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High-Yielding Syntheses of Crown Ether-Based Pyridyl Cryptands

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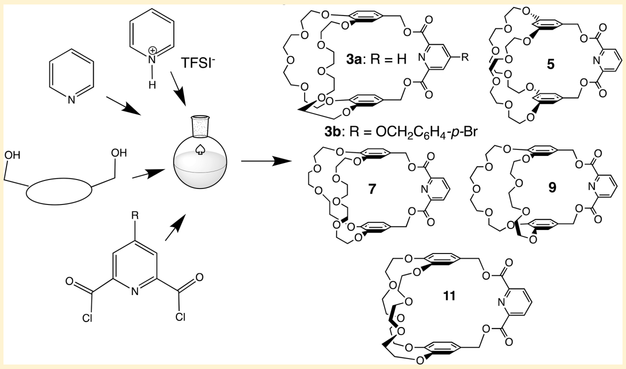
Supporting Information

ABSTRACT: Pyridinium bis(trifluoromethylsulfonyl)imide (PyTFSI)-templated syntheses of 2,6-pyridyl cryptands of *cis*(4,4′)-dibenzo-30-crown-10 (**3a**), the *p*-bromobenzyloxy derivative **3b**, bis(*m*-phenylene)-32-crown-10 (**5**), *cis*(4,4′)-dibenzo-27S-crown-9 (**7**), *cis*(4,4′)-dibenzo-27L-crown-9 (**9**), and *cis*(4,4′)-dibenzo-24-crown-8 (**11**) are reported. Here we provide a fast (12 h), high-yielding (89%, 74%, 80%, and 62% for **3a**, **3b**, **5**, and **9**, respectively) templation method without the use of a syringe pump. The yields for **7** (19%) and **11** (26%) were lower than with the previous pseudo-high-dilution method, indicating ineffective templation in these cases. Coupled with our previously developed templated syntheses of dibenzo crown ethers, this protocol makes powerful cryptand hosts readily available in gram quantities in good yields from methyl 4(or 3)-hydroxy-3(or 4)-benzyloxybenzoate.



INTRODUCTION

Crown ethers have long been studied for their ability to produce supramolecular structures such as pseudorotaxanes and rotaxanes,[1] which can lead to a range of unique molecular architectures and properties such as self-healing and other "smart" materials. Due to the size and shape of the crown ethers' binding cavities, they interact differently with different types of guests. For example, dibenzo-24-crown-8 (DB24C8) and derivatives associate well with dialkyl ammonium salts,[2] bispyridinium ethanes,[3] and imidazolium salts,[4] yielding pseudorotaxanes. Larger crown ethers such as dibenzo-30-crown-10 (DB30C10) and derivatives interact relatively weakly with secondary ammonium salts,[5] and imidazolium salts[4] but well with larger guests such as paraquat and diquat.[6] Previous efforts by our lab capitalized on crown ethers ranging in size from 24 to 34 atoms with either paraquat or dialkyl ammonium salts to produce unique polymeric structures such as hyperbranched polymers,[1a,7] star,[1a,8a] block,[8b] and graft[8c] polymers, polymer chain extensions,[8b] and supramolecular polymers.[1,9] Association constants for these systems range from ∼10^2 to ∼10^3 M^{-1}. Because higher association constants translate into more efficient and controllable systems, our group has invested a considerable amount of energy in the development of higher binding systems.

Efforts to increase association constants are typically carried out by optimization of the host's binding cavity in terms of shape and/or the addition of binding sites. Cryptands, whose cavities are preorganized by the addition of a third (or even fourth) arm to crown ethers, are known to be much more effective hosts than their parent crown ethers.[10] For example, cryptand **3a** (Scheme 1) binds paraquat diol with $K_a = 1 \times 10^5$ M^{-1} and diquat with $K_a = 1.8 \times 10^6$ M^{-1} (acetone, 23 °C),[11] while precursor diol **1** binds these hosts with $K_a = 1 \times 10^3$ M^{-1} and $K_a = 5 \times 10^4$ M^{-1}, respectively.[6e] Similarly, 32-crown-10 diol **4** exhibits $K_a = 570$ M^{-1} with paraquat,[12a] while derived cryptand **5** binds paraquat with $K_a = 5 \times 10^6$ M^{-1}.[12b]

