

# Convenient synthesis of 3,5,7-trimethyl-1-azonia-adamantanes

Hiroshi Izumi\* and Shigeru Futamura

National Institute for Resources and Environment, 16-3 Onogawa,  
Tsukuba, Ibaraki 305-8569, Japan

E-mail: [izumi@nire.go.jp](mailto:izumi@nire.go.jp)

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## Abstract

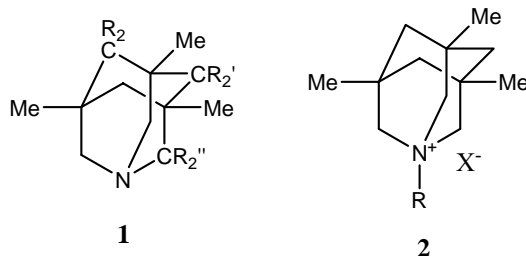
A convenient synthesis of 3,5,7-trimethyl-1-azonia-adamantanes (2) is described. The esterification of *cis,cis*-1,3,5-tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (3) with trifluoromethanesulfonic anhydride, followed by the reaction with primary amines, yields azonia-adamantanes 2. On the other hand, the esterification of triol 3 with TFAA also affords *cis,cis*-1,3,5-tris[(trifluoroacetoxy)methyl]-1,3,5-trimethylcyclohexane (5). However, the reaction of triester 5 with 2-(2-aminoethyl)pyridine does not give the corresponding azonia-adamantane, but 2,2,2-trifluoro-*N*-[2-(pyridin-2-yl)ethyl]-acetamide (6). The  $\beta$ -methylene protons in azonia-adamantane 2a [R = 2-(pyridin-2-yl)ethyl] are very active. Both acids and bases react with 2a to yield 2-vinylpyridine. The elimination reaction of 2a with lithium methoxide is available for the synthesis of 3,5,7-trimethyl-1-aza-adamantane (1).

**Keywords:** Azonia-adamantanes, lithium methoxide, vinylpyridine

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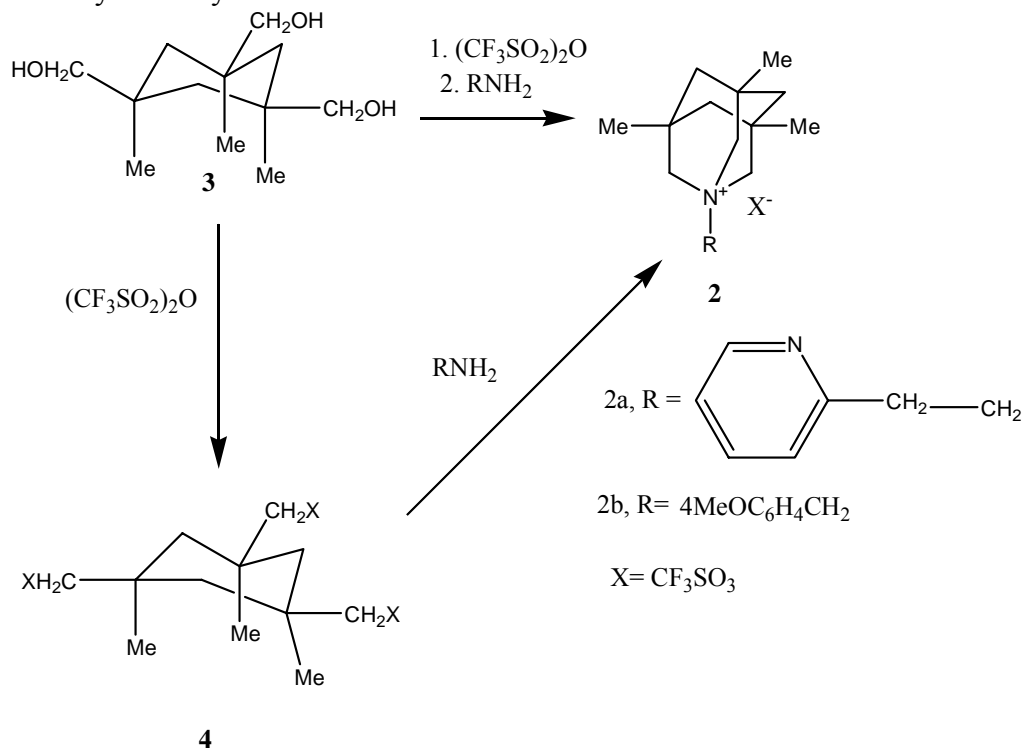
## Introduction

