Supporting Information
for DOI: 10.1055/s-0032-1316737
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Some practical methods for the application of 5-metallo-1-benzyl-1H-tetrazoles in synthesis

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Supplementary Data – For online publication

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Materials</td>
<td>S4</td>
</tr>
<tr>
<td>2. Rate studies</td>
<td></td>
</tr>
<tr>
<td>General procedure</td>
<td>S5</td>
</tr>
<tr>
<td>Raw data</td>
<td>S5</td>
</tr>
<tr>
<td>Graphs of rate data</td>
<td></td>
</tr>
<tr>
<td>Decomposition at -40 °C</td>
<td>S6</td>
</tr>
<tr>
<td>Decomposition at -20 °C</td>
<td>S6</td>
</tr>
<tr>
<td>Decomposition at 0 °C</td>
<td>S7</td>
</tr>
<tr>
<td>3. Additional detailed experimental procedures</td>
<td></td>
</tr>
<tr>
<td>General Experimental</td>
<td>S7</td>
</tr>
<tr>
<td>1-benzyl-1H-tetrazole (8c)</td>
<td>S8</td>
</tr>
<tr>
<td>1-benzyl-5-bromo-1H-tetrazole (9)</td>
<td>S8</td>
</tr>
<tr>
<td>N-benzylcyanamide (13)</td>
<td>S9</td>
</tr>
<tr>
<td>5-[1-(benzyl)-1H-tetrazol-5-yl]-5H-dibenzo[α,δ]cyclohepten-5-ol (14a)</td>
<td>S9</td>
</tr>
<tr>
<td>9-(1-benzyl-1H-tetrazol-5-yl)-9H-fluoren-9-ol (14b)</td>
<td>S10</td>
</tr>
<tr>
<td>(1-benzyl-1H-tetrazol-5-yl)diphenylmethanol (14c)</td>
<td>S10</td>
</tr>
<tr>
<td>1-(1-benzyl-1H-tetrazol-5-yl)(phenyl)methanol (14d)</td>
<td>S11</td>
</tr>
<tr>
<td>5-[1-(benzyl)-1H-tetrazol-5-yl]-10,11-dihydro-5H-dibenzo[α,δ]cyclohepten-5-ol (14e)</td>
<td>S11</td>
</tr>
<tr>
<td>1-(1-benzyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (14f)</td>
<td>S12</td>
</tr>
<tr>
<td>1-(1-benzyl-1H-tetrazol-5-yl)-1-phenylethanol (14g)</td>
<td>S13</td>
</tr>
<tr>
<td>1-(1-benzyl-1H-tetrazol-5-yl)cyclohexanol (14h)</td>
<td>S13</td>
</tr>
<tr>
<td>1-(1-benzyl-1H-tetrazol-5-yl)-3-phenylpropan-1-ol (14i)</td>
<td>S14</td>
</tr>
<tr>
<td>General procedure for 5-(1-hydroxyalkyl)-1H-tetrazoles (3)</td>
<td>S14</td>
</tr>
<tr>
<td>5-[2H-tetrazol-5-yl]-10,11-dihydro-5H-dibenzo[α,δ]cyclohepten-5-ol (3e)</td>
<td>S15</td>
</tr>
<tr>
<td>3-phenyl-1-(2H-tetrazol-5-yl)propan-1-ol (3f)</td>
<td>S15</td>
</tr>
<tr>
<td>5-Hydroxy-5-[1-(2-methoxybenzyl)-1H-tetrazol-5-yl]-10,11-dihydro-N2,N2,N8,N8-tetramethyl-5H-dibenzo[α,δ]cycloheptene-2,8-dicarboxamide (16b)</td>
<td>S16</td>
</tr>
<tr>
<td>(1-benzyl-1H-tetrazol-5-yl)phenylketone (18)</td>
<td>S16</td>
</tr>
<tr>
<td>1-benzyl-5-(phenylthio)-1H-tetrazole (20)</td>
<td>S17</td>
</tr>
<tr>
<td>2-(1-benzyl-1H-tetrazol-5-yl)pyridine (22)</td>
<td>S17</td>
</tr>
<tr>
<td>4. Spectroscopic data</td>
<td></td>
</tr>
<tr>
<td>1-Benzyl-1H-tetrazole (8C)</td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR spectrum</td>
<td>S19</td>
</tr>
<tr>
<td>$^{13}$C NMR spectrum</td>
<td>S20</td>
</tr>
<tr>
<td>DSC plot</td>
<td>S21</td>
</tr>
</tbody>
</table>
1-Benzyl-5-bromo-1\textit{H}-tetrazole (9)
\begin{itemize}
  \item $^1$H NMR spectrum S22
  \item $^{13}$C NMR spectrum S23
  \item DSC plot S24
\end{itemize}

5-[1-(Benzyl)-1\textit{H}-tetrazol-5-yl]-5\textit{H}-dibenzo[\alpha,\delta]cyclohepten-5-ol (14a)
\begin{itemize}
  \item $^1$H NMR spectrum S25
  \item $^{13}$C NMR spectrum S26
\end{itemize}

9-(1-Benzyl-1\textit{H}-tetrazol-5-yl)-9\textit{H}-fluoren-9-ol (14b)
\begin{itemize}
  \item $^1$H NMR spectrum S27
  \item $^{13}$C NMR spectrum S28
\end{itemize}

(1-Benzyl-1\textit{H}-tetrazol-5-yl)diphenylmethanol (14c)
\begin{itemize}
  \item $^1$H NMR spectrum S29
  \item $^{13}$C NMR spectrum S30
\end{itemize}

1-(1-Benzyl-1\textit{H}-tetrazol-5-yl)(phenyl)methanol (14d)
\begin{itemize}
  \item $^1$H NMR spectrum S31
  \item $^{13}$C NMR spectrum S32
\end{itemize}

5-[1-(Benzyl)-1\textit{H}-tetrazol-5-yl]-10,11-dihydro-5\textit{H}-dibenzo[\alpha,\delta]cyclohepten-5-ol (14e)
\begin{itemize}
  \item $^1$H NMR spectrum S33
  \item $^{13}$C NMR spectrum S34
\end{itemize}

1-(1-Benzyl-1\textit{H}-tetrazol-5-yl)-1,2,3,4-tetrahydranaphthalen-1-ol (14f)
\begin{itemize}
  \item $^1$H NMR spectrum S35
  \item $^{13}$C NMR spectrum S36
\end{itemize}

1-(1-Benzyl-1\textit{H}-tetrazol-5-yl)-1-phenylethanol (14g)
\begin{itemize}
  \item $^1$H NMR spectrum S37
  \item $^{13}$C NMR spectrum S38
\end{itemize}

1-(1-Benzyl-1\textit{H}-tetrazol-5-yl)cyclohexanol (14h)
\begin{itemize}
  \item $^1$H NMR spectrum S39
  \item $^{13}$C NMR spectrum S40
\end{itemize}

