.2.9. Synthesis of N-butyl-2-iodopyrimidin-5-amine (**10b**).* Compound **10b** was prepared in the similar procedure as **10a** using *n*-butylbromide instead of methylbromide. Yield: 39%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.84 (s, 2H), 3.80 (br s, 1H), 3.06–3.09 (t, 2H), 1.57–1.60 (m, 2H), 1.36–1.42 (m, 2H), 0.91–0.94 (q, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 144.4, 143.1, 111.4, 42.78, 31.0, 20.0, 13.7. FTIR (KBr, cm^{-1}): 3291, 2949, 1629, 1578, 1496, 1400, 1119, 631. MS (EI, m/z): calcd: 277.0; found: 277 (M^+).

*4.2.10. Synthesis of methyl 3,5-dimethoxy-4-((5-(methylamino)pyrimidin-2-yl) ethynyl)benzoate (**11a**).* A mixture of **10a** (0.168 g, 0.7 mmol), **7** (0.172 g, 0.8 mmol), $PdCl_2(PPh_3)_2$ (0.050 g, 0.07 mmol), and CuI (0.014 mg, 0.07 mmol) was degassed and replaced by argon, to which dried THF (5.5 mL) and diisopropylamine (0.27 mL) were injected subsequently. The mixture was stirred for 24 h at room temperature before evaporation to remove THF. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane=3:1 as the eluent to give a yellow solid of **11a** (0.180 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): 8.11 (s, 2H), 7.21 (s, 2H), 4.01 (br s, 1H), 3.93 (s, 6H), 3.90 (s, 3H), 2.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 168.5, 161.7, 142.4, 140.8, 140.5, 131.3, 105.3, 104.3, 98.7, 56.2, 29.7. FTIR (KBr, cm^{-1}): 3276, 2947, 1725, 1579, 1420, 1326, 1239, 1125, 765. MS (EI, m/z): calcd: 327.1; found: 327 (M^+).

*4.2.11. Synthesis of methyl 4-((5-(butylamino)pyrimidin-2-yl)ethynyl)-3,5-dimethoxybenzoate (**11b**).* Compound **11b** was synthesized in the similar Sonogashira cross-coupling reaction as **11a** starting from **10b** and **7**. Yield: 78%. ^{1}H NMR (600 MHz, $CDCl_3$): 8.07 (s, 2H), 7.19 (s, 2H), 3.96 (br s, 1H), 3.91(s, 6H), 3.89 (s, 3H), 3.12–3.15 (t, J=7.2 Hz, 2H), 1.58–1.61 (quint, J=7.2 Hz, 2H), 1.38–1.40 (sext, J=7.2 Hz, 2H), 0.91–0.94 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 166.5, 161.6, 142.4, 140.6, 140.2, 131.3, 105.3, 104.3, 98.8, 56.2, 52.3, 42.7, 31.1, 20.0, 13.7. FTIR (KBr, cm^{-1}): 3267, 2934, 1731, 1580, 1431, 1329, 1238, 1132, 762. MS (EI, m/z): calcd: 369.2; found: 369 (M^+).

*4.2.12. Synthesis of 4-iodo-3,5-dimethoxyaniline (**12**).* 3,5-Dimethoxyaniline (1.532 g, 10 mmol) was dissolved in THF (25 mL) and H_2O (25 mL) and cooled to 0 °C, to which iodine (2.665 g, 10.5 mmol) and $NaHCO_3$ (0.882 g, 10.5 mmol) were added in three portions, respectively, in 3 h. The mixture was diluted with ether and stirred with K_2SO_3 before the red colour disappeared and then extracted with ether. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation, the residue was recrystallized from methanol and THF to afford **12** as a grey crystal. Yield: 1.25 g, 45%. ^{1}H NMR (600 MHz, DMSO-d_6): 5.93 (s, 2H), 5.37 (br s, 2H), 3.69(s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6): 159.0, 151.0, 91.0, 59.0, 55.7. MS (EI, m/z): calcd: 279.0; found: 279 (M^+).