3,5,7-Trimethyl-1-aza-adamantane structures (1) have been applied as highly twisted amides,<sup>1</sup> self-organization systems,<sup>2</sup> and rigid models.<sup>3</sup> These structures have been also attracting considerable interest because of their pharmacological activity.<sup>4</sup> In contrast, there have been few studies on 3,5,7-trimethyl-1-azonia-adamantanes 2, and many synthetic steps have been needed.<sup>5</sup> In this paper, we report a convenient synthetic method for 3,5,7-trimethyl-1-azonia-adamantanes 2. We also present an elimination reaction of 2a [R = 2-(pyridin-2-yl)ethyl] to give azonia-adamantane 2c (R = H) and 2-vinylpyridine.

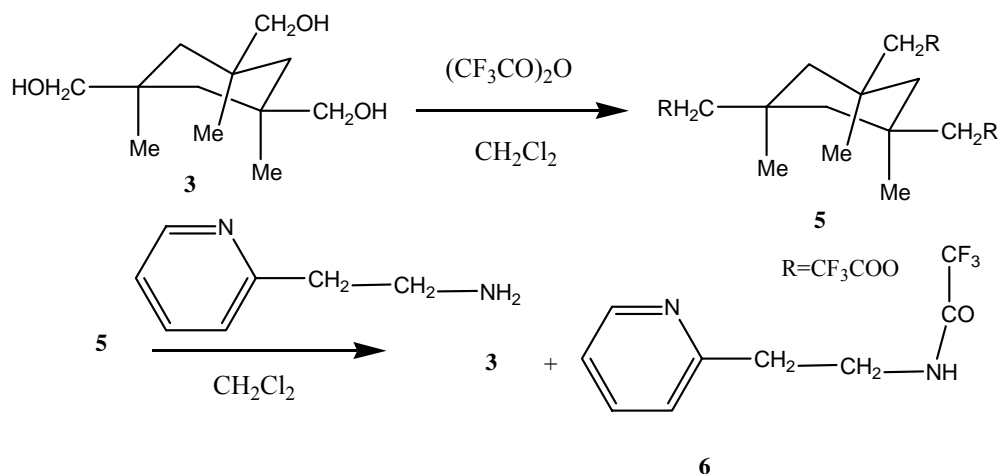


## Results and Discussion

As shown in Scheme 1, the esterification of *cis,cis*-1,3,5-tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (**3**)<sup>6</sup> with trifluoromethanesulfonic anhydride (4 equiv),<sup>7</sup> followed by reactions with primary amines (4 equiv), gave 3,5,7-trimethyl-1-azonia-adamantanes **2** [**2a**, R = 2-(pyridin-2-yl)ethyl, 23%; **2b**, R = 4-methoxybenzyl, 31%]. The <sup>1</sup>H NMR, <sup>13</sup>C NMR (DEPT), <sup>1</sup>H-<sup>13</sup>C COSY spectra supported the structure of **2**. Mayer and co-workers indicated that triester **4** (X = trifluoromethylsulfonyloxy) is easily obtained by the reaction of triol **3** with trifluoromethanesulfonic anhydride and is available for the trisubstituted tripodal ligand.<sup>7</sup> In this case, however, the corresponding triamines could not be obtained. We have already shown that the steric repulsion of the *ipso* methyl groups in the cyclohexane ring causes the unexpected reactions<sup>8</sup> and stabilizes the molecular structures.<sup>9</sup> This finding suggests that the proximity effect works efficiently in the synthesis of azonia-adamantanes **2**.