1-(1-Benzyl-1\textit{H}-tetrazol-5-yl)-3-phenylpropan-1-ol (14i)
\begin{itemize}
  \item $^1$H NMR spectrum S41
  \item $^{13}$C NMR spectrum S42
\end{itemize}

5-[2\textit{H}-tetrazol-5-yl]-10,11-dihydro-5\textit{H}-dibenzo[\alpha,\delta]cyclohepten-5-ol (3e)
\begin{itemize}
  \item $^1$H NMR spectrum S43
  \item $^{13}$C NMR spectrum S44
\end{itemize}

3-Phenyl-1-(2\textit{H}-tetrazol-5-yl)propan-1-ol (3i)
\begin{itemize}
  \item $^1$H NMR spectrum S45
  \item $^{13}$C NMR spectrum S46
\end{itemize}

5-Hydroxy-5-[1-(benzyl)-1\textit{H}-tetrazol-5-yl]-10,11-dihydro-N2,N2,N8,N8-tetramethyl-5\textit{H}-dibenzo[\alpha,\delta]cycloheptene-2,8-dicarboxamide (16a)
\begin{itemize}
  \item $^1$H NMR spectrum S47
  \item $^{13}$C NMR spectrum S48
\end{itemize}

5-Hydroxy-5-[1-(2-methoxybenzyl)-1\textit{H}-tetrazol-5-yl]-10,11-dihydro-N2,N2,N8,N8-tetramethyl-5\textit{H}-dibenzo[\alpha,\delta]cycloheptene-2,8-dicarboxamide (16b)
\begin{itemize}
  \item $^1$H NMR spectrum S49
\end{itemize}
<table>
<thead>
<tr>
<th>Compound</th>
<th>NMR Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1-Benzyl-1H-tetrazol-5-yl)(phenyl)methanone (18)</td>
<td>1H NMR spectrum S50, 13C NMR spectrum S51</td>
</tr>
<tr>
<td>1-Benzyl-5-(phenylthio)-1H-tetrazole (20)</td>
<td>1H NMR spectrum S52, 13C NMR spectrum S53</td>
</tr>
<tr>
<td>2-(1-Benzyl-1H-tetrazol-5-yl)pyridine (22)</td>
<td>1H NMR spectrum S54, 13C NMR spectrum S55</td>
</tr>
</tbody>
</table>
1. Materials

Several known 5-metallotetrazole precursors were evaluated for the present study. Those compounds that had to be separated chromatographically from mixtures of 1- and 2-substituted isomers were not pursued. We focused on tetrazole synthetic equivalents that were readily available from a scalable synthetic process. Crystalline solids were preferred over liquids for further study. Using a modified literature procedure, 8c was prepared from the reaction of benzyl amine with triethyl-orthofomate and sodium azide in acetic acid. The product was isolated in good yield (83%) as a crystalline solid after precipitation with water (Scheme S1).  

Safety Warning: While this reaction was routinely run incident-free on 30 g scale, independent safety testing revealed the presence of explosive HN₃ vapors in the reactor headspace. Prudent safety evaluation should precede any implementation of this procedure.

![Scheme S1. Synthesis of 1-benzyl-1H-tetrazole (8c).](image)

We also studied the o-H 8d

Other tetrazole precursors with pendant oxygen functionality, including benzyloxymethyl (BOM 8b) and trimethylsilylethoxymethyl (SEM 6) employed at •60–•78 °C in addition ² and alkylation ³ reactions, respectively. Crystalline 1-OMB-1 -tetrazole was successfully prepared by analogy to the synthesis of , but the stabilities of its 5-metallo-derivatives were not superior to those of .

Anticipating a need for alternative entries into 5-metallo-1-benzyl-1 -tetrazoles 10

Recently, some 1-substituted-1 -tetrazoles were selectively brominated at the 5-position under acidic conditions. ⁵ Using a modified protocol, was treated with NBS in acetic acid solution at 80 °C. Bromide was isolated in high yield (90%) from this reaction as a crystalline solid after precipitation with water (Scheme S2).

![Scheme S2. Synthesis of 1-benzyl-5-bromo-1 -tetrazole (9).](image)

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Using differential scanning calorimetry (DSC), the onset temperatures for exothermic decomposition of and were measured. Both values were found to be >150 °C, suggesting that these substances may be safely manipulated at temperatures of up to at least 100 °C.

2. Rate Studies

**General procedure for the acquisition of decomposition rate data for tetrazole Grignard reagent 10c.** To a 25 mL round-bottom flask was charged 9 (0.58 g, 2.41 mmol, 1.0 equiv) and 2,6-dimethoxytoluene (IS, 0.14 – 0.20 g) as an internal standard. The flask was purged with nitrogen and THF was added, bringing the total volume to 12 mL (0.20 M). The resulting solution was transferred to four 40 mL reaction vials (3 mL each). The vials were cooled in a cryostatic bath at -42 – -45 °C. Simultaneously, 2-methoxyphenylmagnesium bromide solutions (1.0 M in THF, 0.60 mL, 0.60 mmol, 1.0 equiv) were added to each of the vials over 15 min. The vials were then aged until the desired halogen-metal exchange reaction was deemed complete by HPLC analysis (10 – 30 min). The contents of individual reaction vials were quenched after specific time intervals by addition of acetic acid (0.1 mL, 1.5 mmol, 2.5 equiv). Elapsed time was recorded with respect to the time at which the first quench took place. The resulting solutions were analyzed by HPLC at 215 nm. The amount of Grignard reagent 10c present in a given vial prior to quench was inferred based on the measured amount of tetrazole 8c present in that vial after quench. The relative concentration of 8c in each vial was recorded as a fraction of the absolute amount measured in the first-quenched vial, relative to internal standard: $[10c]_n/[8c]_n = ([8c]_0/[IS]_0)/([8c]_0/[IS]_0)$. Relative concentrations were fit to a first-order exponential function to derive rate constants ($k$).

**Raw Data**

<table>
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<th>Entry</th>
<th>Temp (°C)</th>
<th>15 min</th>
<th>30 min</th>
<th>90 min</th>
<th>$t_{1/2}$ (h)</th>
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</thead>
<tbody>
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<td>−40</td>
<td>ND</td>
<td>98.3</td>
<td>94.9</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>−20</td>
<td>94.2</td>
<td>87.8</td>
<td>71.7</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>70.5</td>
<td>51.0</td>
<td>ND</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Graphs of rate data

**First order kinetics plot (-40 °C)**

\[ y = -0.0349x - 0.0007 \]

\[ R^2 = 0.9988 \]