Of particular interest to our lab are those host−guest interactions that result in very high association constants ($K_a > 10^5$ M^{-1}). This led to the development of crown-based pyridyl cryptand hosts **3a** and **5** for paraquat guests; these high K_a systems enable[13a] the preparation of supramolecular polymers with high degrees-of-polymerization.[13b,c] Despite these remarkable increases in binding constants, the use of pyridyl cryptands such as **3a** and **5** has been limited by the time required for their syntheses (in excess of 9 days per run under pseudo-high-dilution via syringe pump addition) and modest cyclization yields, 40−45%.[11,12b] Long reaction times and modest yields make the production of gram amounts of cryptand challenging and costly. Thus, we set out to find a more efficient and less time-consuming method to produce these cryptands.

RESULTS AND DISCUSSION

After changing the solvent drying method, it was noticed that higher than expected yields were obtained in cyclization reactions of *cis*-DB30C10 diol **1** with diacid chloride **2a**. These results led us to suspect that the formation of cryptand **3a** was being templated in some way. Careful inspection revealed that trace amounts of acidic alumina used in newly adopted drying procedures had made their way into the reaction mixture. We hypothesized that protonation of pyridine

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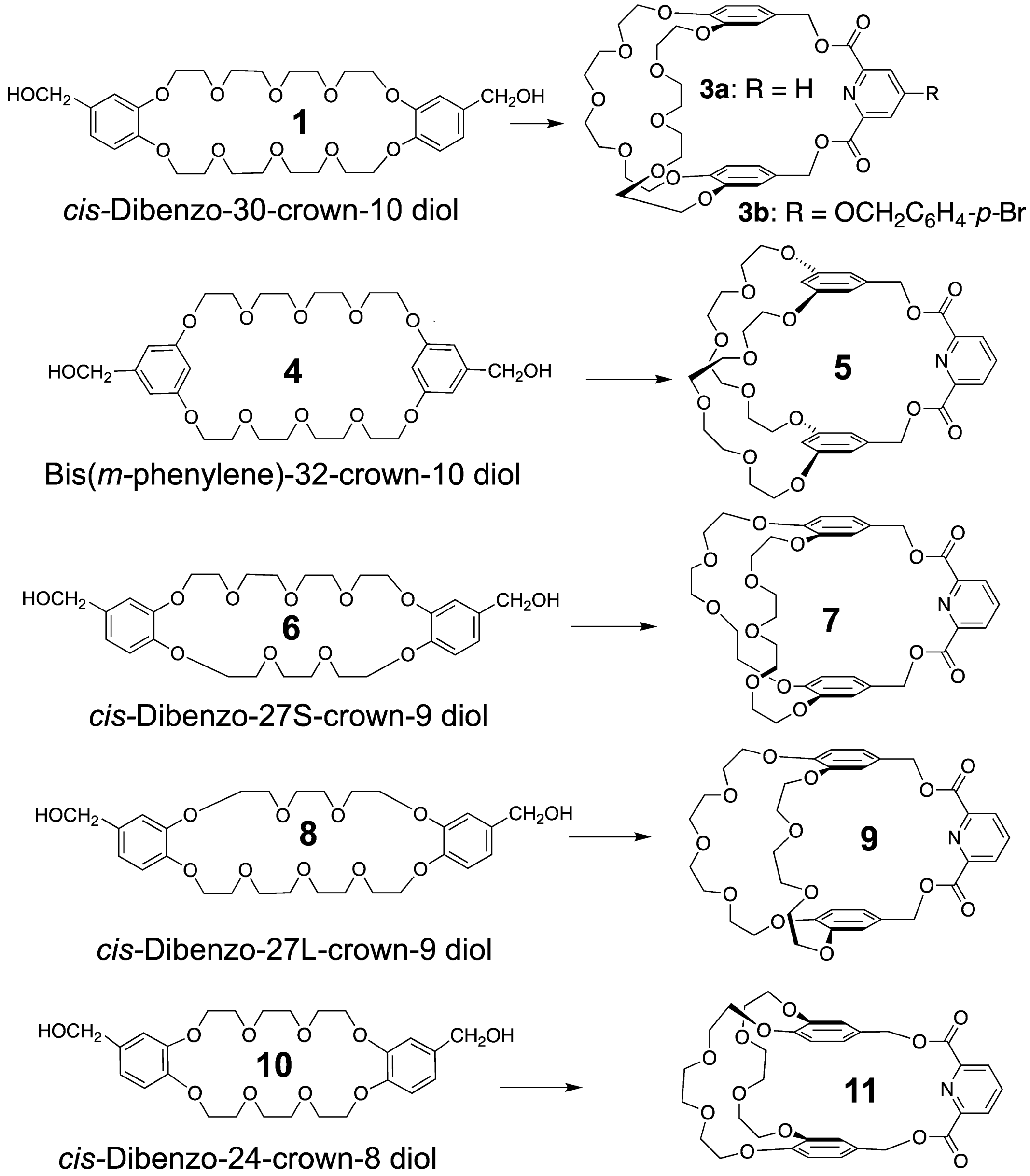
Scheme 1. Pyridyl Cryptand Templations