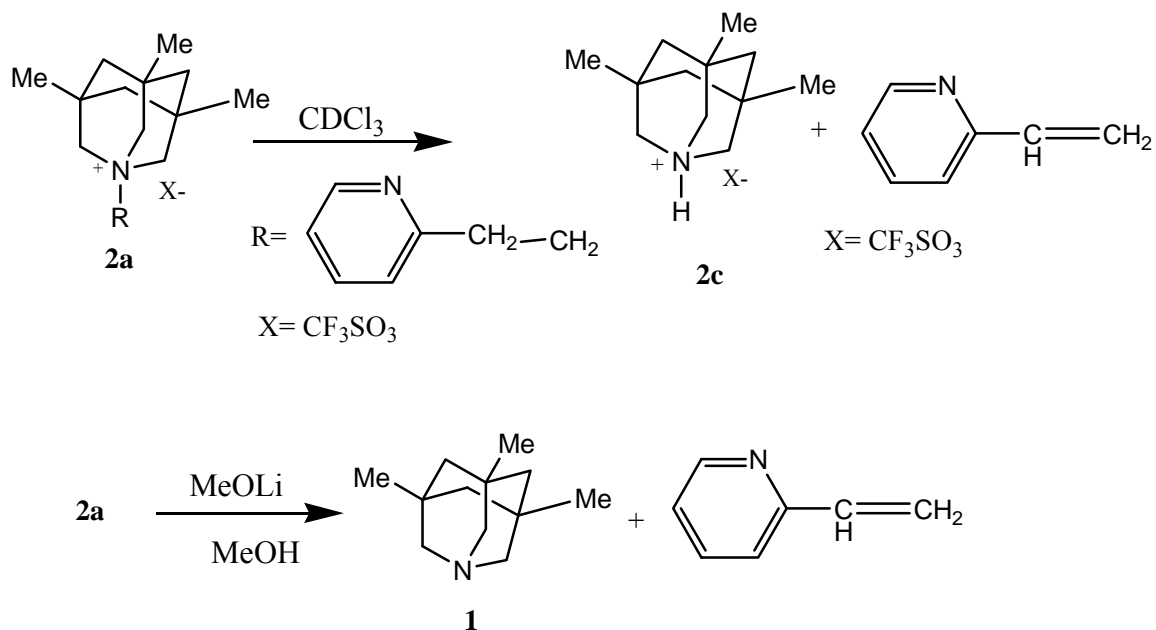
**Scheme 1**



## Scheme 2

On the other hand, the esterification of triol **3** with TFAA (4 equiv) also afforded triester **5** (Scheme 2). However, the reaction of triester **5** with 2-(2-aminoethyl)pyridine (3 equiv) did not give the corresponding azonia-adamantane, but trifluoro-acetamide **6** (Scheme 2). It is well-known that reactions of carboxylic acid esters with amines yield acid amides.<sup>10</sup> The low solubility of triol **3** in  $CH_2Cl_2$  promotes this reaction. It is suggested that trifluoroacetate lacks the function as the counter anion. The reaction of triol **3** with methanesulfonic anhydride (3 equiv) did not give the corresponding triester. The <sup>1</sup>H NMR spectrum of the reaction mixture indicated the signals of unreacted triol **3** and methanesulfonic anhydride.

