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## Improved synthesis of symmetrically & asymmetrically *N*-substituted pyridinophane derivatives†

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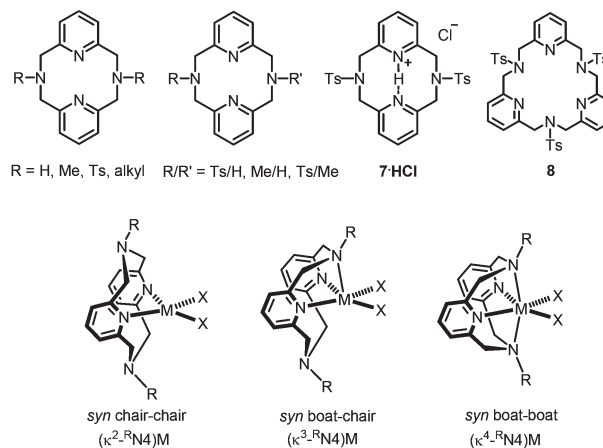
The *N,N'*-di(toluenesulfonyl)-2,11-diaza[3,3](2,6)pyridinophane (<sup>Ts</sup>N4) precursor was sought after as a starting point for the preparation of various symmetric and asymmetric pyridinophane-derived ligands. Various procedures to synthesize <sup>Ts</sup>N4 had been published, but the crucial problem had been the purification of <sup>Ts</sup>N4 from the larger 18- and 24-membered azamacrocycles. Most commonly, column chromatography or other laborious methods have been utilized for this separation, yet we have found an alternate selective dissolution method upon protonation which allows for multi-gram scale output of <sup>Ts</sup>N4·HCl. This optimized synthesis of <sup>Ts</sup>N4 also led to the development of symmetric <sup>R</sup>N4 derivatives as well as the asymmetric derivative *N*-(tosyl)-2,11-diaza[3,3](2,6)pyridinophane (<sup>TsH</sup>N4). Using this <sup>TsH</sup>N4 precursor, different *N*-substituents can be added to create a library of asymmetric <sup>RR'</sup>N4 macrocyclic ligands. These asymmetric <sup>RR'</sup>N4 derivatives expand the utility of the <sup>R</sup>N4 framework in coordination chemistry and the ability to study the electronic, steric, and denticity effects of these pyridinophane ligands on the metal center.

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Azamacrocycles have been used for decades in various applications in both organic and inorganic chemistry. One of this type of macrocycles, tetraazamacrocyclic pyridinophanes, has surprising flexibility due to its ability to adopt various conformations when bound to guest atoms (Chart 1). Because pyridinophanes can adopt both *syn* chair-chair and *syn* boat-boat conformations, the host can accommodate different geometries as needed by the guest in host-guest complexes, and this flexibility has been exploited in different applications.<sup>1–4</sup> In 1988, two groups led by Lehn<sup>1</sup> & Bottino<sup>2</sup> have independently synthesized tetraazamacrocyclic pyridinophanes in the context of host-guest chemistry; this work was also inspired by the work of Cram and coworkers and Baker and coworkers.<sup>3,4</sup> One example of their success was the symmetric *N*-substituted azamacrocycle *N,N'*-alkyl-2,11-diaza[3,3](2,6)pyridinophane (<sup>R</sup>N4, R = alkyl). Through the synthetic scheme outlined by both Lehn and Bottino (see Scheme 1) the 12-membered tetraazamacrocycle <sup>Ts</sup>N4, **7**, was considered the major product, with the 18-membered hexaazamacrocycle *N,N',N''*-tritosyl-2,11,20-triaza[3.3.3](2,6)-pyridinophane (<sup>Ts</sup>N6, **8**) as the main side-product. These two macrocycles were reportedly separated by column



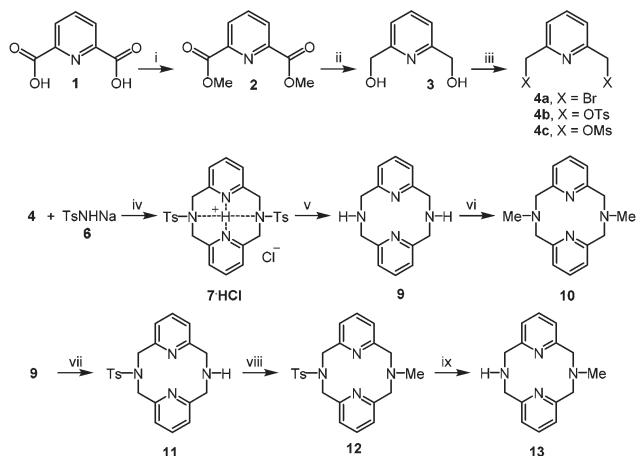
**Chart 1** Pyridinophane macrocycles mentioned in text & common conformations of <sup>R</sup>N4 upon complexation.

chromatography to obtain the desired product **7** at ~50% yield. Both groups further outlined additional procedures on how to deprotect these macrocycles and produce the methylated products <sup>Me</sup>N4 (**10**) and <sup>Me</sup>N6. Unfortunately, we were never able to reproduce such yields, and in our hands the column chromatography separation was quite inefficient.

Starting in the 1990s, many investigators employed <sup>R</sup>N4 pyridinophanes are multidentate ligands to generate various transition metal complexes. In 1994, Che and coworkers developed

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**Scheme 1** Overall synthesis of  $^{\text{Me}}\text{N4}$  and  $^{\text{MeH}}\text{N4}$ . (i) MeOH,  $\text{SOCl}_2$ , reflux, overnight; 91% (ii) MeOH,  $\text{NaBH}_4$ , reflux, overnight; 85% (iii) **4a**:  $\text{CHCl}_3$ ,  $\text{SOBr}_2$ , 4 days; 70% **4b**:  $\text{THF}/\text{H}_2\text{O}$ ,  $\text{TsCl}$ , overnight; 94% **4c**:  $\text{CHCl}_3$ ,  $\text{MsCl}$ , 2 hours; 88% (iv) formaldehyde, formic acid, reflux, 60 hours; 40% (v)  $\text{H}_2\text{SO}_4$  reflux, 2.5 hours; 88% (vi) formaldehyde, formic acid, reflux, overnight; 86%. (vii)  $\text{CHCl}_3$ ,  $\text{TsCl}$ , 3 hours; 44% (viii) formaldehyde, formic acid, reflux, overnight; 80% (ix) conc.  $\text{H}_2\text{SO}_4$  reflux, 24 hours, 90%.