*4.2.13. Synthesis of 2,2,2-trifluoro-N-(4-iodo-3,5-dimethoxyphenyl) acetamide (**13**).* A 10 mL flask was charged with **12** (0.279 g, 1 mmol), then degassed and backfilled with argon. Dried CH_2Cl_2 (5 mL) and pyridine (0.12 mL) were added by injection. The mixture was cooled by ice bath, and then trifluoric acid anhydride (TFAA, 0.2 mL) was added dropwise. The mixture was stirred for 1.5 h at 0 °C, warmed to room temperature, and stirred for 1.5 h. The mixture was quenched with brine and extracted with ethyl acetate, washed with 5% HCl, brine, $NaHCO_3$, and brine, respectively. After evaporation, the yellow residue was purified by column with SiO_2 using ethyl acetate/hexane=1:4 as eluent to give a white crystal of **13**. Yield: 0.3000 g, 80%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.94 (br s, 2H), 6.81 (s, 2H), 3.76 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): 59.8, 154.6, 137.2, 114.6, 96.6, 73.8, 56.7. MS (EI, m/z): calcd: 375.0; found: 375 (M^+).

*4.2.14. Synthesis of N-butyl-2,2,2-trifluoro-N-(4-iodo-3,5-dimethoxyphenyl)acetamide (**14**).* A 50 mL flask was charged with **13** (1.522 g, 4 mmol), K_2CO_3 (1.658 g, 12 mmol), acetone (15 mL) and BuBr (2.58 mL, 24 mmol). The mixture was heated at reflux for 16 h before acetone was removed in vacuum. The residue was extracted with ethyl acetate and the organic phase was dried over $MgSO_4$. After removing the solvents, the residue was purified by column chromatography (on silica gel using EA/hexane=1:6) to give a colourless liquid of **14** (1.500 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$): 6.30

(s, 2H), 3.83 (s, 6H), 3.69–3.69 (t, J=7.7 Hz, 2H), 1.49–1.53 (quint, J=7.7 Hz, 2H), 1.26–1.31 (sext, J=7.7 Hz, 2H), 0.84–0.87 (t, J=7.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 170.9, 165.7, 159.6, 156.6, 156.3, 156.1, 155.8, 141.0, 119.7, 117.4, 115.1, 104.0, 78.1, 56.6, 51.5, 29.0, 19.7, 13.5. FTIR (KBr, cm^{-1}): 3369, 3162, 3081, 2964, 2875, 1690, 1577, 1450, 1115, 955, 849, 821, 754, 683. MS (EI, m/z): calcd: 431.0; found: 431 (M^+).

*4.2.15. Synthesis of methyl 4-((4-(N-butyl-2,2,2-trifluoroacetamido)-2,6-dimethoxyphenyl)ethynyl)-3,5-dimethoxybenzoate (**15**).* A 20 mL flask was charged with compound **14** (0.302 g, 0.7 mmol), **7** (0.166 g, 0.75 mmol), PPh_3 (20 mg, 10%), CuI (14 mg, 10%), and $PdCl_2(PPh_3)_2$ (26 mg, 5%). The mixture was degassed and backfilled with argon before injecting died TEA (4 mL) and dried DMF (7.5 mL). The mixture was sealed with a rubber septum and heated to 60 °C for 30 h, then quenched with NH_4Cl, and extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with brine for 2 times and dried over $MgSO_4$ before the solvents were evaporated in vacuum. The residue was purified with column chromatography on silica gel using ethyl acetate/hexane (1:3) as eluent to give a yellow solid of **15**. Yield: 0.301 g, 82%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.21 (s, 2H), 6.35 (s, 2H), 3.95 (s, 6H), 3.90 (s, 3H), 3.89 (s, 6H), 3.69–3.72 (t, J=7.6 Hz, 2H), 1.52–1.54 (quint, J=7.6 Hz, 2H), 1.29–1.33 (sext, J=7.6 Hz, 2H), 0.87–0.89 (t, J=7.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 166.6, 162.5, 161.4, 160.9, 156.6, 156.4, 140.4, 130.9, 117.3, 115.4, 106.6, 104.6, 104.4, 103.9, 102.9, 91.8, 91.4, 56.6, 56.5, 52.5, 51.5, 29.2, 19.9, 13.7. MS (EI, m/z): calcd: 523.2; found: 523 (M^+).