aided the reaction via preorganization of the crown ether. This led to an investigation of possible templating agents.

The templating agents explored initially were 4,4′-bipyridinium hexafluorophosphate, pyridinium *p*-toluenesulfonate, pyridinium hydrochloride, pyridinium trifluoroacetate, and pyridinium bis(trifluoromethylsulfonyl)imide (PyTFSI); the latter was effective and economical and hence became the focus. The goal was to induce a folded or "taco complex" (Figure 1), as observed in several aromatic crown ether complexes,[6e,14] and complexes from *N*-alkyl and protonated pyridinium salts with crown ethers[15a,c] and cryptands.[15b] It was envisioned that the taco-like wrapping of the diols around a template would bring the alcohol moieties into close proximity and, therefore, ideally positioned to react with the diacid chloride **2**. PyTFSI was chosen for its good solubility in DCM, low cost, and facile deprotonation for removal at the end of the reaction.

To support our hypothesis, we measured the association constants of crown ether diols **1** and **4** and cryptands **3a** and **5** with PyTFSI in DCM at 25 °C using isothermal titration calorimetry (ITC; see Supporting Information (SI): Figures S19−S22) (Table 1). The crown ether diols bind the salt fairly strongly, and the binding constants for 1:1 complexation increased by almost 2 orders of magnitude for cryptands **3a** and **5** relative to the diols. These results are consistent with our hypothesized mechanism of templation.

To better understand the interactions taking place that may be contributing to a templation process, a crystal of **3a**·PyTFSI was grown from an equimolar chloroform solution of the two components by slow evaporation. In the crystal structure (Figure 2) water and chloroform were incorporated with **3a** and PyTFSI in a ratio of 1:1:1:1. All components play an active role in terms of intermolecular interactions. The water acts as a hydrogen bonding bridge between the pyridinium N−H_1 and ether oxygens; the NH−O (D), and the OH−O (E, F) distances are all very short. H_2 of the pyridinium ion interacts with two ether oxygen atoms of the host (G, H). The complex is ion paired, as demonstrated by the interaction between H_3 of