an alternative method of synthesizing  $^{\text{Me}}\text{N4}$  directly from 2,6-bis(bromomethyl)pyridine, **4a**, and succeeded in making the  $^{\text{tBu}}\text{N4}$  variant of the macrocycle.<sup>5</sup> Subsequently, several studies have employed  $^{\text{tBu}}\text{N4}$ ,  $^{\text{Me}}\text{N4}$ , or  $^{\text{H}}\text{N4}$  ligands to isolate stable complexes of V, Mn, Fe, Co, Ni, Cu, and Pd.<sup>5–12</sup> Sherry and co-workers developed a N4 derivative with acetate *N*-substituents and investigated its lanthanide complexes as MRI contrast agents.<sup>13,14</sup>

In 1999, Marchand and coworkers optimized the synthesis of **7** by running the reaction in MeCN.<sup>15</sup> Around this time, metal complexes of  $^{\text{R}}\text{N4}$  were also employed in reactivity studies. ( $^{\text{tBu}}\text{N4}$ )Pd complexes promoted ethylene insertions into a Pd–Me bond.<sup>6</sup> ( $^{\text{H}}\text{N4}$ )Cu complexes have been used to cleave DNA as a nuclease model by hydrolysis of the phosphodiester bond.<sup>16</sup> ( $^{\text{Me}}\text{N4}$ )Fe and ( $^{\text{H}}\text{N4}$ )Fe complexes acted as catalytically active biomimics of catechol deoxygenase and as a complex which promoted spin transitions when bound to catecholate and 1,2-mercaptobenzene.<sup>10,17,18</sup> ( $^{\text{Me}}\text{N4}$ )Mn complexes were examined by high-field electron paramagnetic resonance to find evidence for a low-lying spin triplet state.<sup>19</sup>

Around 2010, groups began to use these complexes as a platform for mechanistic studies. Our groups had initially employed ( $^{\text{tBu}}\text{N4}$ )Pd complexes to generate the first organometallic mononuclear Pd<sup>III</sup> complexes and study that C–C and C–heteroatom bond formation reactivity.<sup>20–22</sup> ( $^{\text{Me}}\text{N4}$ )Fe and ( $^{\text{H}}\text{N4}$ )Fe were used to probe the mechanism of *cis*-dihydroxylation of alkenes.<sup>23</sup> ( $^{\text{R}}\text{N4}$ )Co (where R = Me or *t*Bu) and ( $^{\text{Me}}\text{N4}$ )Fe complexes with acenaphtene-1,2-diimines were used to explore spin crossover states.<sup>24,25</sup> We have also employed  $^{\text{tBu}}\text{N4}$  to generate a series of bis-solvento Fe, Ni, Co, Cu, and Zn complexes.<sup>26</sup> The Fe complex of ( $^{\text{Me}}\text{N4}$ )Fe was used to oxidize water *via* an Fe<sup>IV</sup>=O intermediate seen spectroscopically.<sup>27</sup> Mn complexes of  $^{\text{Me}}\text{N4}$  was used as a biomimic of catalase and ( $^{\text{tBu}}\text{N4}$ )

Mn<sup>II</sup> as a water oxidation catalyst.<sup>28,29</sup> More recently, we have reported the isolation of unique organometallic ( $^{\text{tBu}}\text{N4}$ )Ni<sup>III</sup> and ( $^{\text{Me}}\text{N4}$ )Ni<sup>III</sup> complexes that can undergo both stoichiometric and catalytic C–C and C–heteroatom bond formation reactivity.<sup>30,31</sup> Isolated ( $^{\text{Cy}}\text{N4}$ )Ni<sup>III</sup>–peroxo ( $^{\text{tBu}}\text{N4}$ )Ni<sup>III</sup>–peroxo complexes were also reported.<sup>32</sup> Finally, lanthanide and actinide complexes of  $^{\text{R}}\text{N4}$  were employed in exploring *cis/trans* isomerization of the O–U–O bond angle or as possible MRI contrast agents.<sup>33,34</sup>

As mentioned above,  $^{\text{R}}\text{N4}$  had been widely used in the stabilization of metal centers, and was shown to provide a framework that is fairly rigid, yet it contains flexible chelating arms for accommodate different denticities and coordination geometries.<sup>21</sup> Since  $^{\text{Ts}}\text{N4}$  (**7**) can be considered the key intermediate in the synthesis of most  $^{\text{R}}\text{N4}$  ligands, the synthesis of N4 derivatives could not be feasible if the formation of **7** could not be scaled to moderate amounts, and especially since it is difficult to consistently separate **7** from the larger azamacrocycles such as **8**. As outlined previously in the literature,<sup>1,2,5,15,28</sup> column chromatography or laborious extraction methods were used to separate **7** from **8**, but this proved tedious to perform on larger scales. In this study, a selective dissolution purification method through an ethanol wash upon the addition of one equivalent of HCl is presented that allows the gram-scale purification of **7** from **8**. Additionally, three functionalized 2,6-bis(alkoxymethyl)pyridines (**4a–c**) were employed in order to increase the overall yield of **7**, increase productivity and safety, reduce overall time, and make the overall synthesis more economical.

Another opportunity for this ligand system is to develop asymmetric pyridinophane derivatives with different *N*-substituents. Introducing asymmetry into the macrocycle would enable the study of various ligand steric, electronic, or denticity effects on the metal center. After several synthetic attempts, the chosen strategy involved selective protection of one amine with a tosyl group. Described herein is the synthesis of an asymmetric intermediate,  $^{\text{TsH}}\text{N4}$  (**11**), from which a series of asymmetric ligands,  $^{\text{TsMe}}\text{N4}$  (**12**) and  $^{\text{MeH}}\text{N4}$  (**13**), were generated. Further functionalization of the remaining secondary amine could lead to a wide range of N4 ligand derivatives.

## Results & discussion

As previously stated, the overall synthetic scheme from **1** to **7** was outlined in 1988 by two separate groups: Lehn and coworkers<sup>1</sup> and Bottino and coworkers<sup>2</sup> (Scheme 1). Bottino's method of synthesizing **7·HCl** was ultimately chosen, which followed the conversion of **1** through **7·HCl**. The first step of esterifying **1** to make **2** originally took 100 hours to drive the esterification to completion. Lehn and coworkers have since provided an alternative procedure in which thionyl chloride was added to the reaction mixture to dramatically reduce the time of the reaction to two hours.<sup>35</sup> Our alternate procedure uses **1** and 1 mL of thionyl chloride refluxed in 800 mL of MeOH overnight to give **2** in 91% yield. The reduction of **2** to **3**

was a straightforward reaction, but a more involved purification was needed to extract **3** from the aqueous layer. Extraction with  $\text{CHCl}_3$  proved difficult as **3** is soluble in the aqueous layer. Instead, a liquid–liquid extraction apparatus was employed for continuous extraction of **3** with  $\text{CHCl}_3$  for up to five days.<sup>36</sup> Unfortunately, the scale of the reaction was hindered by the volume of the aqueous  $\text{NaHCO}_3$  solution and the concentration of the dissolved salts. If the aqueous layer is too concentrated, the density becomes greater than  $\text{CHCl}_3$ , leading to poor separation. As such, the capacity of the extractor used with this method restricts running the purification on larger scale. Additionally, the increased density and solubility of  $\text{CHCl}_3$  over DCM was very important. If extraction had been performed with DCM rather than  $\text{CHCl}_3$ , four days would have been required to extract the same amount of product. The dimerization of **4** in the presence of **6** was run in anhydrous DMF at 80 °C in a similar method to Bottino's and will be discussed in more detail below.