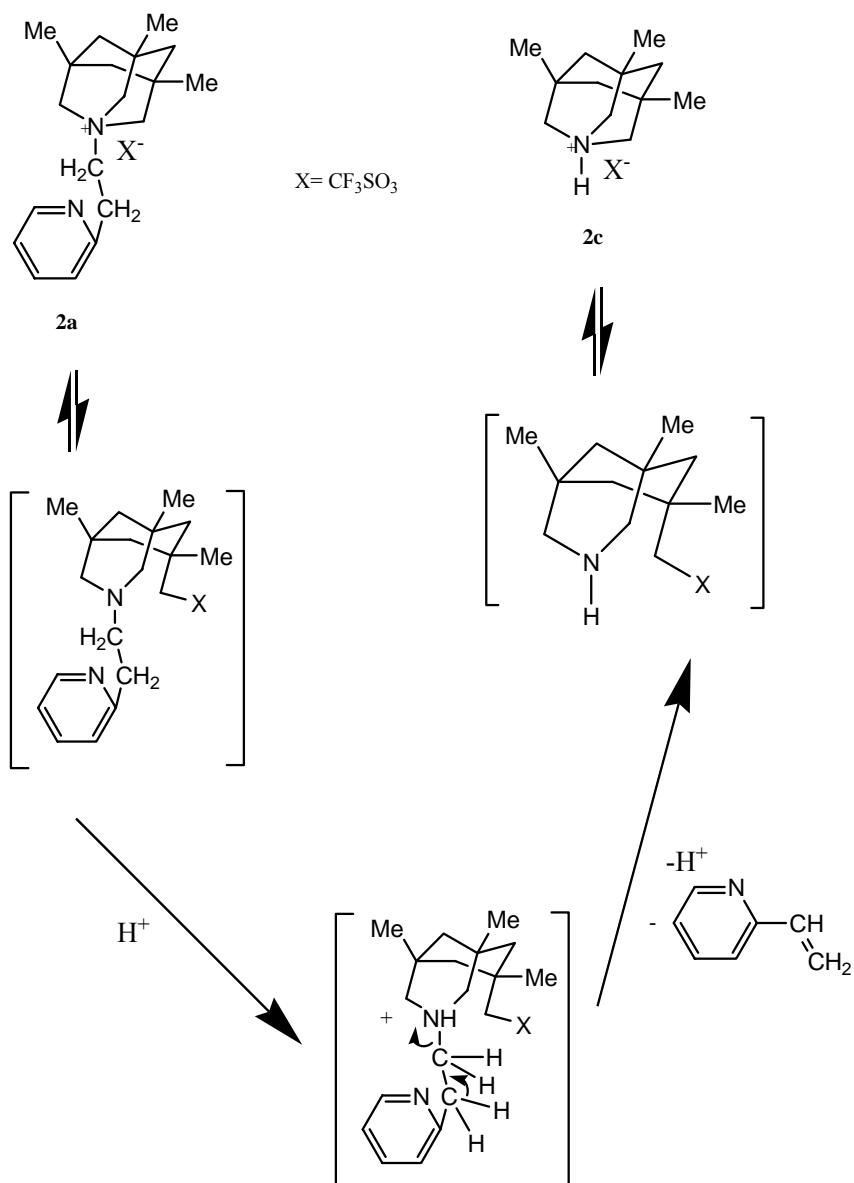
Azonia-adamantane **2a** was not stable in  $CDCl_3$ . Allowing the  $CDCl_3$  solution of **2a** to stand at room temperature for 5 days gave azonia-adamantane **2c** (R = H) and 2-vinylpyridine (Scheme 3). However, **2a** did not yield **2c** either in  $DMSO-d_6$  or in acetone-*d*<sub>6</sub> at room temperature for 2 weeks. We have already described that acid catalysis works in chloroform.<sup>6,8</sup> Scheme 4 shows a plausible mechanism for the reaction of **2a** to **2c**. It has been clarified that 3,5,7-trimethyl-1-aza-adamantane structures easily undergo the interconversion to the corresponding 3-azabicyclo[3.3.1]nonane structures.<sup>1,2</sup> It is suggested that azonia-adamantane **2a** is in equilibrium with the C-N bond cleavage form, and adhesion of a proton to the nitrogen atom in this form yields **2c** and 2-vinylpyridine. This reaction resembles acid-catalyzed alkene formation reactions of alcohols. Azonia-adamantane **2a** reacts not only with acids but also with bases. The reaction of **2a** with lithium methoxide in methanol afforded aza-adamantane **1**<sup>5</sup> and 2-vinylpyridine (Scheme 3). This reaction is also available for the convenient synthesis of aza-adamantane **1**. Triethylamine did not react with **2a** at all. The acidity of  $\beta$ -methylene protons in azonia-adamantane **2a** has a large influence on these reactions.