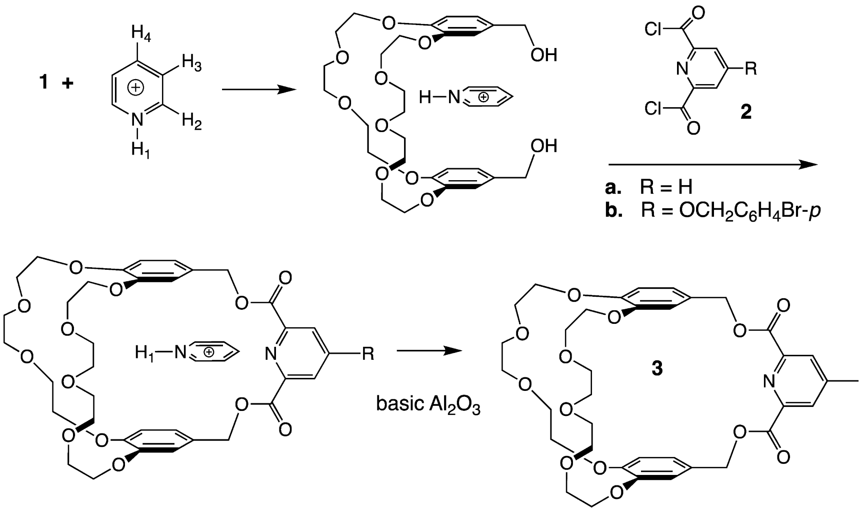


Figure 1. Proposed preorgnization of diol **1** to a "taco complex" brought about by the pyridinium ion and reaction with diacid chloride **2** to form the dibenzo-30-crown-10-based pyridyl cryptand **3**.

Table 1. Association Constants for Binding of PyTFSI by Crown Ether Diols and Cryptands (DCM, 23 °C, ITC)

host	K_a/100 (M^{-1})	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (cal/(mol K))
1	7.46 ± 0.57	−3.89 ± 0.05	−7.40 ± 0.23	−11.9 ± 0.9
3a	234 ± 11	−5.92 ± 0.03	−15.1 ± 0.1	−31.0 ± 0.5
4	5.31 ± 0.69	−3.72 ± 0.11	−4.14 ± 0.24	−1.42 ± 0.20
5	137 ± 8	−5.60 ± 0.03	−11.6 ± 0.1	−20.3 ± 0.4

the pyridinium ion and the TFSI counterion (C). Chloroform is hydrogen bonded to the same TFSI oxygen atom (A, B). The pyridinium ring is nearly coplanar with the two benzo rings of the host, and the centroid to centroid distances reflect the π-stacking interactions in the complex.

Having identified pyridinium TFSI as a suitable templating agent, we turned our attention to optimizing the synthesis of the cryptands. The benchmark for our template investigation was the original report of Pederson et al. in which **3a** was synthesized in 44% yield using pseudo-high-dilution conditions via syringe pump addition (5.82 mmol of diol **1** and 5.78 mmol of diacid chloride **2a** each separately in 40 mL of $CHCl_3$ added to 2 mL of pyridine in 2.5 L of DCM @ 0.5 mL/h).[11] Two methods for cryptand synthesis were used: a pseudo-high-dilution syringe pump addition (0.4554 mmol of **1** and 0.4554 mmol of **2a** separately but simultaneously to 2.71 mmol of PyTFSI in 700 mL of DCM @ 0.5 mL/h) and direct combination ([**1**] = 0.6194 mM, [**2a**] = 0.6194 mM, [PyTFSI] = 3.97 mM in 700 mL of DCM). For these reactions, yields of 74% and 89% were achieved, respectively. By monitoring the reaction via TLC and ^1H NMR, reaction times after the complete addition of all components were reduced from 5 days to 12 h. The isolation procedure mimicked that described by Pederson et al.[11]

Templation ideally should negate the need for pseudo-high-dilution conditions and the use of a syringe pump. To assess the potential of the template presented here, concentrations were varied in direct combination reactions. Table 2 (runs 3, 4, 8) shows the effect of concentration of substrates on yield. Although acceptable yields were obtained over the entire concentration range, a diminishing return was observed as concentration increased, as expected. At a concentration of 0.719 mM without the template, the yield was 31%, compared to the best result of 89% in the templated experiment above at 0.6194 mM, a gain of 58%.

The amount of templating agent was examined as shown in Table 2 (runs 5 vs 6). Under the same conditions ([**1**] = [**2a**] = 0.62 mM) with 15 vs 6.4 equiv of PyTFSI, the yields were 81% and 82%, respectively, indicating that there was no benefit from extra templating agent. Because chloroform is less polar than DCM, it was expected to enhance complexation of **1** by PyTFSI; however, its use as the reaction solvent (run 9) resulted in a 49% yield. This drop in yield from 82% to 89% in DCM (runs 4, 5) was attributed to the decreased solubility of PyTFSI.