**First order kinetics plot (-20°C)**

\[ y = -0.2201x - 0.0069 \]

\[ R^2 = 0.9962 \]
3. Additional detailed experimental procedures

**General Experimental.** All reactions were conducted under nitrogen atmosphere using standard air-free manipulation techniques. Solvents and common reagents were purchased anhydrous (<100 ppm water) from commercial sources and used without further purification. Concentration *in vacuo* refers to the removal of solvent by rotary evaporation at reduced pressure. Flash column chromatography was performed on silica gel (Merck Kieselgel 60 F254 230–400 mesh). Reaction progress was monitored by HPLC (Zorbax SB-C8 4.6 mm × 75 mm, 3.5 μm column) eluted at 1 mL/min with mixtures consisting of acetonitrile and 0.07% aqueous HClO₄. Product purities were measured by quantitative ¹H NMR signal integration versus benzyl benzamide as an internal standard. Samples for ¹H and ¹³C NMR analysis were prepared in DMSO-*d₆* unless otherwise noted, and spectra were recorded using 400 MHz Bruker AVANCE spectrometers. Chemical shifts are expressed in parts per million (ppm). Melting points and decomposition onset temperatures were determined using a differential scanning calorimeter (DSC) operating with a constant temperature ramp of ≤5 °C/min. Only partial data for IR analyses (ATR on Zn/Se) are given. HRMS measurements were made using direct HPLC injection into an ESI-TOF spectrometer.
1-Benzyl-1H-tetrazole (8c). The title compound was prepared according to a modified literature procedure. Safety Warning: While this reaction was routinely run incident-free on 30 g scale, independent testing revealed the presence of explosive HN3 in the reactor headspace. Prudent safety evaluation should precede any implementation of this procedure. To a 250 mL 3-neck flask equipped with reflux condenser and over-head stirring was charged acetic acid (66 mL). Benzylamine (20.0 g, 20.4 mL, 187 mmol) was slowly added to the flask using an ice bath to maintain the internal temperature below 35 ºC. Then, triethylorthoformate (41.5 g, 46.6 mL, 1.5 equiv) and sodium azide (15.8 g, 243 mmol, 1.3 equiv) were charged to the reactor. The resulting slurry was heated to 80 ºC, leading to complete dissolution of suspended solids. Stirring was continued at 80 ºC for 17 h, at which point HPLC analysis indicated >95% conversion to desired product 8c. The reactor was cooled to room temperature and fitted with a short-path distillation head. Vacuum distillation was performed, maintaining the boiling flask temperature constant at 40 ºC (± 5 ºC) by heating and the boiling flask volume constant by slow addition of water. After 100 mL of water had been added, the apparatus was cooled to 20 ºC and the resulting emulsion was seeded with 8c (0.5 g). The product suspension was further stirred at 20 ºC for 2 h to a supernatant concentration of 38 mg/mL 8c. The slurry was then cooled to 10 ºC and filtered through a medium-porosity glass frit. The wet filter cake was washed with water (2x, 25 mL). After drying by passage of nitrogen, the desired compound was isolated as white crystalline solid (25 g, 83% yield). 1H NMR δ 5.72 (s, 2H), 7.33-7.41 (m, 5H), 9.53 (s, 1H). 13C NMR δ 128.1, 128.4, 128.8, 134.8, 144.0. IR 1102, 1161, 1436, 1421, 3112 cm⁻¹. HRMS calculated for C₈H₉N₄⁺ [M+H]⁺ 161.08217, found 161.08226. mp 48–50 ºC; dec. >213 ºC.

1-Benzyl-5-bromo-1H-tetrazole (9). To a 500 mL, 3-neck flask equipped with reflux condenser and over-head stirring was charged 1-benzyl-1H-tetrazole 8c (20.0 g, 125 mmol, 1 equiv) and acetic acid (60 mL) followed by N-bromosuccinimide (26.7 g, 150 mmol, 1.2 equiv). The resulting slurry was heated to 80 ºC to give a homogeneous solution. Stirring was continued at this temperature for 5.5 h at which point HPLC analysis indicated >95% conversion to desired product 9. The reaction was then cooled to 20 ºC, diluted with water (50 mL), and seeded with 9 (0.5 g). The resulting slurry was stirred at 20 ºC for 2 h, and then water (90 mL) was added dropwise, as antisolvent, over one hour. The product suspension was cooled in an ice bath to a supernatant concentration of 6 mg/ml 9 before being filtered through a medium-porosity glass

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7 Comparable results were obtained in this reaction when 0.6 equiv of 1,3-dibromo-5,5-dimethylhydantoin was substituted for 1.2 equiv N-bromosuccinimide.
frit. The wet filter cake was washed with water (2×, 50 mL). After drying by passage of nitrogen, the desired compound was isolated as white crystalline solid (26.9 g, 90%). $^1$H NMR $\delta$ 5.70 (s, 2H), 7.28-7.30 (m, 2H), 7.37-7.43 (m, 3H). $^{13}$C NMR $\delta$ 51.2, 127.8, 128.5, 128.9, 133.6, 134.4. IR 823, 983, 1099, 1171, 1387, 1422, 1453 cm$^{-1}$. HRMS calcd for C$_8$H$_8$BrN$_4$ $^{[\text{M+H}]^+}$ 238.99289, found 238.99306. mp 49–51 °C, dec. >180 °C.

$\text{N-Benzylcyanamide (13).}$ To a round-bottom flask containing a stir bar, solid 1-benzyl-1$H$-tetrazole 8c (200 mg, 1.249 mmol) and THF (4.2 mL, 0.30 M) were added, and the mixture was stirred. The flask was purged with nitrogen, and the mixture was cooled to an internal temperature of 0 °C. A solution of KOt-Bu in THF (1.0 M, 2.50 mL, 2.500 mmol, 2.0 equiv.) was added dropwise over 2-3 minutes, maintaining the internal temperature below 3 °C. Note: Bubbling occurred during addition. The reaction was stirred at 0 °C, and showed >90% conversion after 60 minutes. The reaction was quenched with acetic acid (0.18 mL, 2.5 equiv.), and allowed to warm to 20 °C. To the resulting mixture, 5.0 mL of H$_2$O and 5.0 mL of CH$_2$Cl$_2$ were added, and the resulting layers were separated. The aqueous layer assayed for 0.6 mg (0.4%) benzylcyanamide 13. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo to produce 168 mg of a yellow oil. HPLC analysis indicated 94 wt % N-benzylcyanamide 13 (adj. 158 mg, 95.7% yield), 10.1 mg (6 wt%) 1-benzyl-1$H$-tetrazole 8c, along with small amounts of t-butyl alcohol and THF. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 4.10 (app. s, 2H), 7.23 (broad s, 1H), 7.35 (m, 5H). IR 1455, 1699, 2215, 2924, 3033, 3200.