Scheme 3

## Conclusions

We have described the convenient synthesis of 3,5,7-trimethyl-1-azonia-adamantanes 2. In this synthesis, trifluoromethanesulfonate works as the key counter anion. The similar reaction of triester 5 with 2-(2-aminoethyl) pyridine does not give the corresponding azonia-adamantane, but trifluoro-acetamide 6. We have also shown that the elimination reaction of azonia-adamantane 2 containing  $\beta$ -methylene protons is available for the synthesis of aza-adamantane 1.



Scheme 4

## Experimental Section

**General Procedures.** All reactions were performed in oven-dried glassware equipped with a magnetic stirring bar under an argon atmosphere, using standard syringe techniques.  $\text{CH}_2\text{Cl}_2$  was distilled from  $\text{CaH}_2$  and stored over molecular sieves. All other solvents were of anhydrous grade. *cis,cis*-1,3,5-Tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (3)<sup>6</sup> and *cis,cis*-1,3,5-trimethyl-1,3,5-tris[(trifluoromethylsulfonyloxy)methyl]cyclohexane (4)<sup>7</sup> were prepared by the similar procedures previously reported. All other reagents were of commercial grade.  $^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (125.7 MHz) NMR spectra were recorded in  $\text{CDCl}_3$ ,  $\text{DMSO}-d_6$ , or  $\text{acetone}-d_6$ .

**3,5,7-Trimethyl-1-[2-(pyridin-2-yl)ethyl]-1-azonia-adamantane trifluoromethanesulfonate (2a).**

A solution of trifluoromethanesulfonic anhydride (2.2 mL, 13 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added to a suspension of triol 3 (723 mg, 3.34 mmol) and pyridine (1.2 mL) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0 °C. After the mixture was stirred for 2 h at 0 °C, the precipitates were filtered, and the solution was passed through a silica gel column. Removal of the solvent under reduced pressure gave crude triester 4. Unpurified triester 4 was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and 2-(2-aminoethyl) pyridine (1.85 g, 15.1 mmol) was added to the solution. The solution was stirred for 3 days at room temperature, and dilute aqueous NaOH was added. The CH<sub>2</sub>Cl<sub>2</sub> layer was separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined CH<sub>2</sub>Cl<sub>2</sub> solutions were dried with MgSO<sub>4</sub>, followed by filtration, the filtrate was concentrated to remove volatiles. Azonia-adamantane 2a (338 mg, 23%) was purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/diethyl ether. 2a: colorless crystals; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 0.99 (9H, s, CH<sub>3</sub>), 1.33 (3H, d, <sup>2</sup>J<sub>HH</sub> = 13.0 Hz, CHaHe), 1.50 (3H, d, <sup>2</sup>J<sub>HH</sub> = 13.0 Hz, CHaHe), 3.24 (6H, s, CH<sub>2</sub>N), 3.53–3.57 (2H, m, CH<sub>2</sub>CH<sub>2</sub>pyr), 3.90–3.94 (2H, m, CH<sub>2</sub>CH<sub>2</sub>N), 7.40–7.43 (1H, m, pyrH), 7.85–7.87 (1H, m, pyrH), 7.94–7.97 (1H, m, pyrH), 8.49–8.50 (1H, m, pyrH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ 25.53 (CH<sub>3</sub>), 28.31 (CH<sub>2</sub>CH<sub>2</sub>pyr), 31.56 [(CH<sub>2</sub>)<sub>2</sub>CCH<sub>3</sub>], 46.07 (CCH<sub>2</sub>C), 64.81 (CH<sub>2</sub>CH<sub>2</sub>N), 67.27 (CH<sub>2</sub>N), 123.75 (pyridine carbon), 126.72 (pyridine carbon), 141.04 (pyridine carbon), 145.92 (pyridine carbon), 153.88 (pyridine carbon); IR (KBr) ν/ cm<sup>-1</sup> 1259, 1167, 1026, 637; Anal. Calcd for C<sub>20</sub>H<sub>29</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S: C, 55.28; H, 6.73; N, 6.45. Found: C, 55.22; H, 6.83; N, 6.51.

