

## Article

# Synthesis of 2,2,5-Trisubstituted Tetrahydrofurans by Ferrocenium-Catalyzed Dehydrative Diol Cyclization Reactions

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**Abstract:** A ferrocenium-catalyzed synthesis of trisubstituted tetrahydrofurans by dehydrative cyclization of diols is reported. Treatment of  $\gamma$ -phenyl- $\gamma$ -butyrolactone or valerolactone with 2–3 equivalents of MeLi, *n*-BuLi, or PhLi yielded the corresponding substituted 1,4-butanediols in 41–86% yields. Subsequent dehydrative cyclization of the diols under non-inert conditions using catalytic ferrocenium tetrafluoroborate (10 mol%) produced trisubstituted tetrahydrofurans in 72–83% yields after 48–72 h at 45–70 °C in CH<sub>2</sub>Cl<sub>2</sub>. This study demonstrates ferrocenium-catalyzed dehydrative cyclization for the first time, offering a convenient route to substituted tetrahydrofurans in two steps from commercial or easily accessible starting materials.

**Keywords:** diol cyclizations; trisubstituted tetrahydrofurans; iron catalysis; ferrocenium catalysis

## 1. Introduction

Highly substituted tetrahydrofurans are key structural motifs found in numerous natural products with bioactive properties, including antibiotics, antivirals, and anticancer agents [1,2]. Their architecture contributes to molecular stability, making them valuable scaffolds in drug design and medicinal chemistry [3,4]. Many tetrahydrofurans or polycyclic ethers [5] possess biological activities [6,7], such as amphidinolide X (Scheme 1, top) [8]. Synthetic access to these structures has been described through metal-catalyzed carboetherification reactions [1,9], intramolecular epoxide-opening reactions [10], or hydroalkoxidations [1,11], among other methods [8].

The intramolecular version of the substitution of OH units by another one in the same molecule constitutes the dehydrative cyclization of diols to the corresponding tetrahydrofuran species (Scheme 1, middle). This type of cyclization reaction is underdeveloped [12] and allows access to highly substituted tetrahydrofuran species. Brønsted acids are generally effective in catalyzing diol cyclization reactions and related processes [13], but they often require elevated reaction temperatures [14]. For more complex synthetic targets, Brønsted acid catalysis can pose challenges such as limited functional group tolerance, the need for elevated temperatures, and the risk of carbocation rearrangements. Lewis acids can cyclize diols to give cyclic ethers as well, but also tend to require high reaction temperatures [15,16]. Alternative methods for diol cyclization typically involve using excess reagents, such as carbonate activators [17] or establishing leaving groups [1,18–20]. More complex diol cyclization strategies exist, e.g., employing selenium reagents [21] or cerium(IV) ammonium nitrate, which has been employed in the synthesis of a tertiary, 2,2-vinyl-disubstituted tetrahydrofuran through a radical cyclization mechanism [22].