5-[1-(Benzyl)-1$H$-tetrazol-5-yl]-5$H$-dibenzo[$\alpha$,$\delta$]cyclohepten-5-ol (14a), method “in situ K”. The reaction was carried out according to the General Procedure using dibenzosuberene (5a, 97%, 1.16 g, 5.44 mmol). After the reaction was quenched with acetic acid, water (5.0 mL) was added, and the crude mixture was distilled under vacuum to remove THF (42-50 °C, 100 mbar, ~1 h). After cooling the concentrate to 20 °C, the product was crystallized by adding 10 mL water dropwise over 1 h and stirring overnight at 20 °C. Filtration through a medium-porosity fritted funnel and rinsing with 2.0 mL of a 1:1 mixture of DMAc/water provided the desired compound as a white solid (1.40 g, 95.3% 14a by mass, 67%). HPLC analysis of the filtrate revealed a loss of 110 mg (5.5%) of 14a. $^1$H NMR $\delta$ 4.92 (2H), 6.80 (m, 4H), 7.23 (m, 3H), 7.31 (m, 4H), 7.52 (m, 2H), 7.72 (broad s, 1H), 8.05 (m, 2H). $^{13}$C NMR $\delta$ 50.3, 71.3, 123.2, 127.1, 127.3, 127.7, 128.1, 128.2, 128.4, 130.8, 132.7, 134.0, 138.9, 155.9. IR 917, 1049, 1192, 1413,
3028, 3064, 3201 cm\(^{-1}\). HRMS calculated for C\(_{23}\)H\(_{19}\)N\(_4\)O\(^+\) [M+H\(^+\)] 367.15534, found 367.15629. mp 170-173 °C.

9-(1-Benzyl-1H-tetrazol-5-yl)-9H-fluoren-9-ol (14b), method “in situ Mg”. To a 3-neck flask equipped with an overhead stirrer, charge 9-fluorenone (5b, 98%, 385 mg, 2.091 mmol) and THF (7.50 mL, 0.28M). The flask was purged with nitrogen, and 1-benzyl-5-bromo-1H-tetrazole 9 (550 mg, 2.300 mmol, 1.10 equiv.) was added. The resulting mixture was cooled to -20 °C. Mesitylmagnesium bromide (1M sol’n in THF, 2.30 mL, 2.30 mmol, 1.10 equiv.) was added to the reaction dropwise over 30 minutes, maintaining the internal temperature between -25 °C and -19 °C. The reaction was stirred at -20 °C for 3.5 hours. The reaction was quenched with acetic acid (0.30 mL, 2.50 equiv.). Water (5.0 mL) and MTBE (5.0 mL) were added, and the resulting layers were separated. HPLC analysis of the crude organic layer revealed 663 mg (93.2%) desired product, using an analytical standard of the product. The crude organic layer was concentrated in vacuo. The product was crystallized (unoptimized) by adding 3.0 mL isopropyl acetate and stirring overnight at 20 °C. Filtration through a medium-porosity fritted funnel and rinsing with 1.0 mL isopropyl acetate provided 468 mg of the desired compound as a 90.9 wt% white solid (adj. 425 mg, 59.8%). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 5.94 (app. s, 2H), 7.21-7.28 (m, 6H), 7.33-7.38 (m, 4H), 7.42-7.46 (m, 2H), 7.84-7.86 (m, 2H). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 51.9, 79.1, 120.5, 124.6, 127.7, 128.1, 128.6, 129.8, 135.5, 139.1, 147.1, 156.9. IR 928, 1049, 1090, 1196, 1451, 3043, 3268. HRMS calcd for C\(_{21}\)H\(_{17}\)N\(_4\)O [M+H] 341.13969, found 341.13943; calcd for C\(_{21}\)H\(_{16}\)NaN\(_4\)O [M+Na] 363.12163, found 363.12076. mp 185-189 °C.

(1-Benzyl-1H-tetrazol-5-yl)diphenylmethanol (14c), method “in situ Mg”. The reaction was carried out according to the General Procedure using benzophenone (5c, 99%, 385 mg, 2.09 mmol) was added. Following base addition, the reaction was stirred at -20 °C for 1 hour, then warmed slowly to 20 °C over 3 hours and stirred for 12 hours at 20 °C. The reaction was quenched with acetic acid, and then water (5.0 mL) and MTBE (5.0 mL) were added. The resulting layers were separated. HPLC analysis of the crude organic layer revealed 523 mg (73.0%) of the desired product 14c. The crude organic layer was concentrated in vacuo. Purification by flash chromatography (20 → 40% MTBE/hexanes) provided the desired
compound as a white solid (502 mg, 100% 14c by mass, 70%).  ¥H NMR δ 5.58 (s, 2H), 7.00 (m, 2H), 7.23-7.36 (m, 13H), 7.60 (s, 1H).  ¥3C NMR δ 54.5, 76.1, 126.8, 127.7, 127.9, 128.0, 128.1, 128.3, 134.5, 143.4, 158.5.  IR 692, 1450, 3064, 3286 cm⁻¹.  HRMS calculated for C₂₁H₁₉N₄O⁺ [M+H⁺] 343.15534, found 343.15580.  mp 141-142 °C.

1-(1-Benzyl-1H-tetrazol-5-yl)(phenyl)methanol (14d), method “in situ Mg”. To a 3-neck flask equipped with an overhead stirrer, were charged 1-benzyl-5-bromo-1H-tetrazole 9 (550 mg, 2.300 mmol, 1.10 equiv.) and THF (7.50 mL, 0.28 M). The flask was purged with nitrogen, and benzaldehyde (5d, 211 µL, 2.091 mmol) was added. The resulting mixture was cooled to -20 °C. Mesitylmagnesium bromide (1.0 M sol’n in THF, 2.30 mL, 2.30 mmol, 1.10 equiv.) was added to the reaction dropwise over 30 minutes, maintaining the internal temperature between -24 °C and -20 °C. The reaction was stirred at -20 °C for 2.5 hours, then warmed to 0 °C for 1 hour. The reaction was quenched with acetic acid (0.13 mL, 1.10 equiv.). Water (5.0 mL) and MTBE (5.0 mL) were added, and the resulting layers were separated. HPLC analysis of the crude organic layer revealed 384 mg (69.0%) desired product, using an analytical standard of the product. The crude organic layer was concentrated *in vacuo*. Purification by flash chromatography (silica; 20, 30% MTBE/hexanes) provided 355 mg of the desired compound as a 98.9 wt% white solid (adj. 351 mg, 63.0%). ¥H NMR (400 MHz, DMSO-d₆) δ 5.67 (s, 2H), 6.30 (d, J = 5.9, 1H), 6.89 (d, J = 5.9, 1H), 7.13 (m, 2H), 7.29-7.36 (m, 8H). ¥3C NMR (100 MHz, DMSO-d₆) δ 50.4, 65.1, 128.1, 127.9, 127.9, 128.1, 128.3, 128.5, 134.6, 139.7, 156.4.  IR 833, 1054, 1457, 1596, 3220. HRMS calcd for C₁₅H₁₅N₄O [M+H] 267.12404, found 267.12441; calcd for C₁₅H₁₄NaN₄O [M+Na] 289.10598, found 289.10638. mp 136-137 °C.