To improve the selectivity of the synthesis of **7**, a different synthetic route based on Lehn's method was also tested. In this route, the hydroxy groups in **3** were transformed into amino groups to give **15** through a two-step Gabriel synthesis (Scheme 2).<sup>37</sup> Then **15** was reacted with TsCl to obtain the intermediate **16** (which required column chromatography for purification), and subsequent reaction with **4b** generated **7** with an acceptable yield. Overall, we prefer the synthesis of **7** following the modified protocol of Bottino and coworkers given the lower number of linear synthetic steps.<sup>2</sup>

### Optimization of synthesis of 7·HCl

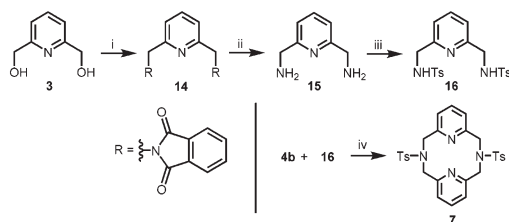
Different syntheses were previously reported for the preparation of **4a** and, of these, four were attempted. The  $\text{PBr}_3$  method<sup>38,39</sup> using **3** obtained a low yield of 42%. Another method which used HBr and acetic acid<sup>40</sup> had a better yield at 71%, but the scale was not easily increased past 7 g of **4a**. The ultimate choice for the bromination agent was thionyl bromide which was attempted with similar yields as the HBr procedure (69%) but with on a larger scale (13 g). This allowed for a larger scale synthesis of **7**. An alternative bromination of lutidine by NBS was previously reported but its low yield rendered it less desirable.<sup>3,41–43</sup> This reaction was attempted in various solvents (DCM, benzene, trifluorotoluene, and di-

methylcarbonate), yet crude mixtures of ~1:1 of the mono- and di-brominated lutidine were obtained with a maximum yield of 45% for **4a**. However, this mixture was very difficult to separate by column chromatography and a large scale, which led to the abandonment of this synthetic pathway.

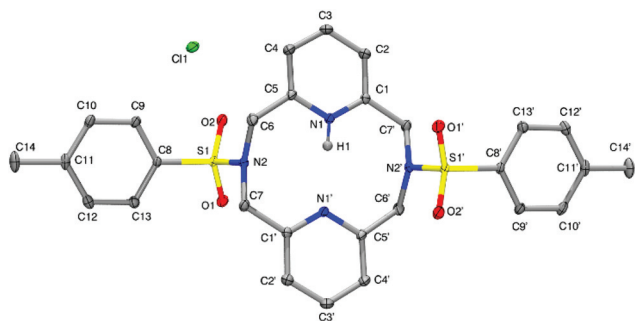
The purification of **7** from the 18-member macrocycle analog **8** usually involved column chromatography.<sup>1,2,5</sup> In our optimization process, the discovery of the usefulness of a selective crystallization technique allowed for the purification on gram scales of **7**. Previous work by Kress and coworkers demonstrating that <sup>4</sup> $\text{BuN}_4$  adopted a *syn* boat–boat conformation upon addition of proton suggested that monoprotection of **7** could be easily achieved.<sup>6</sup> Conversely, the larger, 18-member macrocycle **8** is much larger and should not provide the correct size for a proton and thus should have a lower affinity towards protons. *In essence, we take advantage of 7 acting as a very good proton sponge.* It was found that ethanol can both protonate and dissolve a small amount of **7** within a few hours, and the formed salt can readily dissolve in ethanol. In this vein, by using one equivalent of HCl in 95% ethanol, we were able to selectively dissolve **7** (and generate **7·HCl**) while **8** remained insoluble. The use of 95% EtOH was also noteworthy as the use of 100% EtOH extracted a much smaller amount of **7·HCl**. The extra amount of water was primarily used to increase the solubility of the salt. This solution was filtered and concentrated to yield pure **7·HCl** that was stable at room temperature. Not all of **7** was extracted in the filtrate; some was left in the precipitate. This precipitate was stored as well and re-extracted to yield pure **8** and some extra **7·HCl**. A mass spectrum analysis of the solid mixture showed the presence of **7**, **8**, and a trace amount of the 24-member octaazomacrocyclic derivative. Since the next step in <sup>R</sup>N<sub>4</sub> ligand synthesis is the deprotection of the *N*-tosyl groups under strongly acidic conditions, **7·HCl** can be used directly, without neutralization. If desired, an extraction step using 1 M NaOH and  $\text{CHCl}_3$  would generate the free base **7**. Importantly, this improved synthesis of **7** also generates pure **8**, as a side-product, which can be used in lanthanide and actinide coordination chemistry or in supramolecular chemistry.

In addition to the NMR and MS data, more evidence for the formation of **7·HCl** was obtained through X-ray crystallography (Fig. 1, see also the ESI<sup>†</sup>), showing the proton bound to one pyridine N atom in the macrocycle “pocket” and closely interacting with the other pyridine N atom.

While the **4a** was a useful way to synthesize **7·HCl**, the methods used to make it commonly involved thionyl bromide. This synthesis had a number of drawbacks: the highly corrosive thionyl bromide, safety considerations for chemists since **4a** has been reported to be a strong lachrymator, the maximum scale of 13 g of **4a** per batch, the four-day reaction time, and the cost of reagents. Other common leaving groups have been employed to garner the same effect, including tosyl<sup>36,44</sup> and mesyl.<sup>45,46</sup> Using methods adapted from the literature, **3** was functionalized using TsCl or MsCl to make **4b** and **4c**, respectively. Both synthetic products were synthesized much faster, cheaper, and under less hazardous conditions



**Scheme 2** Synthesis of **7** via Lehn and coworkers (ref. 1). (i) THF,  $\text{PPh}_3$ , phthalimide, diethyl azodicarboxylate diester, overnight; 76% (ii); EtOH, hydrazine hydrate, overnight; 85% (iii)  $\text{CHCl}_3$ ,  $\text{Et}_3\text{N}$ , TsCl, 24 hours; 85% (iv) Step 1: EtOH, Na, reflux, 60 min; Step 2: **4b**, DMF, 100 °C, overnight; 63%.