**1-(4-Methoxybenzyl)-3,5,7-trimethyl-1-azonia-adamantane trifluoromethanesulfonate (2b).**

The similar manner that was employed in the preparation of 2a was used with triol 3 (746 mg, 3.45 mmol), trifluoromethanesulfonic anhydride (2.0 mL, 12 mmol), and 4-methoxybenzylamine (1.91 g, 13.9 mmol). Azonia-adamantane 2b (479 mg, 1.06 mmol) was obtained in 31% yield. 2b: colorless solids; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 0.91 (9H, s, CH<sub>3</sub>), 1.22 (3H, d, <sup>2</sup>J<sub>HH</sub> = 12.8 Hz, CHaHe), 1.38 (3H, d, <sup>2</sup>J<sub>HH</sub> = 12.8 Hz, CHaHe), 3.06 (6H, s, CH<sub>2</sub>N), 3.79 (3H, s, OCH<sub>3</sub>), 4.49 (2H, s, NCH<sub>2</sub>Ar), 6.87 (2H, d, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, ArH), 7.39 (2H, d, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ 25.57 (CH<sub>3</sub>), 31.36 [(CH<sub>2</sub>)<sub>2</sub>CCH<sub>3</sub>], 45.98 (CCH<sub>2</sub>C), 55.33 (OCH<sub>3</sub>), 65.67 (CH<sub>2</sub>N), 69.10 (NCH<sub>2</sub>Ar), 114.45 (aromatic carbon), 117.80 (aromatic carbon), 120.75 (q, <sup>1</sup>J<sub>CF</sub> = 320 Hz, CF<sub>3</sub>), 134.67 (aromatic carbon), 161.20 (aromatic carbon); IR (KBr) ν/ cm<sup>-1</sup> 1265, 1150, 1030, 637; Anal. Calcd for C<sub>21</sub>H<sub>30</sub>F<sub>3</sub>NO<sub>4</sub>S: C, 56.11; H, 6.73; N, 3.12. Found: C, 56.03; H, 6.88; N, 3.19.

**cis,cis-1,3,5-Tris[(trifluoroacetoxy)methyl]-1,3,5-trimethylcyclohexane (5).**

A solution of trifluoroacetic anhydride (2.0 mL, 14 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added to a suspension of triol 3 (725 mg, 3.35 mmol) and pyridine (1.2 mL) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0 °C. After the mixture was stirred for 2.5 h at 0 °C, the solution was passed through a silica gel column. Removal of the solvent under reduced pressure gave triester 5 (1.59 g, 94%). 5: colorless solids; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.25 (9H, s, CH<sub>3</sub>), 1.32 (3H, d, AB, <sup>2</sup>J<sub>HH</sub> = 14.2 Hz, CHaHe), 1.34 (3H, d, AB, <sup>2</sup>J<sub>HH</sub> = 14.2 Hz, CHaHe), 3.94 (6H, s, CH<sub>2</sub>O); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ 25.43 (CH<sub>3</sub>), 34.27 [(CH<sub>2</sub>)<sub>2</sub>CCH<sub>3</sub>], 38.85 (CCH<sub>2</sub>C), 77.40 (CH<sub>2</sub>O), 114.48 (q, <sup>1</sup>J<sub>CF</sub>