5-[1-(Benzyl)-1H-tetrazol-5-yl]-10,11-dihydro-5H-dibenzo[α,δ]cyclohepten-5-ol (14e), method “preformed Mg”. To a 3-neck flask equipped with an overhead stirrer were charged 1-benzyl-5-bromo-1H-tetrazole 9 (550 mg, 2.300 mmol, 1.10 equiv.) and THF (4.00 mL). The flask was purged with nitrogen, and the resulting mixture was cooled to -20 °C. i-Propylmagnesium chloride (2.0 M sol’n in THF, 1.15 mL, 2.30 mmol, 1.10 equiv.) was added to the reaction dropwise over 15 minutes, maintaining the internal temperature between -24 °C and -20 °C. The reaction was stirred at -20 °C for 5 minutes. A solution of dibenzosuberone (5e, 384 µL, 2.091 mmol) in THF (3.50 mL) was added dropwise over 20 minutes, maintaining the
internal temperature below -20 °C. The reaction mixture was stirred at -20 °C for 20 minutes, then allowed to warm to 0 °C. After 2.5 hours, the reaction was quenched with acetic acid (0.13 mL, 1.10 equiv.). Water (5.0 mL) and MTBE (5.0 mL) were added, and the resulting layers were separated. HPLC analysis of the crude organic layer revealed 609 mg (79.0%) desired product, using an analytical standard of the product. The crude organic layer was concentrated in vacuo. The product was crystallized (unoptimized!) by adding 3.0 mL iso-propyl acetate and stirring overnight at 20 °C. Filtration through a medium-porosity fritted funnel and rinsing with 1.0 mL iso-propyl acetate provided 561 mg of the desired compound as a 99.3 wt% white solid (adj. 557 mg, 72.3%). 1H NMR (400 MHz, DMSO-d6) δ 2.53-2.72 (m, 4H), 5.27 (app. s, 2H), 6.79 (d, J = 6.94, 2H), 7.04 (d, J = 7.34, 2H), 7.17-7.29 (m, 7H), 7.63 (s, 1H), 7.91 (d, J = 6.94, 2H). 13C NMR (100 MHz, DMSO-d6) δ 30.9, 50.7, 71.4, 124.2, 125.9, 127.7, 127.9, 128.1, 128.2, 130.6, 133.8, 136.7, 141.4, 157.7. IR 1042, 1184, 1453, 1948, 3033, 3262. HRMS calcd for C23H21N4O [M+H] 369.17099, found 369.17103; calcd for C23H20NaN4O [M+Na] 391.15293, found 391.15287. mp 184-186 °C.

1-(1-benzyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (14f), method “in situ Mg”.

To a 25 mL 3-neck round-bottom flask was charged 9 (0.523 g, 2.19 mmol, 1.10 equiv). The flask was equipped with a nitrogen inlet, overhead stirring, and a thermocouple. After the flask was purged with N2, THF (7.1 mL) and α-tetralone (5f, 0.300 g, 1.99 mmol, 1.00 equiv) were added, and the reaction mixture was cooled to -20 °C. A solution of 2-mesitylmagnesium bromide (1.0 M in THF, 2.19 mL, 2.19 mmol, 1.10 equiv) was added dropwise by syringe pump over 30 min. After an additional 2 h of stirring at -20 °C, the reaction was quenched with acetic acid (0.14 ml, 2.5 mmol, 1.1 equiv), and the resulting solution was warmed to 20 °C. HPLC analysis of this solution indicated 84.2% assay yield. Next, the solution was partitioned between MTBE and water (5 mL each). The aqueous phase was further extracted with MTBE (5 mL), and the combined organic phases were washed with brine, dried over Na2SO4, filtered, and concentrated to ~1.1g of org oil. The concentrate was diluted with EtOAc and hexanes (1 mL each), seeded with 10 mg of product 14f, and stirred for 10 min. Hexanes (5 mL) was then added at a rate of 1.5 mL/h. The product suspension was filtered and washed with 4:1 hexanes/ EtOAc (2 mL). After the filter was dried under N2, 452 mg of product was collected as an off-white solid (69.6%, 94.0% 14f by weight based on quantitative 1H NMR analysis versus triphenylmethane standard). mp 91-96 °C. IR 3351 (b), 1493, 1442, 1282, 1101, 987 cm-1. 1H NMR (400 MHz, CDCl3) δ 7.4-7.3 (m, 3H), 7.28 (dd, J = 7.2, 1.8 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.1-7.0 (m, 2H), 6.90 (dd, J = 7.9, 0.9 Hz, 1H), 5.62 (d, J = 15.1 Hz, 1H), 5.23 (d, J = 15.0 Hz, 1H), 3.26 (bs, 1H), 2.88 (dt, J = 17.6, 4.8 Hz, 1H), 2.76 (ddd, J = 16.9, 10.4, 5.5, 1H), 2.1-1.8 (m, 4H). 13C NMR (100 MHz) δ 159.8, 137.4, 136.5, 134.1, 129.6, 129.1, 128.9, 128.6, 128.4, 127.8, 127.1, 71.9, 52.3, 38.5, 29.2, 18.5. HRMS (TOF) calculated for C18H19N4O+ [M+H+] 307.15534, found 307.15577.
1-(1-Benzyl-1H-tetrazol-5-yl)-1-phenylethanol (14g), method “preformed Mg”. The reaction was carried out according to the General Procedure using i-propylmagnesium chloride (2M sol’n in THF, 1.15 mL, 2.30 mmol, 1.10 equiv.) and acetophenone (5g, 99%, 247 μL, 2.091 mmol). After electrophile addition, the reaction was stirred at -20 °C for 1 hour, then allowed to warm to 0 °C overnight. After 24 h, the reaction was quenched with acetic acid, and then water (5.0 mL) and MTBE (5.0 mL) were added. HPLC analysis of the crude organic layer revealed 354 mg (60.4%) desired product 14g. The crude organic layer was separated and concentrated in vacuo. The product was crystallized by addition of i-propyl acetate (3.0 mL), followed by dropwise addition of heptane (2.0 mL) over 1 hour, and finally stirring overnight at 20 °C. Filtration through a medium-porosity fritted funnel and rinsing with 2.0 mL of 1:1 IPA/ heptane provided of the desired compound as a white solid (359 mg, 91.2% 14g by mass, 56%). HPLC analysis of the filtrate revealed a loss of 22 mg (3.7%) of 14g. 1H NMR 1.99 (s, 3H), 5.44 (app. s, 2H), 6.88 (m, 2H), 6.97 (s, 1H), 7.17-7.34 (m, 8H). 13C NMR δ 31.3, 50.9, 70.9, 124.5, 127.5, 127.9, 128.0, 128.3, 128.5, 134.6, 144.4, 158.9. IR 1115, 1440, 1627, 2982, 3320 cm⁻¹. HRMS calculated for C₁₆H₁₇N₄O⁺ [M+H⁺] 281.13969, found 281.13969. mp 103 °C.