**Fig. 1** ORTEP plot (50% probability ellipsoids) of **7·HCl**. All hydrogens except the pyridine H were omitted for clarity. Selected bond distances (Å): N1–H1 0.82(4); N1'–H1 1.97(1).

than the synthesis of **4a** that used thionyl bromide. For comparison, the average yield of the three functionalized pyridines can be seen in Table 1. The most significant facet of the different functionalized pyridine compounds was the reaction to make the final desired product **7·HCl**. Following the different optimizations of time, temperature, and dilution (*vide infra*), when the effects of the leaving group were studied, the mesylated pyridine showed the highest yields of **7** (up to 62% yield) while the bromide had the lowest (up to 25% yield). Both of these groups were fairly small and could allow for easier  $S_N2$  reactions to occur. However, the mesylate was considered a better leaving group than the bromide. The tosylate had a lower yield than the mesylate, most probably due to steric bulk around both the nucleophilic amine nitrogen (carrying a tosyl group) and the electrophilic carbon during the  $S_N2$  reaction.

When the overall conversion of **3** to **7·HCl** was compared, use of the tosyl- and mesyl-protected intermediates gave similar overall yields (Table 1). The synthesis of **4b** was high yielding and easily manipulated but the resulting dimerization was around 40%. The yield of the dimerization using **4c** was slightly higher than using **4b**; however, the synthesis of **4c** proved more difficult to perform consistently and resulted in a larger variation of product yields. Between the choice of the tosyl or mesyl protecting groups, the former intermediate (*i.e.*, **4b**) seemed to be more shelf-stable and easier to scale up compared to the mesyl counterpart, thus making it the more effective precursor to **7·HCl** than **4c**.

Multigram-scale production of **7** is desired for ligand synthesis. As such, the synthesis of **7** or **7·HCl** needed to be scaled beyond the previously reported 1 g. The maximum scale that did not diminish the yield of **7·HCl** was ~16 g of **6** in 1 L of

DMF. The addition of **6** can be performed in two different ways: adding two equal portions of **6** at separate times during the reaction or alternatively starting with the entire portion of **6**. Using the stepwise procedure, the ability to restrict the formation of the larger oligomers should be higher as there is less **6** to act as a base. However, when these two methods were directly compared, there was minimal difference in overall isolated yield.

Other factors that have a direct effect on the **7** : **8** product ratio include the temperature of the reaction, the reaction time at the temperature of choice, and the dilution of the reactants. When performing optimizations for these variables, the same batch and amount of **4b** (1 g) was used to allow a direct comparison between different conditions. A table containing a summary of the optimization yields is shown Table S1.† The effect of temperature on the reaction was pronounced. By increasing the temperature to 120 °C from 80 °C, the final product yielded exclusively **8**. This showed that the heat should have been maintained high enough to react but low enough to favor **7** formation. The effects of time were probed by allowing the reaction to stir for two additional days at 80 °C. Comparing the control reaction results and the extended time showed that by increasing the time of reaction to two more additional days, the yield **7** was increased by about 10%. As such, increasing the reaction time at a stable 80 °C should increase the overall yield of **7**. This behavior held true for both **7** made by **4b** and **4c** but not for the bromide, **4a**. When the reaction was run with **4a** for two extra days, only **8** was recovered in 19% yield.

Finally, the concentration of both constituents were doubled and the solvent amount decreased for an overall six-fold increase in concentration. The reaction was run for two days and no **7** was obtained. This supports the suggestion that the solution of **6** should be very dilute to prevent the rapid reaction with **4** immediately upon addition to the solution. If **6** is in found in a high concentration, **4** would rapidly be converted into a diamine species that could react with more than one equiv of **4** and lead to larger macrocycles. When the concentration of **6** is low, there is a greater change for the formation of a monoamine species to form from **4** and that should promote the preferential formation of **7**. Additionally, the use of other cations, most notably potassium, led to a decrease in the yield of **7** formation and an increase in the yield of **8**.<sup>47</sup> This suggested that the presence of sodium ions act as a template and lead to an increased selectivity for **7** over the larger macrocycles. Considering all these factors, it is expected that ratio of **7** to **8** could vary significantly. While we reported an average ratio of 4 : 1 (**7** : **8**), ratios between 1.5 : 1 to 15 : 1 were obtained in different cases. While the ratio ranged, the total amount of crude mixture of **7** and **8** remained similar from batch to batch.

**Table 1** Synthesis yields of **7·HCl** from various precursors

Starting material	Yield of <b>4a/4b/4c</b>	Yield of <b>7·HCl</b>	Overall yield <b>3</b> to <b>7·HCl</b>
<b>4a</b>	69%	26%	18%
<b>4b</b>	94%	39%	37%
<b>4c</b>	72%	58%	41%

#### Asymmetric N4 ligands – synthesis of <sup>MeH</sup>N4

The optimization of the asymmetric <sup>R,R</sup>N4 groups hinged on the synthesis of the key asymmetric precursor, <sup>TsH</sup>N4 (**11**). Attempts at the partial deprotection of **7** led to inconsistent

degrees of detosylation, but usually to the fully deprotected product **9**. This was rectified by intentionally fully detosylating **7** to yield **9**, and the subsequent selective monofunctionalization by the addition of one equivalent of TsCl. This reaction produced also a small amount of **7** along with **11**, yet that could be reliably separated through an isopropanol wash. Once **11** has been produced, the ability to append two different *N*-substituents through various functionalization reactions could create a library of different asymmetric  $R^R N_4$  ligand derivatives. As outlined by Scheme 1, the remainder of our synthesis to **13** followed the methylation of **11** to generate  $TsMe N_4$ , **12**. This asymmetric macrocycle could be employed as a “pseudo-tridentate” ligand with a bulky electron-withdrawing Ts protecting group altering the binding affinity of the corresponding N atom. Auspiciously, **12** was stable and could be stored for months if needed. Finally, the deprotection of the remaining tosyl group in **12** under acidic conditions generates  $Me^H N_4$ , **13**, which can be employed in further functionalization steps to generate new asymmetric  $R^{Me} N_4$  ligands.

## Conclusions

Presented herein is the optimized procedure for the multi-gram-scale production of **7·HCl**. This shelf-stable macrocycle was purified by a developed selective separation of **7·HCl** upon addition of one equivalent of HCl to a mixture of **7** & **8** and suspension in 95% ethanol. In addition, the effect of the different leaving groups during the cyclization step (*i.e.*, bromide, tosylate, & mesylate) was probed and the use of the tosylate precursor was chosen as having the optimal combination of yield, cost efficiency, and safety for the synthesis of **7·HCl**. This **7·HCl** product can then be reacted using reported methods to make symmetric  $R N_4$  ligands, or it could be employed to introduce asymmetry by installing two different *N*-substituents. The synthesis of **13** revolved around the introduction of asymmetry by mono-tosylation of **9** rather than the selective mono-detosylation of **7**. Once the asymmetry was introduced, functionalization of the **13** can be performed using various common synthetic techniques. These asymmetric  $R^R N_4$  derivatives expand the utility of the  $R N_4$  framework in coordination chemistry and the ability to study the electronic, steric, and denticity effects of these pyridinophane ligands on the metal center.