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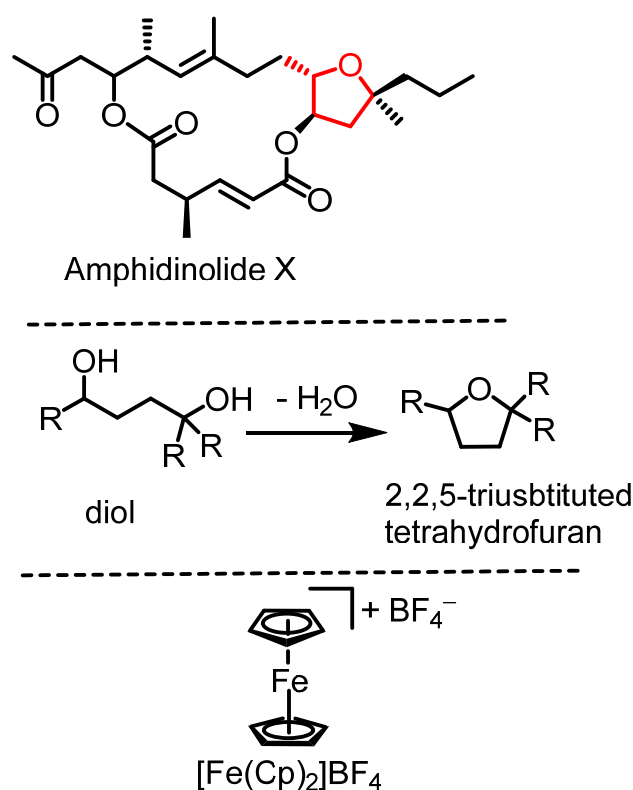
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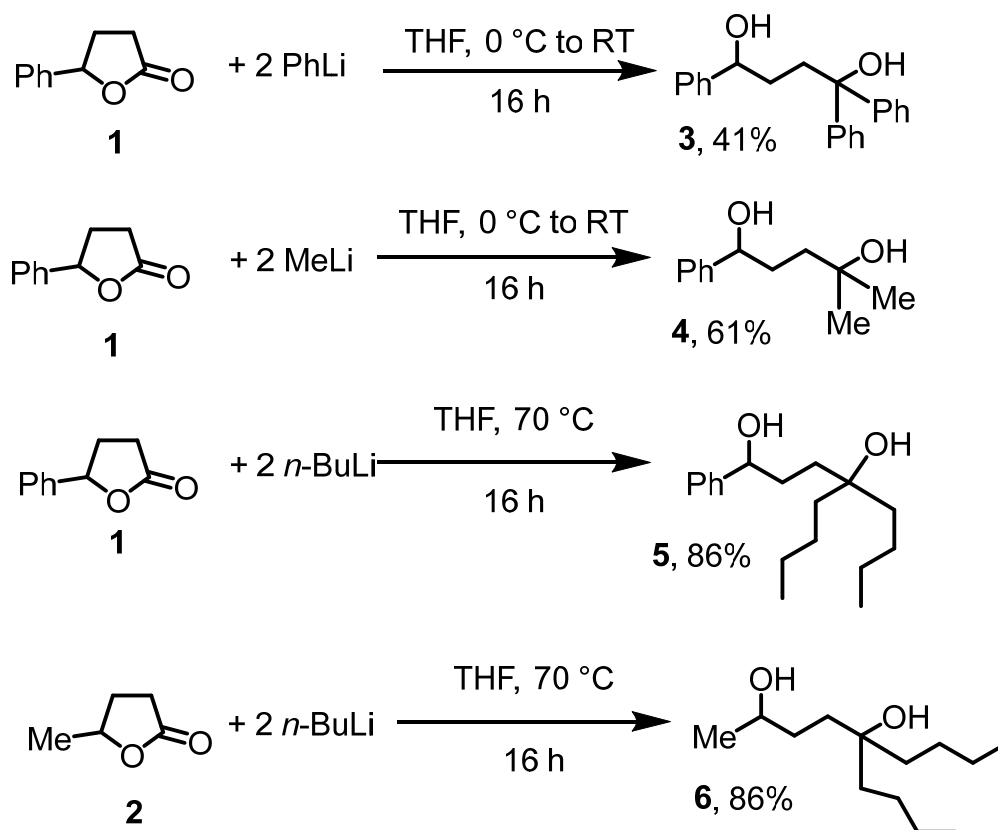
**Scheme 1.** Amphinolide X, dehydrative diol cyclization, and ferrocenium tetrafluoroborate.

Access to 1,4-disubstituted and 1,2,3,4-tetrasubstituted tetrahydrofurans by diastereoselective, dehydrative cyclizations of diols has been described to be catalyzed by  $\text{FeCl}_3$  (20% catalyst load) [23]. To the best of our knowledge, other iron-catalyzed dehydrative cyclization reactions to produce highly substituted tetrahydrofuran derivatives have not been reported. Catalytic, dehydrative cyclization offers a significant advantage by eliminating the need for complex reagents or auxiliaries (such as leaving groups), generating only water as a byproduct in accordance with green chemistry principles [24]. Iron catalysis [25] plays a crucial role in developing new catalytic methods due to its abundance, low cost, relative non-toxicity, and environmental friendliness [26,27]. Ferrocenium cations have emerged as effective and versatile catalysts in the past two decades [28,29], valued for their tunability, benchtop stability, and ease of handling. For example, ferrocenium salts are air-stable, whereas  $\text{FeCl}_3$  is water-sensitive. Herein, we present dehydrative cyclization reactions catalyzed by  $[\text{FeCp}_2]\text{BF}_4$  (Scheme 1, bottom) without the exclusion of air or water for the synthesis of trisubstituted tetrahydrofurans. The approach allows for access to 2,2,5-trisubstituted tetrahydrofuran derivatives in two steps from commercial or easily accessible starting materials.