1-(1-benzyl-1H-tetrazol-5-yl)cyclohexanol (14h), method “preformed Mg”. To a 25 mL 3-neck round-bottom flask was charged 9 (0.599 g, 2.51 mmol, 1.10 equiv). The flask was equipped with a nitrogen inlet, overhead stirring, and a thermocouple. After the flask was purged with N₂, THF (8.1 mL) was added, and the resulting solution was cooled to -40 °C. A solution of o-tolylmagnesium chloride (1.0 M in THF, 2.51 mL, 2.51 mmol, 1.10 equiv) was added dropwise by syringe pump over 15 min. After an additional 15 min of stirring at -40 °C, cyclohexanone (5h, 0.224 g, 2.28 mmol, 1.00 equiv) was added and the reaction solution was warmed to -20 °C over 80 min. After an additional 3.5 h stirring at -20 °C, the reaction solution was allowed to warm to 0 °C overnight. Next, the reaction was quenched with acetic acid (0.14 mL, 2.5 mmol, 1.1 equiv), and the resulting solution was warmed to 20 °C. Next, the suspension was partitioned between MTBE and water (5 mL each). The aqueous phase was further extracted with MTBE (5 mL), and the combined organic phases were washed with brine, dried over Na₂SO₄, and filtered. HPLC analysis of the resulting solution indicated 52.9% assay yield.
The crude product solution was concentrated and loaded onto a column of silica 0.75" wide × 6" tall and eluted with 4:1 → 3:1 hexanes/EtOAc. The product-containing fractions were found to be contaminated with N-benzyl cyanamide; thus, they were partially concentrated, diluted with hexanes, heated to reflux, seeded with 5 mg product 14h, cooled slowly to room temperature and finally diluted to ~8 mL total volume by slow addition of hexanes. The resulting suspension was filtered and dried to provide 206 mg of the desired product as a granular white solid (35.0%, >99% 14h by weight based on quantitative 1H NMR analysis versus triphenylmethane standard). mp 113-115 °C. IR 3384 (b), 1447, 1247, 1151, 978 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.4-7.2 (m, 5H), 5.84 (s, 2H), 2.08 (m, 2H), 1.82 (m, 2H), 1.7-1.6 (m, 5H), 1.37 (m, 1H). 13C NMR (100 MHz) δ 159.1, 135.1, 128.9, 128.4, 127.6, 70.9, 52.2, 37.1, 24.8, 21.1. HRMS (TOF) calculated for C₁₄H₁₉N₄O⁺ [M+H⁺] 259.15534, found 259.15564.

1-(1-Benzyl-1H-tetrazol-5-yl)-3-phenylpropan-1-ol (14i), method “preformed Mg”. To a 3-neck flask equipped with an overhead stirrer, were charged 1-benzyl-5-bromo-1H-tetrazole 9 (550 mg, 2.300 mmol, 1.10 equiv.) and THF (4.00 mL). The flask was purged with nitrogen, and the reacting mixture was cooled to -20 °C. i-Propylmagnesium chloride (2M sol’n in THF, 1.15 mL, 2.30 mmol, 1.10 equiv.) was added to the reaction dropwise over 15 minutes, maintaining the internal temperature between -23 °C and -18 °C. The resulting mixture was stirred at -20 °C for 5 minutes. A solution of hydrocinnamaldehyde (5i, 95%, 295 mg, 2.091 mmol) in THF (3.50 mL) was added dropwise over 20 minutes, maintaining the internal temperature between -25 °C and -19 °C. The reaction was stirred at -20 °C for 1 hour, then warmed to 20 °C. After 3 hours at 20 °C, the reaction was quenched with acetic acid (0.30 mL, 2.50 equiv.). Water (5.0 mL) and MTBE (5.0 mL) were added, and the resulting layers were separated. HPLC analysis of the crude organic layer revealed 454 mg (73.8%) desired product, using an analytical standard of the product. The crude organic layer was concentrated in vacuo. Purification by flash chromatography (silica; 35, 50, 70% MTBE/hexanes) provided 463 mg of the desired compound as a 98.9 wt% white solid (adj. 458 mg, 74.4%). 1H NMR (400 MHz, DMSO-d₆) δ 2.07 (m, 2H), 2.53-2.74 (m, 2H), 4.98 (m, 1H), 5.72 (m, 2H), 6.18 (s, 1H), 7.12-7.19 (m, 3H), 7.24-7.28 (m, 4H), 7.33-7.40 (m, 3H). 13C NMR (100 MHz, DMSO-d₆) δ 30.8, 36.8, 50.3, 62.5, 125.8, 127.8, 128.2, 128.2, 128.3, 128.7, 134.8, 141.1, 156.5. IR 926, 1022, 1100, 1362, 1418, 1446, 1455, 1497, 2929, 3061, 3257. HRMS calcd for C₁₇H₁₉N₄O⁺ [M+H⁺] 295.15597; calcd for C₁₇H₁₉NaN₄O⁺ [M+Na⁺] 317.13728, found 317.13743. mp 84-87 °C.

General procedure for 5-(1-hydroxyalkyl)-1H-tetrazoles (3). To a round bottom flask was added a magnetic stir bar, 5-(1-hydroxyalkyl)-1-benzyl-1H-tetrazole 14 (100 mg) and MeOH (1.0-2.0 mL). The flask was purged with nitrogen, and Pd/C (5% on wet C, 5.0 mg, 5 wt %) was added. The flask was then purged with hydrogen, attached to a hydrogen gas-filled balloon, and stirred at 50 °C until the reaction was deemed complete according to HPLC analysis. The crude
reaction mixture was filtered through a PTFE filter, and concentrated in vacuo. Purification by flash chromatography provided the desired compounds.

5-[2H-tetrazol-5-yl]-10,11-dihydro-5H-dibenzo[α,δ]cyclohepten-5-ol (3e). The reaction was carried out according to the General Procedure using 5-[1-(benzyl)-1H-tetrazol-5-yl]-10,11-dihydro-5H-dibenzo[α,δ]cyclohepten-5-ol (14e, 99%, 100 mg, 0.271 mmol) and MeOH (2.00 mL). The reaction was deemed complete after stirring at 50 °C for 72 h. Purification by flash chromatography (70 → 100% MTBE/hexanes) provided a white solid that retained significant amounts of MTBE. The solid was redissolved in DCM (5 mL) and concentrated in vacuo. This process was repeated three times to yield the desired compound as a white solid (78 mg, 89.3% 3e by mass, 92%). 1H NMR (methanol-d4) δ 2.76-2.84 (m, 2H), 2.90-2.98 (m, 2H), 7.12-7.14 (m, 2H), 7.20-7.29 (m, 4H), 7.42-7.44 (m, 1H), 7.99-8.02 (m, 2H). 13C NMR (methanol-d4) δ 33.6, 73.4, 126.8, 127.4, 129.6, 131.8, 132.1, 139.5, 142.7. IR 1080, 1963, 3030, 3450 cm⁻¹. HRMS calculated for C16H15N4+ [M+H+] 263.12912, found 263.12943.