## Experimental

### General specifications

All manipulations were carried out under a nitrogen atmosphere using a glove box or standard Schlenk techniques if not indicated otherwise. All reagents for which the synthesis is not given were commercially obtained from Sigma-Aldrich, Acros, or Alfa Aesar and were used as received without further purification. Solvents were purified to use by passing through a column of activated alumina using an MBRAUN Solvent

Purification System or dried by calcium hydride distillation.  $^1H$ -NMR (300 MHz) and  $^{13}C$ -NMR (75 MHz) spectra were recorded on a Varian Mercury-300 or Varian Unity Inova-500 spectrometer. ESI-MS experiments were performed using a Thermo FT or Bruker Maxis Q-TOF mass spectrometer with an electrospray ionization source.

### Synthesis of 2,6-pyridinedicarboxylic acid dimethyl ester: 2

**H<sub>2</sub>SO<sub>4</sub> method.** The previously reported procedure was slightly modified.<sup>36</sup> A solution of 2,6-pyridinedicarboxylic acid, **1**, (100.24 g, 0.60 mol) and concentrated sulfuric acid (1 mL) in MeOH (800 mL) was stirred at reflux for 100 h. After the reflux, the solvent was removed to dryness and the residue was redissolved in DCM (800 mL) and washed with saturated solution of sodium bicarbonate (2 × 400 mL) and water (400 mL). The organic layer was dried with potassium carbonate, filtered, and solvent removed under reduced pressure to give white powder, **2** (104.83 g, 0.54 mol, 89.5%).

**SOCl<sub>2</sub> method.** A solution of **1** (100.24 g, 0.60 mol) and thionyl chloride (1 mL) in MeOH (800 mL) was stirred at reflux for 18 h. After the reflux, the solvent was removed to dryness under reduced pressure to give white powder, **2** (107.37 g, 0.55 mol, 91.4%).

$\delta_H$ (300 MHz, CDCl<sub>3</sub>): 8.33 (d, *J* = 7.8 Hz, 2 H), 8.02 (t, *J* = 7.8 Hz, 1 H), 4.02 (s, 6 H); ESI-MS (*m/z*): 196.0605; calculated: 196.0605 (M + H<sup>+</sup>).

### Synthesis of 2,6-bis(hydroxymethyl)pyridine: 3

The previously reported procedure was slightly modified.<sup>36</sup> To a solution of **2** (40.75 g, 0.21 mol) in MeOH (400 mL), sodium borohydride (32.42 g, 0.86 mol) was slowly added in small portions which resulted in reflux. When the additions were complete, the reaction was stirred overnight. To work up the reaction, the solvent was removed to dryness, and the residue was redissolved in a saturated solution of sodium bicarbonate (400 mL). The solution was then loaded into a continuous liquid-liquid extraction apparatus. The extraction with CHCl<sub>3</sub> was allowed for one day. After the extraction, the organic layer was separated and evaporated to dryness to yield white powder, **3** (24.80 g, 0.18 mol, 85.4%).  $\delta_H$ (300 MHz, DMSO-*d*<sub>6</sub>): 7.78 (t, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 5.38 (s, 2 H), 4.51 (s, 4 H);  $\delta_H$ (300 MHz, CDCl<sub>3</sub>): 7.69 (t, *J* = 7.8 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 4.78 (s, 4 H); ESI-MS (*m/z*): 140.0706; calculated: 140.0706 (M + H<sup>+</sup>). These values closely match literature values. Depending on source of sodium borohydride, resultant **3** can be colored due to impurities.

### Synthesis of 2,6-bis(bromomethyl)pyridine: 4a

**PBr<sub>3</sub> method.** The previously reported procedures were slightly modified.<sup>38,39</sup> A solution of **3** (7.33 g, 52.7 mmol) in DCM (500 mL) was stirred at 0 °C. To this solution phosphorus tribromide (15 mL, 158 mmol) was slowly added. The resulting suspension was allowed to warm slowly to room temperature and was stirred in the dark for two days. After two days, the reaction mixture was poured into 100 mL of ice-cold water. The aqueous layer was then neutralized to pH 7–8 without sep-

aration by addition of 10 M NaOH solution. The organic layer was separated, washed with 1 M NaOH (200 mL), H<sub>2</sub>O (200 mL), and dried with magnesium sulfate. The solution was filtered and evaporated to dryness to give brownish-white powder, **4a** (5.88 grams, 22.2 mmol, 42%).

**HBr/AcOH method.** The previously reported procedure was followed closely.<sup>40</sup> A solution of **3** (4.97 g, 35.7 mmol) in 30 wt% hydrobromic acid in acetic acid (80 mL) was stirred at 100 °C for 1.5 hours and then poured onto ice (125 mL) and neutralized to a pH of 7–8 with aqueous 1 M NaOH. The resulting precipitate was collected and recrystallized from ethyl acetate with the addition of small aliquots of hexane. The solution was left at –20 °C overnight, and the resulting precipitate was filtered and dried to give brownish-white powder, **4a** (6.71 g, 25.3 mmol, 71%).

**SOBr<sub>2</sub> method.** A solution of **3** (10.0 g, 71.9 mmol) in DCM (500 mL) was stirred at 0 °C. To this solution thionyl bromide (20 mL, 258 mmol.) in DCM (125 mL) was slowly added. The resulting suspension was allowed to warm slowly to room temperature and was stirred in the dark for four days. After four days, the reaction mixture was poured into ice-cold water (400 mL). The aqueous layer was then neutralized to pH 7–8 without separation by addition of 10 M sodium hydroxide solution. The organic layer was separated, washed with 1 M NaOH (200 mL), H<sub>2</sub>O (200 mL), and dried with magnesium sulfate. The solution was filtered and evaporated to dryness to give white powder, **4a** (13.1 g, 49.4 mmol, 69%).

$\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>): 7.71 (t, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 2 H), 4.54 (s, 4 H);  $\delta_{\text{C}}$ (75 MHz, CDCl<sub>3</sub>): 156.54, 138.01, 122.69, 33.39; ESI-MS (*m/z*): 265.8998; calculated: 265.8998 (M + H<sup>+</sup>).