## 2. Results and Discussion

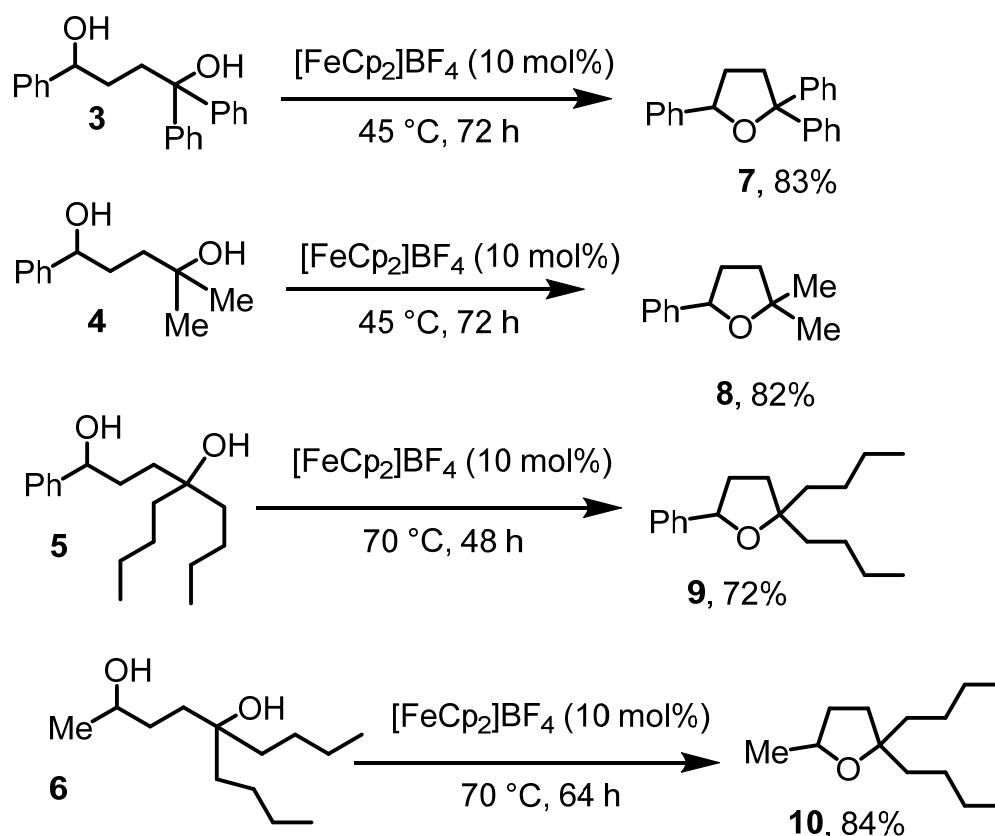
First, we sought access to substituted 1,4-diol precursor compounds. The nucleophilic ring opening of cyclic butyrolactones has previously been employed for that purpose [30]. Accordingly, we treated commercial  $\gamma$ -phenyl- $\gamma$ -butyrolactone (**1**) with three equivalent lithium organyls, followed by quenching with water and extraction with diethyl ether (Scheme 2). That way, reaction of **1** with  $\text{PhLi}$ ,  $\text{MeLi}$ , and  $n\text{-BuLi}$  gave the trisubstituted diols **3**, **4**, and **5** in 86 to 41% isolated yields. The cyclic, commercial valerolactone **2** gave under similar conditions the purely aliphatic diol **6**. The structure of the diols was unequivocally established by NMR and IR. The  $\text{C}=\text{O}$  stretch for the ester functionality in **1** disappeared. Instead, a broad band around  $3400\text{ cm}^{-1}$  was observed for the OH groups in the diols

3–6, establishing the presence of the alcohols. The OH groups were also observed as broad resonances in the  $^1\text{H}$  NMR spectra between 2 and 3 ppm. Furthermore, a diagnostic resonance for the  $\text{HCOH}$  proton was observed for all three diols around 4.5 ppm. Diols 3 [31] and 4 [32] are documented in the literature and were obtained through alternative synthetic routes; the NMR data are consistent with published values.