3-Phenyl-1-(2H-tetrazol-5-yl)propan-1-ol (3i). The reaction was carried out according to the General Procedure. To a round bottom flask with a stir bar were charged secondary alcohol 14i (100 mg, 0.3397 mmol) and MeOH (1.00 mL, 10 volumes). The flask was purged with nitrogen, and Pd/C (5% on wet C, 5.0 mg, 5 wt %) was added. The flask was purged with hydrogen, and stirred at 50 °C for 36 hours. The crude reaction filtered through a PTFE filter, and concentrated in vacuo. Purification by flash chromatography (silica; 0, 2, 4% MeOH/MTBE) provided 69.1 mg of the desired compound as a 91 wt% white solid (adj. 62.9 mg, 90.7%). 1H NMR (methanol-d4) δ 2.20 (m, 2H), 2.75 (m, 2H), 5.02 (dd, J = 7.8, 5.1 Hz, 2H), 7.14-7.28 (m, 6H). 13C NMR (100 MHz, Methanol-d4) δ 32.2, 39.6, 65.5, 127.2, 129.6, 129.7, 142.6, 161.5. IR 1150, 1640, 2929, 3262, 3460. HRMS calcd for C10H13N4O [M+H] 205.10839, found 205.10833; calcd for C10H12NaN4O [M+Na] 227.0933, found 227.09088.
5-Hydroxy-5-[1-(2-methoxybenzyl)-1H-tetrazol-5-yl]-10,11-dihydro-\(N_2,N_2,N_8,N_8\)-tetramethyl-5\(H\)-dibenzo[\(\alpha,\beta\)]cycloheptene-2,8-dicarboxamide (16b), method “in situ K”. The reaction was carried out according to the General Procedure using 10,11-dihydro-\(N_2,N_2,N_8,N_8\)tetramethyl-5\(H\)-dibenzo[\(\alpha,\beta\)]cyclohepten-5-one-2,8-dicarboxamide (15, 99%, 0.50 g, 1.40 mmol) and 1-(2-methoxybenzyl)-1H-tetrazole (8d, 99%, 0.54 g, 2.80 mmol) in place of 1-benzyl-1H-tetrazole. After the reaction was quenched with acetic acid, water (0.5 mL) was added, and the crude mixture was distilled under vacuum to remove THF (40–50 °C, 150 mbar, ~0.5 h). After cooling the concentrate to 20 °C, the product was crystallized by adding 2.5 mL water dropwise over 2.5 h and stirring overnight at 20 °C. Filtration through a medium-porosity fritted funnel provided the desired compound as a white solid (0.53 g, ~95% 16b by mass, 66%). HPLC analysis of the filtrate revealed a loss of 30 mg (4%) of 16b. \(^1\)H NMR δ 7.84 (d, \(J = 8.2\) Hz, 2H), 7.20 (ddd, \(J = 8.4, 6.8, 2.4\) Hz, 1H), 7.11 (dd, \(J = 8.2, 1.8\) Hz, 2H), 6.94 (d, \(J = 1.8\) Hz, 2H), 6.78 (m, 3H), 6.11 (bs, 1H), 5.29 (s, 2H), 3.78 (s, 3H), 2.97 (bs, 6H), 2.85 (bs, 6H), 2.76 (m, 4H).

\((1\)-benzyl-1H-tetrazol-5-yl)phenylketone (18), method “in situ Mg”. To a 25 mL 3-neck round-bottom flask was charged 9 (0.601 g, 2.51 mmol, 1.10 equiv). The flask was equipped with a nitrogen inlet, overhead stirring, and a thermocouple. After the flask was purged with N\(_2\), THF (8.1 mL) and N-methoxy-N-methylbenzamide (17, 0.385 g, 2.28 mmol, 1.00 equiv) were added, and the resulting solution was cooled to -20 °C. A solution of 2-mesitylmagnesium bromide (1.0 M in THF, 2.51 mL, 2.51 mmol, 1.10 equiv) was added dropwise by syringe pump over 30 min. After an additional 1 h of stirring at -20 °C, the reaction was quenched with acetic acid (0.14 ml, 2.5 mmol, 1.1 equiv), and the resulting suspension was warmed to 20 °C. Next, the suspension was partitioned between MTBE and water (5 mL each). The aqueous phase was further extracted with MTBE (5 mL), and the combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\), and filtered. HPLC analysis of the resulting solution indicated 76.8% assay yield. The crude product solution was concentrated and loaded onto a column of silica 0.75"
wide × 6” tall and eluted with 8:1 hexanes/EtOAc. Concentration of the product-containing fractions provided 0.420 g of 18 as a colorless oil (68.9%, 99.0% 18 by weight based on quantitative ¹H NMR analysis versus triphenylmethane standard). IR 1663, 1597, 1263, 1175, 918 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (m, 2H), 7.70 (m, 1H), 7.54 (m, 2H), 7.4-7.3 (m, 5H), 5.96 (s, 2H). ¹³C NMR (100 MHz) δ 181.5, 149.2, 135.1, 134.9, 133.6, 131.1, 129.0, 128.9, 128.8, 128.4, 53.0. HRMS (TOF) calculated for C₁₅H₁₃N₄O⁺ [M+H⁺] 265.10839, found 265.10900.

1-Benzyl-5-(phenylthio)-1H-tetrazole (20), method “in situ Mg”. The reaction was carried out according to the General Procedure “in situ Mg” using phenyldisulfide (19, 99%, 461 mg, 2.09 mmol) as the electrophile. Following base addition, the reaction was stirred at −20 °C for 3.5 hours, then warmed to 20 °C overnight. The reaction was quenched with acetic acid, and then water (5.0 mL) and MTBE (5.0 mL) were added. The resulting layers were separated. HPLC analysis of the crude organic layer revealed 392 mg (70%) of the desired product. The crude organic layer was concentrated in vacuo. Purification by flash chromatography (10 → 25% MTBE/heptane) provided the desired compound as a white solid (372 mg, 96.2% 20 by mass, 64%). ¹H NMR δ 5.68 (s, 2H), 7.24 (m, 2H), 7.35-7.48 (m, 8H). ¹³C NMR δ 50.7, 127.9, 128.1, 128.4, 128.8, 129.3, 129.7, 132.2, 133.8, 152.1. IR 978, 1104, 1259, 1390, 1453, 2971 cm⁻¹. HRMS calculated for C₁₄H₁₃N₄S⁺ [M+H⁺] 269.08554, found 269.08626. mp 59–60 °C.

2-(1-Benzyl-1H-tetrazol-5-yl)pyridine (22). A modified literature procedure for Negishi-type coupling was used.⁸ To a 3-neck flask equipped with an overhead stirrer, were charged 1-benzyl-5-bromo-1H-tetrazole 9 (550 mg, 2.30 mmol, 1.50 equiv) and THF (6.00 mL). The flask was purged with nitrogen, and the resulting mixture was cooled to −20 °C. i-Propylmagnesium chloride (2.0 M in THF, 1.15 mL, 2.30 mmol, 1.50 equiv) was added to the reaction dropwise over 30 min, maintaining the internal temperature between −25–−20 °C. The resulting mixture was stirred at −20 °C for 5 min. A solution of zinc chloride (1.0 M in Et₂O, 2.3 mL, 2.30 mmol, 1.50 equiv) was added dropwise over 15 min. The reaction mixture was further stirred for 5 min, then warmed to 20 °C over 1 h. Separately, 2-bromopyridine (21, 99%, 150 µL, 1.53 mmol) was dissolved in THF (3.5 mL). Solid Pd(PPh₃)₄ (89 mg, 0.0766 mmol, 5 mol %) was added with stirring at 20 °C, and the flask was purged with nitrogen. The tetrazole-Zn mixture was filtered through a 0.2 µm PTFE filter, and charged to the bromide/Pd solution at 20 °C. After 48 h at 20 °C.