Changes in [pyridine]/[**1**] ratio over the range of 2.5 to 56 (runs 4 and 5 vs 7) had no significant effect on the yield. The use of less pyridine, however, was advantageous in simplifying the workup procedure, allowing column chromatography with basic alumina directly after solvent evaporation, thus providing a time-saving advantage.

Excited by the significant increase in yield for the DB30C10-based cryptand **3a**, we explored the syntheses of the other cryptands in Scheme 1 using the previously stated reaction conditions. The results are gathered in Table 3.

The yields of cryptands **3a**, **3b**, **5**, and **9** gratifyingly were greatly improved vs the previous results using pseudo-high-dilution. However, the yields of cryptands **7** and **11** unexpectedly were lower than by the previous method. We hypothesize that the low yield (19%) in the case of the 27-crown-9-short cryptand **7** was due to the lack of a suitable interaction of the PyTFSI template with the tri(ethyleneoxy) arm that is para to the ester moiety; in Figure 2 water forms a bridge between the N−H of the template and two oxygen atoms of the tetra(ethyleneoxy) arm of host **3a**, but the geometry of the tri(ethyleneoxy) arm in **6** and **7** may preclude this. In the case of 27-crown-9-long cryptand **9** the geometry due to the asymmetric arm lengths may weaken the complexation with PyTFSI, resulting in a lowered yield (62%) relative to **3a**, but this still represents a significant improvement over the yield by pseudo-high-dilution.

The low yield (26%) in the case of the 24-membered cryptand **11** is believed to be due to involvement of two crown moieties (**10**) in the complex with PyTFSI in analogy to its complex with dimethyl paraquat.[2b] This would actually block the hydroxyl groups from reacting with the diacid chloride **2a**.