= 285 Hz, CF<sub>3</sub>), 157.38 (q, <sup>2</sup>JCF = 43 Hz, COO); Anal. Calcd for C<sub>18</sub>H<sub>21</sub>F<sub>9</sub>O<sub>6</sub>: C, 42.87; H, 4.20. Found: C, 43.54; H, 4.14.

**2,2,2-Trifluoro-N-[2-(pyridin-2-yl)ethyl]-acetamide (6).** 2-(2-aminoethyl)pyridine (1.28 g, 10.4 mmol) was added to a CH<sub>2</sub>Cl<sub>2</sub> solution (10 mL) of triester 5 (1.59 g, 3.16 mmol). While the solution was stirred for 3 h at room temperature, precipitates were formed. The precipitates were filtered and washed with diethyl ether. Triol 3 (658 mg, 3.04 mmol) was obtained in 96% yield. After the filtrate was concentrated to remove volatiles, the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. Removal of the solvent under reduced pressure gave acetamide 6 (1.99 g, 96%). Further purification was carried out by recrystallization from diethyl ether/hexane. 6: pale yellow crystals; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 3.00–3.02 (2H, m, CH<sub>2</sub>), 3.72–3.75 (2H, m, CH<sub>2</sub>), 7.13–7.16 (2H, m, pyrH), 7.59–7.63 (1H, m, pyrH), 8.40 (1H, br. s, NH), 8.47–8.48 (1H, m, pyrH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ 35.13 (CH<sub>2</sub>), 38.66 (CH<sub>2</sub>), 115.97 (q, <sup>1</sup>JCF = 287 Hz, CF<sub>3</sub>), 121.90 (pyridine carbon), 123.43 (pyridine carbon), 136.91 (pyridine carbon), 149.02 (pyridine carbon), 156.97 (q, <sup>2</sup>JCF = 37 Hz, CO), 158.94 (pyridine carbon); IR (KBr)/v cm<sup>-1</sup> 3202, 1724; Anal. Calcd for C<sub>9</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O: C, 49.55; H, 4.16; N, 12.84. Found: C, 49.62; H, 4.19; N, 12.81.

**3,5,7-Trimethyl-1-aza-adamantane (1).**<sup>5</sup> A solution of azonia-adamantane 2a (76.3 mg, 0.18 mmol) in methanol (20 mL) was added to a 12% lithium methoxide methanol solution (2 mL) at 0 °C. After the mixture was stirred for 18 h at room temperature, water (1 mL) was added to the solution. Volatiles were removed under reduced pressure, and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. Removal of the solvent under reduced pressure gave aza-adamantane 1<sup>5</sup> (24.9 mg, 79%).

**NMR Monitoring experiment.** Azonia-adamantane 2a (2.1 mg, 0.005 mmol) was added to CDCl<sub>3</sub> (0.8 mL) in an NMR tube. Allowing the solution to stand at room temperature for 5 days gave azonia-adamantane 2c (R = H) and 2-vinylpyridine. 2c: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 0.96 (9H, s, CH<sub>3</sub>), 1.37 (3H, d, <sup>2</sup>JHH = 12.7 Hz, CHaHe), 1.44 (3H, d, <sup>2</sup>JHH = 12.7 Hz, CHaHe), 3.00 (6H, s, CH<sub>2</sub>N), 10.70 (1H, br. s, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ 25.89 (CH<sub>3</sub>), 30.05 [(CH<sub>2</sub>)<sub>2</sub>CCH<sub>3</sub>], 47.22 (CCH<sub>2</sub>C), 59.53 (CH<sub>2</sub>N).

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