#### Synthesis of 2,6-bis(tosylmethyl)pyridine: **4b**

The previously reported procedures were slightly modified.<sup>36,44</sup> To a three-neck round-bottom flask, **3** (25.03 g, 0.18 mol), sodium hydroxide (21.56 g, 0.54 mol), THF (80 mL), and water (80 mL) were all added and stirred at 0 °C for 30 minutes under N<sub>2</sub>. A solution of TsCl (70.30 g, 0.37 moles) dissolved in THF (100 mL) was added drop-wise at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred overnight. To work up, water (300 mL) was added to the THF solution and then extracted with CHCl<sub>3</sub> (3 × 300 mL) and the organic fractions were combined. The organic fraction was washed with water (3 × 500 mL), dried with anhydrous sodium sulfate, and the solvent removed under reduced pressure. The peach-colored solid was dried for at least 24 hours on vacuum line to yield a pink powder, **4b** (75.61 g, 0.17 mol, 93.9%). Depending on source of sodium borohydride, resultant **3** and **4b** compounds can be colored. A wash with ethanol (95%, 100 mL, 30 min) will remove the colored impurities from **4b**.  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>): 7.80 (m, 4H), 7.69 (m, 1H), 7.33 (m, 6H), 5.05 (s, 4H), 2.44 (s, 6H); ESI-MS (*m/z*): 448.0883, calc: 448.0883 (M + H<sup>+</sup>).

#### Synthesis of 2,6-bis(mesylmethyl)pyridine: **4c**

The previously reported procedures were slightly modified.<sup>45,46</sup> Triethylamine (22 mL, 0.229 mol), **3** (10 g, 0.072 mol), and

400 mL of CHCl<sub>3</sub> added to a 1 L round-bottom flask chilled to 0 °C. To this solution, MsCl (13.00 mL, 0.1673 mol) diluted in CHCl<sub>3</sub> (75 mL) was added drop-wise. During addition, the reaction mixture was vigorously stirred and maintained at 0 °C. Upon completion of the addition, the reaction mixture was left to stir for an additional two hours at 0 °C. The organic layer was washed with saturated sodium chloride solution (400 mL) and water (400 mL) and dried with anhydrous magnesium sulfate. The solvent was removed and the residue was triturated with diethyl ether (200 mL) and the suspension was stirred for twenty minutes. The solid was then separated by vacuum filtration and rinsed with more diethyl ether. The off-white powder, **4c**, was then dried on vacuum line briefly and stored in the –20 °C freezer (18.57 g, 0.063 mol, 87% yield).  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>): 7.83 (t, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 5.30 (s, 4 H), 3.09 (s, 6 H);  $\delta_{\text{C}}$ (75 MHz, CDCl<sub>3</sub>): 153.77, 138.34, 122.24, 71.01, 38.09; ESI-MS (*m/z*): 295.0165, calc: 295.0184 (M + H<sup>+</sup>).

#### Synthesis of sodium tosylamide salt: **6**

The previously reported procedure was slightly modified.<sup>2</sup> A solution of sodium ethoxide was prepared as follows: metallic sodium (15.53 g, 0.68 mol) was placed into a crystallization dish filled with dry hexane. The metallic sodium was cut into smaller pieces under the hexane and then added portion wise into a stirring 2 L three neck round-bottom flask filled with absolute ethanol (100%, 600 mL). The reaction flask was covered with a rubber septum and put under N<sub>2</sub>. Once the sodium was completely dissolved, the solution was heated to 60–70 °C. The solid tosylamide (101.01 g, 0.59 mol) was added portion-wise to the stirred solution (effective stirring is necessary). The reaction was refluxed under N<sub>2</sub> for two hours. After cooling down to room temperature, the formed white precipitate was vacuum filtered, washed with absolute ethanol, and dried under vacuum for at least 24 hours. The white crystalline solid, **6**, was stored in a desiccator (105.99 g, 0.55 mol, 93%).

#### Synthesis of <sup>15</sup>N<sub>4</sub> hydrochloride: **7-HCl**

The previously reported procedure was slightly modified.<sup>2</sup>

**4a method.** **6** (2.47 g, 12.8 mmol) was suspended in anhydrous DMF (250 mL) and stirred at 80 °C. To this solution, **4a** (3.29 g, 12.5 mmol) in anhydrous DMF (50 mL) was added drop-wise. After the addition was complete, the reaction was stirred at 80 °C for an additional hour when another portion of **6** (2.47 g, 12.8 mmol) was added. The resulting solution was heated at 80 °C overnight. After the reaction was complete, the solvent was removed by rotary evaporation, and the solid residue was stirred with 120 mL of MeOH for 30 minutes. The MeOH suspension was filtered and washed with water and a small amount of MeOH. The white solid was dried by vacuum (1.35 g mixture of **7** and **8**, 3.7 : 1 respectively). To isolate the **7** from the **8**, the solid was suspended in 95% ethanol (200 mL) to which one equivalent of 1 M HCl (1.75 mL) was added. This suspension was stirred overnight (or up to two days) and then filtered by vacuum filtration. The solid and the filtrate were

dried separately which gave **8** (0.42 g, 0.51 mmol, 12%) and **7·HCl** (0.93 g, 1.59 mmol, 26%) respectively.

**4b method.** **6** (33.07 g, 171 mmol) was dissolved in anhydrous DMF (1600 mL) and stirred at 80 °C. To this solution, **4b** (38.00 g, 84.9 mmol) in anhydrous DMF (400 mL) was added drop-wise. After the addition was complete, the reaction was stirred at 80 °C for up to sixty hours. After the reaction was complete, the DMF was removed by rotary evaporation, and the solid residue was stirred with 400 mL of MeOH for 30 minutes. The MeOH suspension was filtered and washed with water and a small amount of MeOH. The white solid was dried *in vacuo* (15.77 g mixture of **7** and **8**, 4.44 : 1). To isolate the **7** from the **8**, the solid was suspended in 95% ethanol (1000 mL) to which one equivalent of 1 M HCl was added. The suspension was stirred overnight and then filtered by vacuum filtration. The solid and filtrate were dried separately which gave **8** (6.81 g, 8.27 mmol, 29%) and **7·HCl** (9.62 g, 16.4 mmol, 39%) respectively.

**4c method.** **6** (16.29 g, 84.3 mmol) was dissolved in anhydrous DMF (750 mL) and stirred at 80 °C. To this solution, **4c** (12.13 g, 41.1 mmol) in anhydrous DMF (250 mL) was added drop-wise. After the addition was complete, the reaction was stirred at 80 °C for up to sixty hours. Then, the solvent was removed by rotary evaporation, and the solid residue was stirred with 400 mL of MeOH for 30 minutes. The MeOH suspension was filtered and washed with water and a small amount of MeOH. The white solid was dried *in vacuo* (12.17 g mixture of **7** and **8**, 4.53 : 1). To isolate the **7** from the **8**, the solid was suspended in 95% ethanol (600 mL) to which one equivalent of 1 M HCl was added. The suspension was stirred overnight and then filtered by vacuum filtration. The solid and filtrate were dried separately which gave **8** (4.36 g, 5.42 mmol, 39%) and **7·HCl** (7.01 g, 11.9 mmol, 58%) respectively.