**Scheme 2.** Diol syntheses.

We next sought cyclization of the diols to the tetrahydrofurans, drawing knowledge from the literature referenced above about Lewis acid-catalyzed dehydrative diol cyclization reactions [12]. After brief screening efforts, we determined that ferrocenium tetrafluoroborate,  $[\text{FeCp}_2]\text{BF}_4$ , is catalytic active for the title reaction (Scheme 3). Accordingly, when the diols 3–6 were treated with  $[\text{FeCp}_2]\text{BF}_4$  in  $\text{CH}_2\text{Cl}_2$  at 45–70  $^\circ\text{C}$  for two to three days, the corresponding trisubstituted tetrahydrofurans 7–10 were isolated by filtration through  $\text{Al}_2\text{O}_3$  in 83–72% yields. The isolation by filtration was easy, because the catalyst and potential residual amounts of the diols were much more polar than the substituted tetrahydrofuran products 7–10. The identity of the products was again established by IR and NMR. The OH stretch of the diol starting materials in the IR spectra disappeared for the products. The diagnostic resonance for the  $\text{HCOH}$  proton shifted by about 0.4 ppm upfield. Most importantly, the formation of the five-membered ring system rendered some of the ring protons and side chain carbons diastereotopic, resulting in characteristic peak splitting in the NMR spectra that were not observed in the starting materials. The tetrahydrofuran derivatives 7 and 8 were known. For 7, no spectroscopic details were published [33] and for 8, NMR data matched the literature values [34]. Especially products 9 and 10 contained small amounts of ferrocene, derived from the ferrocenium salt employed in the reactions. Although ferrocene could be removed by column chromatography, the prolonged reaction time for products 9 and 10 appeared to cause the decomposition of the ferrocenium salts, facilitating their removal.



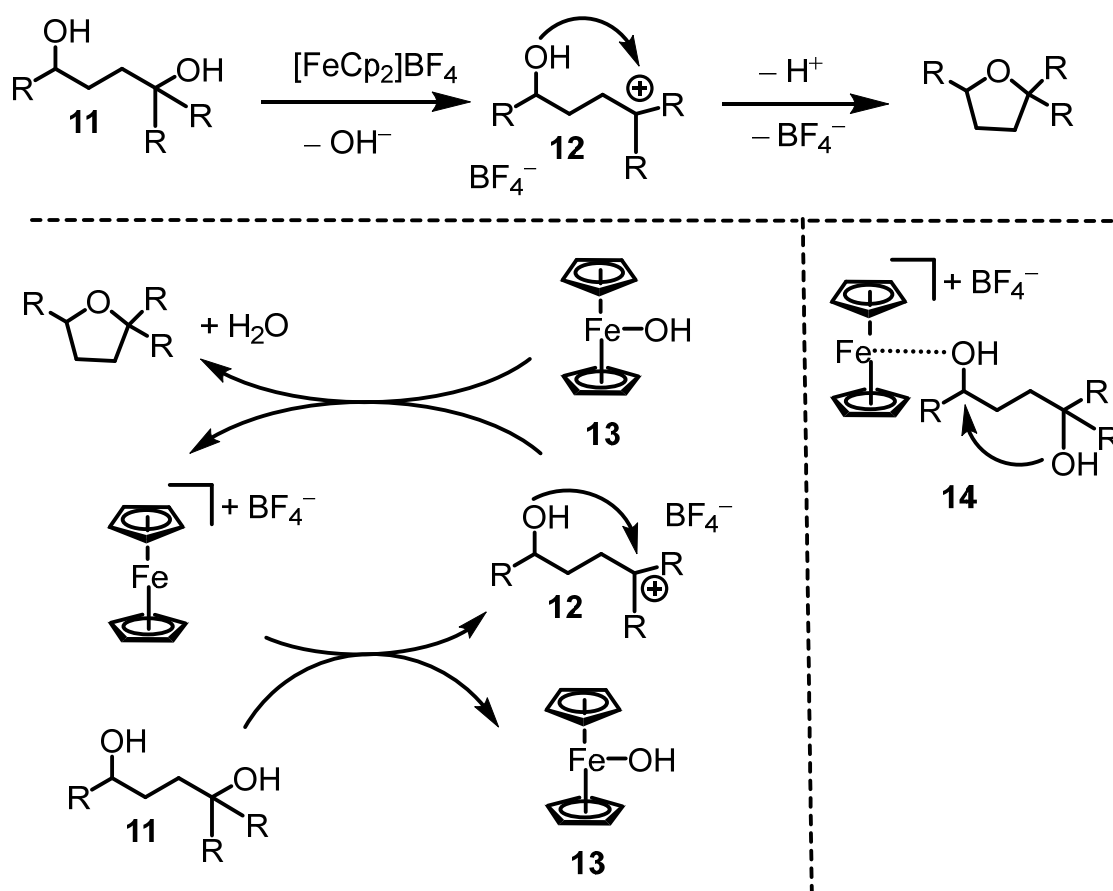
**Scheme 3.** Diol cyclizations to afford substituted tetrahydrofurans.

The chemistry in Scheme 3 establishes for the first time ferrocenium cations as catalysts for dehydrative etherification reactions of diols. While the reaction does not work at room temperature at appreciable rates, the reaction temperature of  $45^\circ\text{C}$  is similar or lower than other Lewis acid-catalyzed dehydrative cyclization reactions to afford tetrahydrofuran derivatives [14]. The reactions to afford **8** and **9** can also be performed at lower temperatures with comparable yields. Consequently, the reaction temperature can be adjusted to the desired time frame.