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⁸ Fang, Y.-Q.; Hanan, G. S. *Synlett* 2003, 852.
°C, significant precipitation was observed. The crude reaction mixture was poured onto a mixture of MTBE (10 mL) and 10% aqueous EDTA-H (10 mL). The mixture was stirred 1 h, and then the layers were separated. The crude organic layer was concentrated in vacuo. Purification by flash chromatography (30 → 40% MTBE/hexanes) provided the desired compound as a colorless oil (113 mg, 99.3% by mass, 31%). \(^1\)H NMR (methanol-\(d_4\)) \(\delta\) 6.21 (s, 2H), 7.23-7.30 (m, 5H), 7.53 (ddd, \(J = 1.2\), 4.9, 7.7, 1H), 7.97 (ddd, \(J = 1.8\), 7.8, 7.9 Hz, 1H), 8.21 (ddd, \(J = 0.9\), 1.2, 7.9 Hz, 1H), 8.77 (ddd, \(J = 0.9\), 1.8, 4.8 Hz, 1H). \(^1^3\)C NMR (methanol-\(d_4\)) \(\delta\) 53.8, 125.6, 127.2, 129.3, 129.5, 129.9, 136.6, 139.1, 145.8, 151.0, 153.4. IR 1115, 1434, 1590, 2923, 3034 cm\(^{-1}\). HRMS calculated for \(\text{C}_{13}\text{H}_{12}\text{N}_5\)\(^+\) [M+H]\(^+\) 238.10872, found 238.10971.
4. Spectroscopic data

1-Benzyl-1H-tetrazole (8c) $^1$H NMR spectrum
1-Benzyl-1H-tetrazole (8c) NMR spectrum

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100318-69-21_11.DX

![NMR Spectrum of 1-Benzyl-1H-tetrazole (8c)](image-url)

Chemical Shift (ppm)
1-Benzyl-1H-tetrazole (8c) DSC Plot
1-Benzyl-5-bromo-1H-tetrazole (9) $^1$H NMR spectrum
1-Benzyl-5-bromo-1\textit{H}-tetrazole (9) $^{13}\text{C}$ NMR spectrum
1-Benzyl-5-bromo-1H-tetrazole (9) DSC Plot
5-[1-(Benzyl)-1H-tetrazol-5-yl]-5H-dibenzo[α,δ]cyclohepten-5-ol (14a) $^1$H NMR spectrum
5-{1-(Benzyl)-1H-tetrazol-5-yl]-5H-dibenzo[α,δ]cyclohepten-5-ol (14a) $^{13}$C NMR spectrum
9-(1-Benzyl-1H-tetrazol-5-yl)-9H-fluoren-9-ol (14b) $^1$H NMR spectrum
9-(1-Benzyl-1H-tetrazol-5-yl)-9H-fluoren-9-ol (14b) $^{13}$C NMR spectrum
(1-Benzyl-1H-tetrazol-5-yl)diphenylmethanol (14c) $^1$H NMR spectrum
(1-Benzyl-1H-tetrazol-5-yl)diphenylmethanol (14c) $^{13}$C NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)(phenyl)methanol (14d) $^1$H NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)(phenyl)methanol (14d) $^{13}$C NMR spectrum
5-[(1-(Benzy1)-1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[α,β]cyclohepten-5-ol (14e) \(^1\)H NMR spectrum
5-[1-(Benzyl)-1H-tetrazol-5-yl]-10,11-dihydro-5H-dibenzo[α,δ]cyclohepten-5-ol (14e) $^{13}$C NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (14f) $^1$H NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (14f) $^{13}$C NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)-1-phenylethanol (14g) $^1$H NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)-1-phenylethanol (14g) $^{13}$C NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)cyclohexanol (14h) $^1$H NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)cyclohexanol (14h) $^{13}$C NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)-3-phenylpropan-1-ol (14i) $^1$H NMR spectrum
1-(1-Benzyl-1H-tetrazol-5-yl)-3-phenylpropan-1-ol (14i) $^{13}$C NMR spectrum
5-(10,11-Dihydro-5H-dibenzo[α,δ]cycloheptene-5-ol)-2H-tetrazole (3e) $^1$H NMR spectrum
5-(10,11-Dihydro-5H-dibenzo[α,δ]cycloheptene-5-ol)-2H-tetrazole (3e) $^{13}C$ NMR spectrum
3-Phenyl-1-(2H-tetrazol-5-yl)propan-1-ol (3i) $^1$H NMR spectrum
3-Phenyl-1-(2H-tetrazol-5-yl)propan-1-ol (3i) $^{13}$C NMR spectrum
5-Hydroxy-5-[1-(benzyl)-1H-tetrazol-5-yl]-10,11-dihydro-\(N_2,N_2,N_8,N_8\)-tetramethyl-5\(H\)-dibenzo[\(a,\delta\)]cycloheptene-2,8-dicarboxamide (16a) \(^1\)H NMR spectrum
5-Hydroxy-5-[1-(benzyl)-1H-tetrazol-5-yl]-10,11-dihydro-N2,N2,N8,N8-tetramethyl-5H-dibenzo[a,δ]cycloheptene-2,8-dicarboxamide (16a) $^{13}$C NMR spectrum
5-Hydroxy-5-[1-(2-methoxybenzyl)-1H-tetrazol-5-yl]-10,11-dihydro-N2,N2,N8,N8-tetramethyl-5H-dibeno[α,δ]cycloheptene-2,8-dicarboxamide (16b) $^1$H NMR spectrum
(1-Benzyl-1H-tetrazol-5-yl)phenylketone (18) $^1$H NMR spectrum
(1-Benzyl-1H-tetrazol-5-yl)phenylketone (18) $^{13}$C NMR spectrum
1-Benzyl-5-(phenylthio)-1H-tetrazole (20) $^1$H NMR spectrum
1-Benzyl-5-(phenylthio)-1H-tetrazole (20) $^{13}$C NMR spectrum
2-(1-Benzyl-1H-tetrazol-5-yl)pyridine (22)  

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\text{H NMR spectrum}
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2-(1-Benzyl-1H-tetrazol-5-yl)pyridine (22)  
$^{13}$C NMR spectrum

NMR spectrum of 2-(1-Benzyl-1H-tetrazol-5-yl)pyridine (22) showing chemical shifts in ppm.