*4.2.16. Synthesis of methyl 4-((4-(butylamino)-2,6-dimethoxyphenyl) ethynyl)-3,5- dimethoxybenzoate (**16**).* A 10 mL flask was charged with **15** (0.130 g, 0.25 mmol), K_2CO_3 (1.380 g, 10 mmol), dichloromethane (2 mL), and methanol (2 mL). The mixture was stirred at 40 °C for 48 h and then quenched with aqueous NH_4Cl. The solution was extracted with $CHCl_3$ (10 mL×3), washed with brine, and dried over $MgSO_4$. After evaporation, the yellow residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1:3) as eluent to give a yellow solid of **16**. Yield: 0.070 g, 66%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.20 (s, 2H), 5.73 (s, 2H), 3.90 (br s, 1H), 3.89 (s, 3H), 3.88 (s, 6H), 3.10–3.12 (t, J=7.2 Hz, 2H), 1.58–1.61 (quint, J=7.2 Hz, 2H), 1.40–1.44 (sext, J=7.2 Hz, 2H), 0.93–0.96 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 166.9, 162.5, 159.9, 150.7, 129.0, 108.3, 104.5, 95.7, 91.0, 88.4, 88.1, 56.5, 56.3, 52.2, 43.4, 31.6, 20.3, 13.9. FTIR (KBr, cm^{-1}): 3397, 2933, 2198, 1692, 1583, 1458, 1238, 1186, 1129, 749. MS (EI, m/z): calcd: 427.2; found: 427 (M^+).

*4.2.17. Synthesis of the cyclic triamide **CTA-1b**.* Aminoester **AE-1b** (0.236 g, 0.77 mmol) was dissolved in dried THF (38 mL) under argon before LiHMDS (1 M in THF, 0.92 mL, 1.2 equiv) was injected. The mixture was stirred at room temperature for 2 h followed by quenched with NH_4Cl. The solution was extracted with $CHCl_3$ (20 mL×3) and the organic phase was dried over anhydrous $MgSO_4$. The solvents were removed under vacuum to afford a yellow solid, which was then purified by preparative HPLC using $CHCl_3$ as the eluent to give a yellow solid of **CTA-1b**. Yield: 0.106 g, 50%. ^{1}H NMR (600 MHz, $CDCl_3$): 7.23–7.25 (d, J=8.2 Hz, 6H), 7.20–7.22 (d, J=8.2 Hz, 6H), 7.13–7.15 (d, J=8.2 Hz, 6H), 6.87–6.89 (d, J=8.2 Hz, 6H), 3.89–3.92 (t, J=7.2 Hz, 6H), 1.57–1.58 (quint, J=7.2 Hz, 6H), 1.32–1.35 (sext, J=7.2 Hz, 2H), 0.87–0.90 (t, J=7.2 Hz, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): 169.5, 143.1, 135.9, 132.2, 130.8, 128.4, 127.6, 123.8, 121.1, 89.7, 89.5, 49.5, 29.7, 20.1, 13.7. FTIR (KBr, cm^{-1}): 3449, 2957, 2870, 1648, 1515, 1382, 1295, 1120, 761. MALDI-TOF mass: 827.15 $(M+H)^+$.