<sup>15</sup>N<sub>4</sub>-HCl (**7·HCl**) δ<sub>H</sub>(300 MHz, CDCl<sub>3</sub>): 7.91 (t, *J* = 7.5 Hz, 2 H), 7.71 (d, *J* = 7.8 Hz, 4 H), 7.45 (d, *J* = 7.5 Hz, 4 H), 7.35 (d, *J* = 7.8 Hz, 4 H), 5.00 (s, 8 H), 2.42 (s, 6 H); δ<sub>H</sub>(300 MHz, DMSO-*d*<sub>6</sub>): 8.27 (t, 2 H), 7.84 (d, 4 H), 7.77 (d, 4 H), 7.48 (d, 4 H), 4.92 (s, 8 H), 2.42 (s, 6 H) δ<sub>C</sub>(75 MHz, DMSO-*d*<sub>6</sub>): 156.27, 144.99, 134.34, 130.68, 128.07, 123.24, 53.38, 21.55; ESI-MS (*m/z*): 549.1627, calc: 549.1630 (M + H<sup>+</sup>).

<sup>15</sup>N<sub>6</sub> (**8**) δ<sub>H</sub>(300 MHz, CDCl<sub>3</sub>): 7.64 (d, *J* = 7.8 Hz, 6 H), 7.40 (t, *J* = 7.5 Hz, 3 H), 7.26 (d, *J* = 7.8 Hz, 6 H), 7.11 (d, *J* = 7.5 Hz, 6 H), 4.26 (s, 12 H), 2.42 (s, 9 H).

#### Synthesis of <sup>15</sup>N<sub>4</sub>: **7**

The previously reported procedure was slightly modified.<sup>1</sup> **16** (1.0 g, 2.24 mmol) dissolved in 100% ethanol (25 mL) was added to a solution of sodium metal (0.12 g, 5 mmol) in 100% ethanol (20 mL). The mixture was refluxed for one hour and then cooled to form the disodium salt of **16**, which was isolated by filtration and used without additional purification. The disodium salt of **16** (0.45 g, 0.92 mmol) was dissolved in anhydrous DMF (20 mL) and heated to 100 °C. To this, a solution of **4b** (0.41 g, 0.92 mmol) dissolved in anhydrous DMF (20 mL) was added dropwise over one hour. Once the addition was complete, the mixture was stirred for an additional five

hours. Then the solvent DMF was removed under reduced pressure and the residue was dissolved in CHCl<sub>3</sub> (100 mL). This solution was washed with water (5 × 15 mL), dried with magnesium sulfate, and concentrated to dryness under reduced pressure to yield 0.44 g of solid. Recrystallization of the solid in CHCl<sub>3</sub>/EtOH gave **7** as a white solid (0.32 g, 63%).

<sup>15</sup>N<sub>4</sub> (**7**) δ<sub>H</sub>(300 MHz, CDCl<sub>3</sub>): 7.79 (d, *J* = 7.8 Hz, 4 H), 7.38 (d, *J* = 7.8 Hz, 4 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.16 (d, *J* = 7.5 Hz, 4 H), 4.47 (br. s, 8 H), 2.47 (s, 6 H); δ<sub>C</sub>(75 MHz, CDCl<sub>3</sub>): 154.83, 143.75, 137.27, 136.03, 130.04, 127.03, 123.29, 56.59, 21.60; ESI-MS (*m/z*): 549.1625, calc: 549.1630 (M + H<sup>+</sup>).

#### Synthesis of <sup>15</sup>N<sub>4</sub>: **9**

The previously reported procedures were slightly modified.<sup>2</sup> **7·HCl** (3.46 g, 5.91 mmol) was dissolved in 90% sulfuric acid (30 mL). This mixture was stirred and refluxed at 110 °C for 2.5 hours. After cooling, the solution was diluted with water (50 mL). In an ice bath, the solution was treated with NaOH to make the solution basic. The resulting solution was extracted with CHCl<sub>3</sub> (4 × 100 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and the solvent was removed under reduced pressure to yield white solid, **9** (1.25 g, 5.20 mmol, 88.0%). δ<sub>H</sub>(300 MHz, CDCl<sub>3</sub>): 7.08 (t, *J* = 7.5 Hz, 2H), 6.50 (d, *J* = 7.5 Hz, 4H), 3.94 (s, 8H); δ<sub>C</sub>(75 MHz, CDCl<sub>3</sub>): 159.67, 135.92, 119.98, 56.23; ESI-MS (*m/z*): 241.1448, calc: 241.1453 (M + H<sup>+</sup>).

#### Synthesis of <sup>13</sup>C<sub>4</sub>: **10**

The previously reported procedures were slightly modified.<sup>1,2</sup> **9** (0.54 grams, 2.25 mmol) was dissolved in concentrated formic acid (100 mL, 2650 mmol) and 40% formaldehyde solution (22 mL, 239 mmol). This mixture was stirred and refluxed at 110 °C for 24 hours. After cooling, the solution was treated with 12 mL concentrated HCl. After 30 minutes, the solution was concentrated to dryness. The residue was then basified with sodium hydroxide solution and extracted with CHCl<sub>3</sub> (4 × 100 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated to dryness to give pale yellow powder, **10** (0.52 g, 1.94 mmol, 86.0%). δ<sub>H</sub>(300 MHz, CDCl<sub>3</sub>): 7.14 (t, *J* = 7.5 Hz, 2H), 6.79 (d, *J* = 7.5 Hz, 4H), 3.86 (s, 8H), 2.73 (s, 6H); δ<sub>C</sub>(75 MHz, CDCl<sub>3</sub>): 157.42, 135.70, 127.73, 66.33, 49.29.

#### Synthesis of <sup>13</sup>C<sub>4</sub>: **11**

**9** (1.25 g, 5.20 mmol) and triethylamine (726 μL, 5.21 mmol) were dissolved in DCM (150 mL) at 0 °C. To this solution, TsCl (0.9917 g, 5.20 mmol) in DCM (450 mL) was added dropwise. After the addition was complete, the reaction was stirred at 0 °C for an additional three hours. Then the reaction mixture was washed with a solution of saturated sodium bicarbonate (100 mL). The organic layer was dried with potassium carbonate, filtered, and concentrated to dryness to isolate a mixture of **11** and **7** (1.74 g). The mixture was suspended in isopropanol (500 mL), stirred up to 24 hours, and then filtered. The solid and filtrate were dried separately which gave **7** (0.84 g, 1.53 mmol, 29.4%) and **11** (0.90 grams, 2.28 mmol, 43.9%)

respectively. NMR of **11**:  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ): 7.81 (d,  $J = 7.8$  Hz, 2H), 7.39 (d,  $J = 7.8$  Hz, 2H), 7.19 (t,  $J = 7.5$  Hz, 2H), 7.06 (d,  $J = 7.5$  Hz, 2H), 6.60 (d,  $J = 7.5$  Hz, 2H), 4.52 (s, 4H), 3.91 (s, 4H), 2.48 (s, 3H);  $\delta_{\text{C}}$ (75 MHz,  $\text{CDCl}_3$ ): 158.60, 155.31, 143.60, 136.37, 129.94, 126.91, 122.06, 120.88, 57.16, 55.75, 21.54; ESI-MS ( $m/z$ ): 395.1535; calc: 395.1563 ( $\text{M} + \text{H}^+$ ).