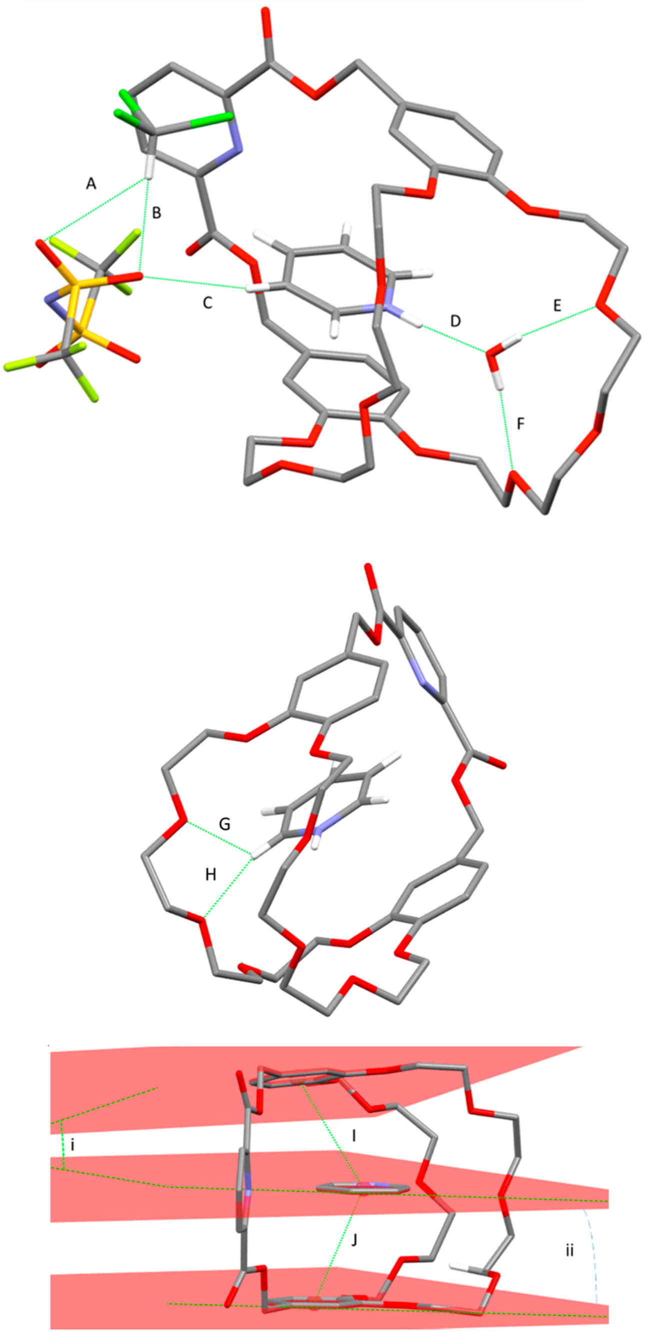


Figure 2. Crystal structure of **3a**·PyTFSI grown by slow solvent evaporation of an equimolar chloroform solution; hydrogens of **3a** have been removed for clarity; (top) side view showing hydrogen bonding involving chloroform, water and TFSI; (middle) top view showing hydrogen bonding involving the *meta*-ethyleneoxy chain (chloroform, water, and TFSI removed for clarity); (bottom) planes of stacked aromatic rings shown with centroids of stacked rings and plane inclinations indicated. Hydrogen-bond parameters: C···O distances (Å), C−H···O distances (Å), C−H···O angles (deg) A: 3.633, 2.969, 124.71; B: 3.282, 2.289, 172.28; C: 3.503, 2.589, 161.71; D: 2.660, 1.793, 167.73; E: 2.901, 2.097, 169.41; F: 2.861, 2.060, 170.62; G: 3.205, 2.663, 116.72; H: 3.315, 2.415, 157.98. Face-to-face π-stacking parameters: centroid−centroid distance (Å): I: 3.972; J: 3.801; ring plane/ring plane inclinations (deg): i: 12.74°; ii: 0.18°. Errors in distances are less than 0.0006 Å, and errors in angles are less than 0.05°.

■ CONCLUSIONS

An efficient method for the production of crown ether-based pyridyl cryptands has been developed. PyTFSI is effective for the templation of the syntheses of cryptands **3a**, **3b**, **5**, and **9**, with yields of 60−90%. The direct combination of reagents without pseudo-high-dilution, the simplified workup, and the improved yields enable facile syntheses of gram quantities of cryptands within 1 day's time. Coupled with our previous Wang−Pederson−Wessels (WPW) K$^+$ templation protocol for syntheses of dibenzo crown ethers such as **1**, **6**, **8**, and **10**[2c,11,20] the present method allows syntheses of cryptands **3a** and **3b** and similar hosts in gram quantities in yields exceeding 65% overall from methyl 4(or 3)-benzyloxy-3(or 4)-hydroxybenzoate.

■ EXPERIMENTAL SECTION

General Information. All chemicals were used as received unless otherwise specified. DCM and pyridine were dried by distillation over CaH$_2$. Diols **1**,[11] **4**,[21] **6**,[18] **8**,[18] and **10**[2c] were prepared as described in the literature. Diacid chloride **2b** was prepared as reported elsewhere.[16] Pyridinium TFSI was synthesized as described by Montavon et al.[22] ^{1}H NMR spectra were obtained on Bruker-500 and Agilent-NMR-vnmrs-400 spectrometers; ^{13}C NMR spectra were collected at 125 and 101 MHz, respectively. HR-MS were obtained using an Agilent LC-ESI-TOF system using acetonitrile as solvent. ITC results were obtained using an MCS system from Microcal, Inc.

Example of ITC Titration. The following is a detailed description of titration of **1** with PyTFSI; the other systems were examined similarly with slightly different concentrations. The ITC titrations were carried out in DCM at 25 °C. Host **1** was loaded into the cell of the instrument at a concentration of 1.46 mM, while a 250 μL ITC syringe was loaded with PyTFSI at a concentration of 22.4 mM. The instrument was set to high gain (high sensitivity). The titration was achieved through 50 injections of 5.00 μL every 180 s; a primary filter period of 2 s and a secondary filter period of 4 s were applied (filter period switch time was set to 120 s). A background titration used exactly the same titration conditions with the exception that the solution of **1** was replaced with pure DCM. The heats for the dilution experiment were subtracted from the heats for the titration of PyTFSI with **1**; the first point was not used in the analysis. Analysis of the data was carried out using software provided by the manufacturer. A "One Set of Sites" model was used; stoichiometries other than 1:1 provided unsatisfactory fits.