We conducted control experiments to evaluate the efficiency of the catalytic system. The cyclization of **6** failed in the absence of a catalyst, confirming that the dehydrative diol cyclization reaction requires a Lewis acid, as previously demonstrated by others [15,16]. Using  $\text{KPF}_6$  as a Lewis acid catalyst (which is not very well soluble in  $\text{CH}_2\text{Cl}_2$ ), the cyclization of **6** yielded 53% of product **10** under otherwise identical reaction conditions and workup methods. Similarly, catalytic amounts of  $\text{FeCl}_3$  facilitated the cyclization of **5**, producing **9** in a 56% yield under the same conditions. However, the NMR spectra (see Supplementary Data) of products **9** and **10** from both reactions were less clean compared to those obtained using  $[\text{FeCp}_2]\text{BF}_4$  as the catalyst and the yields were also lower. Nevertheless, diols **3–6** can generally be cyclized with a Lewis acid catalyst. Ferrocenium salts offer an advantage over purely inorganic Lewis acids, as their catalytic properties can be fine-tuned through modifications to their cyclopentadienyl ring systems and they tend to be well soluble in  $\text{CH}_2\text{Cl}_2$ .

Mechanistically, we assumed the reaction proceeds through a tertiary carbocation intermediate (**12**, Scheme 4, top). Ferrocenium ions are known to generate carbocations from alcohols. Ferroceniumboronic acid hexafluoroantimonate has been reported to generate benzylic carbocations, which persist in solution as solvated ion pairs with the hexafluoroantimonate counterion [35]. Within the carbocation **12** (persisting as an ion pair with the  $\text{BF}_4^-$  counterion), an intramolecular attack of the other OH group on the carbocation would

afford the tetrahydrofuran product. As shown in the detailed cycle in Scheme 4 (bottom left), carbocation formation would generate the Fe-OH species **13**, though its presence in our reaction was not confirmed. While species **13** has been reported in the literature [36], it remains relatively unexplored [37]. Cyclization of **12** would release a proton, regenerating the ferrocenium cation and yielding the tetrahydrofuran product along with a molecule of water. Alternatively, the ferrocenium cation could polarize one of the C–OH bonds in the diol starting material through species **14** (Scheme 4, bottom right). In this pathway, bond polarization may occur at the sterically less hindered secondary carbon, facilitating intramolecular attack. As indicated above, the products contained varying amounts of ferrocene. This may be an indication that the ferrocenium cation does not completely decompose during catalysis, and **13** or **14** are transient species throughout the catalytic cycle that are finally reduced to ferrocene.



**Scheme 4.** Mechanistic picture.

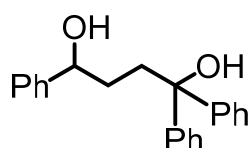
We did not perform mechanistic experiments to verify the mechanism. However, cyclization of 1,4-butanediol, a primary diol, was not possible under the conditions in Scheme 4, presumably due to the fact that it does not form stable carbocations. We are currently investigating if a ferrocenium cation with a chiral counterion can generate enantiomeric excesses through asymmetric counterion-directed catalysis [38–40].

### 3. Experimental Section

**General.** Commercial  $\gamma$ -phenyl- $\gamma$ -butyrolactone (**1**, TCI America, Portland, OR, USA), valorolactone (**2**), ferrocenium tetrafluoroborate ( $[\text{FeCp}_2]\text{BF}_4$ ), and magnesium sulfate (Sigma-Aldrich, St. Louis, MO, USA) were used as received. PhLi in cyclohexane ether (7:3), MeLi in diethyl ether, and BuLi in hexanes (all Sigma-Aldrich, St. Louis, MO, USA)

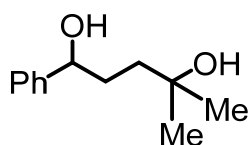
were used as received and titrated prior to use [41]. THF and diethyl ether were distilled from Na/benzophenone, and  $\text{CH}_2\text{Cl}_2$  was distilled from  $\text{P}_2\text{O}_5$  prior to use. Column chromatography was performed with silica gel 60 (70–230 mesh, SiliCycle, Québec City, QC, Canada) or  $\text{Al}_2\text{O}_3$  (neutral, Brockmann I, 50–100  $\mu\text{m}$ , Acros Organics, Newark, NJ, USA). The diol syntheses were performed under inert conditions utilizing Schlenk techniques. The cyclization reactions were performed without exclusion of air and water with dried  $\text{CH}_2\text{Cl}_2$ . NMR spectra were obtained at room temperature on a Bruker Avance 300 MHz instrument (Bruker, Billerica, MA, USA) and referenced a residual solvent signal; all assignments are tentative. EI mass spectrometry was performed on a Bruker Maxis Plus (maXis HD) quadrupole time-of-flight mass spectrometer. IR spectra were recorded on Thermo Nicolet 670 FTIR (Thermo Fisher Scientific, Waltham, MA, USA).