#### Synthesis of $^{\text{TSMe}}\text{N4}$ : **12**

**11** (0.32 grams, 0.81 mmol) was dissolved in concentrated formic acid (50 mL, 1325 mmol) and 40% formaldehyde solution (5 mL, 54 mmol). This mixture was stirred and refluxed at 110 °C for 24 hours. After cooling, the solution was treated with 5 mL concentrated HCl. After 30 minutes, the solution was concentrated to dryness. The residue was then basified with 1 M sodium hydroxide solution and extracted with  $\text{CHCl}_3$  ( $4 \times 100$  mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated to dryness to give **12** (0.26 g, 0.64 mmol, 79%).  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ): 7.78 (d,  $J = 7.8$  Hz, 2H), 7.40 (d,  $J = 7.8$  Hz, 2H), 7.23 (t,  $J = 7.5$  Hz, 2H), 7.10 (d,  $J = 7.5$  Hz, 2H), 6.86 (d,  $J = 7.5$  Hz, 2H), 4.52 (s, 4H), 3.80 (s, 4H), 2.72 (s, 3H), 2.49 (s, 3H);  $\delta_{\text{C}}$ (75 MHz,  $\text{CDCl}_3$ ): 157.16, 154.55, 143.56, 136.33, 135.99, 129.86, 127.20, 123.20, 122.53, 65.76, 56.56, 49.04, 21.49; ESI-MS ( $m/z$ ): 409.1695, calc: 409.1620 ( $\text{M} + \text{H}^+$ ).

#### Synthesis of $^{\text{MeH}}\text{N4}$ : **13**

**12** (1.01 g, 2.47 mmol) was placed into a 100 mL three-neck round-bottom flask. A condenser was connected, and the entire apparatus was evacuated and refilled with nitrogen three times. Then **12** was dissolved in concentrated sulfuric acid (20 mL). This solution was stirred and refluxed at 100 °C for 24 hours. After cooling, the solution was diluted with 50 mL of water. At 0 °C, the pH of the solution was adjusted with sodium hydroxide to 14. The resulting solution was extracted with  $\text{CHCl}_3$  ( $4 \times 300$  mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated to dryness to give **13** (0.56 g, 2.20 mmol, 90%).  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ): 7.10 (t,  $J = 7.5$  Hz, 2H), 6.72 (d,  $J = 7.5$  Hz, 2H), 6.50 (d,  $J = 7.5$  Hz, 2H), 3.94 (s, 4H), 3.85 (s, 4H), 2.74 (s, 3H);  $\delta_{\text{C}}$ (75 MHz,  $\text{CDCl}_3$ ): 158.47, 157.62, 135.53, 121.93, 120.29, 66.37, 55.65, 48.92; ESI-MS ( $m/z$ ): 255.1586; calc: 255.1610 ( $\text{M} + \text{H}^+$ ).

#### Synthesis of 2,6-bis(phthalimidomethyl)pyridine: **14**

The previously reported procedure was slightly modified.<sup>37</sup> Triphenylphosphine (19.0 g, 72.6 mol) and **3** (5 g, 35.9 mmol) were dissolved in THF (300 mL) and chilled to 0 °C. Once cooled, phthalimide (10.9 g, 74.4 mmol) was added. To this solution, diethyl azodicarboxylate ester (35.7 mL, 40% in toluene, 78 mmol) was added dropwise. Upon completion of the addition, the reaction was allowed to slowly warm to room temperature and left to stir overnight. The solvent was removed by filtration and 400 mL of DCM/THF (8:1) was added to the residue and stirred for 30 min. This solution was filtered to obtain white powder, **14** (10.8 g, 27.2 mmol, 76%). The product was used to make **15** without further purification.

$\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ): 7.80–7.65 (m, 8 H), 7.59 (t,  $J = 7.8$  Hz, 1 H), 7.12 (d,  $J = 7.6$  Hz, 2 H), 4.92 (s, 4 H).

#### Synthesis of 2,6-bis(aminomethyl)pyridine: **15**

The previously reported procedures were slightly modified.<sup>1,37</sup> Hydrazine hydrate (10.3 mL, 209 mmol) was added to a solution of **14** (8.3 g, 21 mmol) in 210 mL of 95% ethanol and refluxed overnight to generate a white solid. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was washed with  $\text{CHCl}_3$  (300 mL) and filtered. The filtrate was dried over magnesium sulfate and concentrated under reduced pressure to yield colorless crystals of **15** (2.4 g, 17.8 mmol, 85%).  $\delta_{\text{H}}$ (300 MHz,  $\text{DMSO}-d_6$ ): 7.68 (t,  $J = 7.8$  Hz, 1 H), 7.25 (d,  $J = 7.8$  Hz, 2 H), 3.75 (s, 4 H), 1.85 (br. s, 4 H);  $\delta_{\text{C}}$ (75 MHz,  $\text{DMSO}-d_6$ ): 167.16, 141.92, 123.68, 52.57.

#### Synthesis of 2,6-bis(toluenesulfonylmethylamine)pyridine: **16**

The previously reported procedures were slightly modified.<sup>1,36,48</sup> Triethylamine (5.6 mL, 40 mmol) and **15** (2.6 g, 19 mmol) were dissolved in DCM (100 mL) and cooled to 0 °C. To this solution, TsCl (7.62 g, 40 mmol) diluted in DCM (150 mL) was added dropwise. Upon completion of the addition, the reaction mixture was left to stir for an additional 24 h, allowing the solution to warm to room temperature. The organic layer was washed with water and saturated NaCl solution (250 mL each), dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to yield an orange solid. The crude product was purified by silica gel column chromatography (DCM:EtOAc, 95:5) to obtain **16** as white powder (7.21 g, 16.2 mmol, 85%).  $\delta_{\text{H}}$ (300 MHz,  $\text{CDCl}_3$ ): 7.73 (d,  $J = 8.0$  Hz, 4 H), 7.54 (t,  $J = 7.5$  Hz, 1 H), 7.27 (d,  $J = 8.0$  Hz, 4 H), 7.07 (d,  $J = 7.5$  Hz, 2 H), 5.50 (t,  $J = 6.0$  Hz, 2 H), 4.18 (d,  $J = 6.0$  Hz, 4 H), 2.41 (s, 6 H).

## Conflicts of interest

The authors declare no competing financial interest.

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