***cis*(4,4′)-Dibenzo-30-crown-10-Based Cryptand 3a via Syringe Pump Addition Using "Alumina Templation".** To a round-bottom flask containing DCM (2.5 L) were added acidic alumina (1.00 g) and pyridine (2.00 mL, 24.7 mmol). The contents were mixed for 15 min. Diol **1** (0.2942 g, 0.4931 mmol) and diacid chloride **2a** (0.1006, 0.4931 mmol) were each dissolved separately in DCM (25 mL) and loaded into syringes and added at 1 mL/h, after which the reaction mixture was stirred for 12 h and filtered. Following removal of solvent from the filtrate, the crude material was dissolved in DCM (50 mL) and washed with 1 M HCl (3 × 15 mL) and water (3 × 15 mL). Solvent was removed by rotary evaporation, and the crude material was subjected to column chromatography using basic alumina, eluting with DCM and then DCM:MeOH (99:1 v:v). **3a** was isolated as a colorless solid, 0.2773 g (77%), mp: 160.8−162.9 °C (lit.[11] mp 160.9−162.7 °C, previous yield 44% by pseudo-high-dilution).[11] The ^{1}H NMR spectrum (SI: Figure S1) matched the previous report. ^{13}C NMR spectrum (101 MHz, CDCl$_3$, SI: Figure S2): δ 164.8, 149.0, 148.9, 148.4, 138.1, 128.2, 128.0, 121.6, 114.2, 113.9, 71.0, 70.8, 70.7, 70.6, 69.7, 69.5, 69.0, 68.8, 67.6 (19 signals expected and 19 signals found). For HR ESI MS, see SI: Figure S3.

Standard Templation Procedure for Cryptand Synthesis. *cis*(4,4′)-Dibenzo-30-crown-10-Based Cryptand 3a via Direct

Table 2. Effect of Concentration in the Synthesis of Cryptand 3a[a]

run no.	[1] = [2a] (mM)	[pyridine] (mM)	[PyTFSI] (mM)	[pyridine]/[1]	[PyTFSI]/[1]	% yield
1	0.719	1.7	0	2.6	0	31
2	2.22	6.0	13.9	2.7	6.3	64
3	0.691	1.7	3.97	2.5	5.7	69
4	0.6194	1.7	3.97	2.7	6.4	89
5	0.618[b]	1.7	3.97	2.8	6.4	82
6	0.622	1.7	9.33	2.7	15	81
7	0.619	35	3.97	56	6.4	76
8	0.173	0.48	1.11	2.8	6.4	81
9	0.619	1.7	3.6	2.7	5.6	49[c]

[a] Direct combination of reagents in DCM; reaction at 23 °C for 12 h, followed by isolation by column chromatography. [b] Averages from four test runs; see SI. [c] Solvent chloroform instead of DCM.

Table 3. Cryptand Yields from Templated Cyclizations[a]

diol	cryptand	% yield	previous % yield[b]
1	**3a**	89	44[11]
1	**3b**	74	46[16]
4	**5**	80	45[17]
6	**7**	19	36[18]
8	**9**	62	38[18]
10	**11**	26	42[19]

[a] [2] = [1] = 0.60 mM, [pyridine] = 1.7 mM and [PyTFSI] = 3.97 mM). [b] By pseudo-high-dilution with syringe pump addition.

Addition Using PyTFSI Templation. A round-bottom flask containing DCM (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), and diol **1** (0.2587 g, 0.4336 mmol) was stirred for 15 min. Diacid chloride **2a** (0.0885 g, 0.434 mmol) was then added all at once. Stirring was continued for 12 h, at which time solvent was removed by rotary evaporation, and the crude material was subjected to column chromatography on basic alumina, eluting with DCM and then DCM:MeOH (99:1 v:v). **3a** was isolated as a colorless solid, 0.2807 g (89%), mp 159.0–160.8 °C (lit.[11] mp 160.9–162.7 °C, previous yield 44% by pseudo-high-dilution).[11] ^{1}H NMR, ^{13}C NMR, and HR MS as above.