*4.2.18. Synthesis of cyclic triamide **CTA-2a**.* Aminoester **AE-2a** (0.098 g, 0.3 mmol) was dissolved in dried THF (15 mL) under argon. LiHMDS (0.36 mL, 1 M in THF) was added by injection. The mixture was stirred at room temperature for 2 h before it was quenched with aqueous NH_4Cl. The solution was extracted with $CHCl_3$ (10 mL×3) and the organic phase was dried over $MgSO_4$. The solvents were removed under vacuum to give a yellow solid, which was then purified by preparative HPLC to give a yellow solid of **CTA-2a**. Yield: 0.046 g, 52%. ^{1}H NMR (600 MHz, $CDCl_3$): 8.38 (s, 6H), 6.36 (s, 6H), 3.70 (s, 18H), 3.53 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): 169.9, 162.7, 154.5, 150.8, 138.1, 137.2, 104.6, 102.4, 97.3, 81.7, 56.8, 38.0. FTIR (KBr, cm^{-1}): 3423, 2924, 2223, 1655, 1602, 1567, 1428, 1237, 1129, 846, 794. MALDI-TOF mass: 887.10 $(M+H)^+$.

*4.2.19. Synthesis of **CTA-2b**.* A 50 mL flask was placed aminoester **AE-2b** (0.369 g, 1 mmol), followed by degassing and replacing argon. Then 25 mL THF was injected and the solid was dissolved with the assistance of microwave. LiHMDS (1.3 mL, 1 M in THF) was added by injection under argon. The mixture was stirred at room temperature for 2 h before it was quenched with NH_4Cl. The solution was extracted with $CHCl_3$ (10 mL×3) and the organic phase was dried over $MgSO_4$. The solvents were removed under vacuum to afford a yellow solid (0.290 g), which was then purified by preparative HPLC to give a yellow solid of **CTA-2b** (0.134 g, 40%). ^{1}H NMR (600 MHz, $CDCl_3$): 8.28 (s, 6H), 6.27 (s, 6H), 3.81–3.84 (t, J=7.6 Hz, 6H), 3.63 (s, 18H), 1.47–1.50 (quint, J=7.6 Hz, 6H), 1.23–1.27 (sext, J=7.6 Hz, 6H), 0.78–0.81 (t, J=7.6 Hz, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): 168.9, 161.9, 154.7, 150.1, 137.1, 136.1, 103.8, 101.2, 96.5, 81.1, 56.1, 49.2, 29.5, 19.7, 13.4. FTIR (KBr, cm^{-1}): 3449, 2958, 2871, 2221, 1656, 1602, 1566, 1533, 1498, 1427, 1334, 1279, 1237, 1129, 846, 795, 761. MALDI-TOF mass: 1013.12 $(M+H)^+$.

*4.2.20. Synthesis of cyclic triamide **CTA-3**.* Aminoester **AE-3** (42.7 mg, 0.1 mmol) was dissolved in dried THF (2 mL) under argon before the mixture of LiHMDS (1 M in THF, 0.12 mL, 1.2 equiv) and 0.5 mL dried THF was added dropwise in 0.5 h. The mixture was stirred at room temperature for another 2 h followed by quenching with aqueous NH_4Cl. The solution was extracted with $CHCl_3$ (10 mL×3) and the organic phase was dried over anhydrous $MgSO_4$. The solvents were removed under vacuum to afford a yellow solid, which was then purified by preparative HPLC using $CHCl_3$ as the eluent to give a yellow solid of **CTA-3** (6.8 mg, 20%). ^{1}H NMR (600 MHz, $CDCl_3$): 6.48 (s, 6H), 6.13 (s, 6H), 3.89–3.94 (t, J=7.2 Hz, 6H), 3.68 (s, 18H), 3.67 (s, 18H), 1.58–1.61 (quint, J=7.2 Hz, 6H), 1.33–1.36 (sext, J=7.2 Hz, 2H), 0.88–0.90 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 169.4, 161.1, 160.2, 144.6, 136.6, 104.2, 103.8, 103.2, 100.9, 90.7, 56.6, 56.4, 49.7, 30.0, 20.2, 13.8. FTIR (KBr, cm^{-1}): 2935, 1646, 1567, 1460, 1409, 1235, 1186, 1130, 746. MALDI-TOF mass: 1187.11 $(M+H)^+$

Acknowledgements

This work was financially supported by National Natural Science Foundation of China (No. 51273209, No. 21102156), Projects from Ningbo Science and Technology Bureau (2012D10009, 2013D10013, 2013A610032) and the External Cooperation Program of the Chinese Academy of Sciences (No. GJHZ1219).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.06.062.