1,1,4-triphenylbutane-1,4-diol (3):



To a Schlenk flask,  $\gamma$ -phenyl- $\gamma$ -butyrolactone (**1**, 0.10 g, 0.61 mmol) and diethyl ether (3 mL) were added and cooled to 0 °C. After that, phenyl lithium (0.77 M in cyclohexane-ether, 2 mL, 1.54 mmol) was added dropwise, using a needle and a syringe, and the mixture was stirred for 6 h at 0 °C. After 6 h, the reaction mixture was allowed to warm to room temperature and quenched with water (5 mL). The aqueous and the organic layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined ether fractions were dried with  $\text{MgSO}_4$  and filtered, and the solvent was removed to obtain the product as a white solid (0.08 g, 0.251 mmol, 41%). NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$ : 7.27–7.23 (m, 4H, aromatic), 7.14–7.09 (m, 11H, aromatic), 4.50 (t, 1H,  $J_{\text{HH}} = 6$  Hz, OCH), 3.01 (br s, 2H, OH), 2.31–2.23 (m, 2H,  $\text{CH}_2$ ), 1.67–1.61 (m, 2H,  $\text{CH}_2$ ).  $^{13}\text{C}$  ( $^1\text{H}$ ): 146.9 (s, aromatic), 144.5 (s, aromatic), 128.5 (s, aromatic), 128.2 (s, aromatic), 127.5 (s, aromatic), 126.84 (s, aromatic), 126.76 (s, aromatic), 126.22 (s, aromatic), 126.16 (s, aromatic), 125.9 (s, aromatic), 78.0 (s, COH), 74.6 (s, COH), 38.0 (s,  $\text{CH}_2$ ), 33.4 (s,  $\text{CH}_2$ ). IR (ATR, neat):  $\nu$  3293 (br), 3056 (w), 3026 (w), 2927 (m), 2861 (m)  $\text{cm}^{-1}$ .

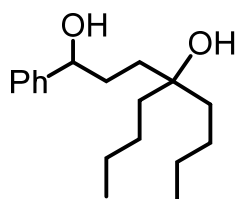
1,1,4-trimethylbutane-1,4-diol (4):



To a Schlenk flask,  $\gamma$ -phenyl- $\gamma$ -butyrolactone (**1**, 0.501 g, 3.09 mmol) and diethyl ether (3 mL) were added and cooled to 0 °C. After that, methyl lithium (1.3 M in diethyl ether, 6 mL, 7.8 mmol) was added dropwise, using a needle and a syringe, and the mixture was stirred for 6 h at 0 °C. After 6 h, the reaction mixture was allowed to warm to room temperature and quenched with water (5 mL). The aqueous and the organic layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined ether fractions were dried with  $\text{MgSO}_4$  and filtered, and the solvent was removed to obtain the product as a yellow oil (0.368 g, 1.89 mmol, 61%). NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$ : 7.26–7.18 (m, 5H, aromatic), 4.57 (dd, 1H,  $J_{\text{HH}} = 8$  Hz,  $J_{\text{HH}} = 5$  Hz, OCH), 2.83 (br s, 2H, OH), 1.78–1.72 (m, 2H,  $\text{CH}_2$ ), 1.57–1.54 (m, 1 H, CHH), 1.45–1.40 (m, 1 H, CHH), 1.11 (br s, 6H,  $\text{CH}_3$ ).  $^{13}\text{C}$  ( $^1\text{H}$ ): 145.0 (s, aromatic), 128.5 (s, aromatic), 128.4 (s, aromatic), 127.3 (s, aromatic), 125.9 (s, aromatic),

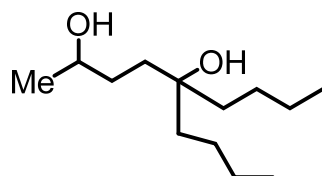
74.6 (s, COH), 70.6 (s, COH), 39.8 (s, CH<sub>2</sub>), 34.0 (s, CH<sub>2</sub>), 29.7 (s, CH<sub>3</sub>), 28.9 (s, CH<sub>3</sub>'). IR (ATR, neat):  $\nu$  3398 (br), 3062 (w), 2962 (m), 2933 (m) cm<sup>-1</sup>.