***cis*(4,4′)-Dibenzo-30-crown-10 Cryptand 3a via Direct Addition Using PyTFSI and Chloroform.** A round-bottom flask containing chloroform (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), and diol **1** (0.2582 g, 0.4327 mmol) was stirred for 15 min. Diacid chloride **2a** (0.0883 g, 0.433 mmol) was then added all at once. Stirring was continued for 12 h; the solvent was removed by rotary evaporation and the crude material was subjected to column chromatography on basic alumina eluting, with DCM and then DCM:MeOH (99:1 v:v). **3a** was isolated as a colorless solid, 0.1536 g (49%).

***cis*(4,4′)-Dibenzo-30-crown-10-Based Cryptand 3b.** Application of the standard procedure with DCM (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), diol **1** (0.2842 g, 0.4763 mmol), and diacid chloride **2b** (0.1853 g, 0.4763 mmol) resulted in the isolation of **3b** as a colorless solid, 0.3217 g (74%), mp 188.8–192.7 °C (lit.[16] mp 188.8–192.7 °C, previous yield 46% by pseudo-high-dilution).[16] The ^{1}H and ^{13}C NMR spectra (SI: Figures S4 and S5) matched the previous report. For HR ESI MS, see SI: Figure S6.

Bis(*m*-phenylene)-32-crown-10-Based Cryptand 5. Application of the standard procedure with DCM (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), diol **4** (0.2507 g, 0.4202 mmol), and **2a** (0.0857 g, 0.420 mmol) yielded 245.1 mg (80%) of **5**, mp 147.9–151.2 °C, lit.[12b] mp 153.5–155.3 °C, previous yield 45% by pseudo-high-dilution.[17] The ^{1}H and ^{13}C NMR spectra (SI: Figures S7 and S8) matched the previous report. For HR MS, see SI: Figure S9.

***cis*(4,4′)-Dibenzo-27S-crown-9-Based Cryptand 7.** Application of the standard procedure with DCM (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), **6** (0.20601 g, 0.3728 mmol), and **2a** (0.07604 g, 0.3727 mmol) yielded 0.0491 g (19%) of **7**, mp 172.2–173.7 °C, lit.[18] mp 173.8–174.5 °C, previous yield 36% by pseudo-high-dilution.[18] The ^{1}H and ^{13}C NMR spectra (SI: Figures S10 and S11) matched the previous report. For HR MS (ESI-TOF), see SI: Figure S12.

***cis*(4,4′)-Dibenzo-27L-crown-9-Based Cryptand 9.** Application of the standard procedure with DCM (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), **8** (0.16069 g, 0.2908 mmol), and **2a** (0.05929 g, 0.2906 mmol) yielded 0.1239 g (62%) of **9**, mp 158.4–160.2 °C, lit.[18] mp 149.1–151.1 °C, previous yield 38% by pseudo-high-dilution.[18] The ^{1}H and ^{13}C NMR spectra (SI: Figures S13 and S14) matched the previous report. For HR ESI MS, see SI Figure S15.

***cis*(4,4′)-Dibenzo-24-crown-8-Based Cryptand 11.** Application of the standard procedure with DCM (700 mL), PyTFSI (1.00 g, 2.78 mmol), pyridine (0.10 mL, 1.2 mmol), diol **10** (0.2491 g, 0.4898 mmol), and **2a** (0.0999 g, 0.490 mmol) yielded 81.2 mg (26%) of **11**, mp 160.0–163.3 °C, lit.[19] mp 162.0–162.5 °C, previous yield 42% by pseudo-high-dilution.[19] The ^{1}H and ^{13}C NMR spectra (SI: Figures S16 and S17) matched the previous report. For HR MS (ESI-TOF), see SI: Figure S18.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01389.

Spectra (^{1}H NMR, ^{13}C NMR, mass) of compounds and ITC analyses of complexation (PDF)

X-ray crystal data of **3a**·PyTFSI (CIF)

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Notes

The authors declare no competing financial interest.

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