References and notes

1. Orr, G. W.; Barbour, L. J.; Atwood, J. L. *Science* **1999**, *285*, 1049.
2. He, L.; An, Y.; Yuan, L. H.; Feng, W.; Li, M. F.; Zhang, D. C.; Yamato, K.; Zheng, C.; Zeng, X. C.; Gong, B. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10850.
3. Sawai, T.; Sato, K.; Ise, T.; Shiomi, D.; Toyota, K.; Morita, Y.; Takui, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3988.

4. Gao, D.; Meier, H. *Asian J. Org. Chem.* **2014**, *3*, 244, http://dx.doi.org/10.1002/ajoc.201300224.
5. Aeluri, M.; Pramanik, C.; Chetia, L.; Mallurwar, N. K.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Org. Lett.* **2013**, *15*, 436.
6. Amendola, V.; Boiocchi, M.; Colasson, B.; Fabbrizzi, L.; Douton, M. J. R.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6920.
7. Chernikova, E.; Berdnikova, D.; Fedorov, Y.; Fedorova, O.; Peregudov, A.; Isaacs, L. *Chem. Commun.* **2012**, 7256.
8. Baxter, P. N. W.; Gisselbrecht, J.-P.; Karmazin-Brelot, L.; Varnek, A.; Allouche, L. *Chem.—Eur. J.* **2013**, *19*, 12336.
9. Bucher, C.; Zimmerman, R. S.; Lynch, V.; Král, V.; Sessler, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2099.
10. Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621.
11. Mutihac, L.; Lee, J. H.; Kim, J. S.; Vicens, J. *Chem. Soc. Rev.* **2011**, *40*, 2777.
12. Wang, M.-X. *Chem. Commun.* **2008**, 4541.
13. Korendovych, I. V.; Cho, M.; Butler, P. L.; Staples, R. J.; Rybak-Akimova, E. V. *Org. Lett.* **2006**, *8*, 3171.
14. Chmielewski, M. J.; Jurczak, J. *Chem.—Eur. J.* **2006**, *12*, 7652.
15. Hennig, A.; Fischer, L.; Guichard, G.; Matile, S. *J. Am. Chem. Soc.* **2009**, *131*, 16889.
16. Hossain, M. A.; Kang, S. O.; Kut, J. A.; Day, V. W.; Bowman-James, K. *Inorg. Chem.* **2012**, *51*, 4833.
17. Li, F.; Gan, G.; Xue, L.; Wang, Z.-M.; Jiang, H. *Tetrahedron Lett.* **2009**, *50*, 2367.
18. (a) Yokohama, A.; Maruyama, T.; Tagami, K.; Masu, H.; Katagiri, K.; Azumaya, I.; Yokozawa, T. *Org. Lett.* **2008**, *10*, 3207; (b) Yokoyama, A.; Shimizu, Y.; Saito, J.; Yokozawa, T. *Chem. Lett.* **2008**, *37*, 8.
19. Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shuodo, K. *Tetrahedron* **1995**, *51*, 5277.
20. Bryantsev, V. S.; Hay, B. P. *J. Am. Chem. Soc.* **2005**, *127*, 8282.
21. Li, Y.; Flood, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2649.
22. McDonald, K.; Hua, P. Y.; Lee, S.; Flood, A. H. *Chem. Commun.* **2012**, 5065.
23. Lee, S.; Flood, A. H. *J. Phys. Org. Chem.* **2013**, *26*, 79.
24. Masu, H.; Okamoto, T.; Kato, T.; Katagiri, K.; Tominaga, M.; Goda, H.; Takayanagi, H.; Azumaya, I. *Tetrahedron Lett.* **2006**, *47*, 803.
25. Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987.
26. Liu, G.; Gooding, J. J. *Langmuir* **2006**, *22*, 7421.
27. US Patent, 2003, US181465 A1.