1,1,4-tri(*n*-butyl)butane-1,4-diol (5):



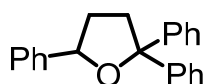
To a pressure vial with a Teflon screw cap,  $\gamma$ -phenyl- $\gamma$ -butyrolactone (**1**, 0.250 g, 1.54 mmol) and THF (5 mL) were added. *n*-Butyl lithium (1.3 M in hexanes, 6 mL, 7.8 mmol) was added dropwise, using a needle and a syringe. The pressure vial was closed, and the yellow mixture was kept for 16 h at 65 °C, resulting in a dark red solution. The reaction mixture was allowed to cool to room temperature and quenched with water (10 mL). The aqueous and the organic layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined ether fractions were dried with MgSO<sub>4</sub> and filtered, and the solvent was removed to obtain the product as a yellow oil (0.369 g, 1.33 mmol, 86%). NMR ( $\delta$ , CDCl<sub>3</sub>) <sup>1</sup>H: 7.24–7.16 (m, 5H, aromatic), 4.54 (dd, 1H,  $J_{\text{HH}} = 8$  Hz,  $J_{\text{HH}} = 5$  Hz, OCH), 2.78 (br s, 2H, OH), 1.74–1.63 (m, 2H, CH<sub>2</sub>), 1.54–1.37 (m, 2H, CH<sub>2</sub>), 1.34–1.29 (m, 3H, CH<sub>2</sub>), 1.20–1.05 (m, 9H, CH<sub>2</sub>), 1.11 (t,  $J_{\text{HH}} = 7$  Hz, 6H, 2CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H}: 145.0 (s, aromatic), 128.4 (s, aromatic), 127.4 (s, aromatic), 125.9 (s, aromatic), 74.8 (s, COH), 74.3 (s, COH), 39.1 (s, CH<sub>2</sub>), 38.6 (s, CH<sub>2</sub>), 35.4 (s, CH<sub>2</sub>), 33.2 (s, CH<sub>2</sub>), 25.8 (s, CH<sub>2</sub>), 25.7 (s, CH<sub>2</sub>), 23.3 (s, CH<sub>2</sub>), 14.2 (s, CH<sub>3</sub>). IR (ATR, neat):  $\nu$  3400 (br), 3026 (vw), 2952 (s), 2928 (s), 2858 (s) cm<sup>-1</sup>. HRMS ESI [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>Na<sup>+</sup> 301.2143; found 301.2248.

5-butylnonane-2,5-diol (6):



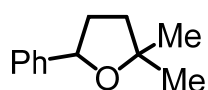
To a pressure vial with a Teflon screw cap, valerolactone (**2**, 0.300 g, 3.00 mmol) and THF (3 mL) were added. *n*-Butyl lithium (1.4 M in hexanes, 6 mL, 8.4 mmol) was added dropwise, using a needle and a syringe. The pressure vial was closed, and the yellow mixture was kept for 16 h at 65 °C, resulting in a dark red solution. The reaction mixture was allowed to cool to room temperature and quenched with water (10 mL). The aqueous and the organic layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined ether fractions were dried with MgSO<sub>4</sub> and filtered, and the solvent was removed to obtain the product as a light yellow oil (0.560 g, 2.59 mmol, 86%). NMR ( $\delta$ , CDCl<sub>3</sub>) <sup>1</sup>H: NMR ( $\delta$ , CDCl<sub>3</sub>) <sup>1</sup>H: 3.74–3.69 (m, 1H, OCH), 2.72 (br s, 2H, OH), 1.54–1.36 (m, 8H, CH<sub>2</sub>), 1.30–1.20 (m, 8H, CH<sub>2</sub>), 1.13 (t, 3H,  $J_{\text{HH}} = 6$  Hz, CH<sub>3</sub>), 0.85 (t, 6H,  $J_{\text{HH}} = 6$  Hz, 2CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H}: 74.2 (s, COH), 68.4 (s, COH), 39.1 (s, CH<sub>2</sub>), 38.5 (s, CH<sub>2</sub>), 35.4 (s, CH<sub>2</sub>), 32.9 (s, CH<sub>2</sub>), 25.8 (s, CH<sub>2</sub>), 25.7 (s, CH<sub>2</sub>), 23.5 (s, CH<sub>2</sub>), 23.3 (s, CH<sub>3</sub>), 14.1. (s, CH<sub>3</sub>). IR (ATR, neat):  $\nu$  3380 (br), 2956 (s), 2927 (s), 2859 (s) cm<sup>-1</sup>.

2,2,5-triphenyltetrahydrofuran (7):



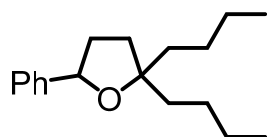
In a 7 mL vial with Teflon screw cup, the diol **3** (0.050 g, 0.157 mmol) and  $[\text{FeCp}_2]\text{BF}_4$  (0.005 g, 0.018 mmol) were combined and the mixture was stirred at 45 °C for 3 days. The reaction mixture was filtered through a short pad of silica gel, and the solvent was removed in high vacuum to obtain the product (**7**) as a yellow, viscous oil (0.039 g, 0.130 mmol, 83%). NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$ : 7.50–7.44 (m, 4H, aromatic), 7.30–7.13 (m, 11H, aromatic), 5.08 (t, 1H,  $J_{\text{HH}} = 7$  Hz, OCH), 2.73–2.67 (m, 1H, CH), 2.62–2.52 (m, 1H, CH), 2.30–2.23 (m, 1H, CH), 1.92–1.85 (m, 1H, CH).  $^{13}\text{C}\{^1\text{H}\}$ : 146.9 (s, aromatic), 146.7 (s, aromatic), 143.5 (s, aromatic), 143.5 (s, aromatic), 128.5 (s, aromatic), 128.40 (s, aromatic), 128.35 (s, aromatic), 128.28 (s, aromatic), 128.2 (s, aromatic), 127.32 (s, aromatic), 127.30 (s, aromatic), 126.81 (s, aromatic), 126.79 (s, aromatic), 126.22 (s, aromatic), 126.20 (s, aromatic), 126.1 (s, aromatic), 126.0 (s, aromatic), 125.9 (s, aromatic), 88.8 (s, CO), 80.5 (s, CO), 38.5 (s,  $\text{CH}_2$ ), 34.7 (s,  $\text{CH}_2$ ). IR (ATR, neat):  $\nu$  3055 (w), 3022 (w), 2969 (w), 2869 (w)  $\text{cm}^{-1}$ . HRMS ESI  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{21}\text{O}^+$  301.1592; found 301.1572.

2,2-dimethyl-5-phenyltetrahydrofuran (**8**):



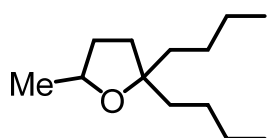
In a 7 mL vial with Teflon screw cup, the diol **4** (0.077 g, 0.396 mmol) and  $[\text{FeCp}_2]\text{BF}_4$  (0.011 g, 0.04 mmol) were combined and the mixture was stirred at 45 °C for 3 days. The crude product was purified by filtration over  $1.5 \times 5$  cm  $\text{Al}_2\text{O}_3$ , using  $\text{CH}_2\text{Cl}_2$ /hexanes 1:1 to pack/elute. The solvent was removed under high vacuum to obtain the product (**8**) as a yellow, viscous oil (0.057 g, 0.323 mmol, 82%). NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$ : 7.29–7.21 (m, 4H, aromatic), 7.17–7.15 (m, 1H, aromatic), 4.91–4.85 (m, 1H, OCH), 2.28–2.17 (m, 1H, CH), 1.86–1.75 (m, 3H,  $\text{CH} + \text{CH}_2$ ), 1.31 (s, 3H,  $\text{CH}_3$ ), 1.31 (s, 3H,  $\text{CH}_3'$ ).  $^{13}\text{C}\{^1\text{H}\}$ : 143.7 (s, aromatic), 128.3 (s, aromatic), 127.2 (s, aromatic), 125.9 (s, aromatic), 81.3 (s, CO), 80.6 (s, CO), 39.1 (s,  $\text{CH}_2$ ), 35.8 (s,  $\text{CH}_2$ ), 29.2 (s,  $\text{CH}_3$ ), 28.5 (s,  $\text{CH}_3'$ ). IR (ATR, neat):  $\nu$  3030 (w), 3020 (w), 2964 (m), 2900 (w)  $\text{cm}^{-1}$ .

2,2-dibutyl-5-phenyltetrahydrofuran (**9**):



In a 7 mL vial with Teflon screw cup, the diol **5** (0.100 g, 0.359 mmol) and  $[\text{FeCp}_2]\text{BF}_4$  (0.010 g, 0.036 mmol) were combined and kept at 70 °C for 48 h. The crude product was purified by filtration over  $1.5 \times 5$  cm  $\text{Al}_2\text{O}_3$ , using  $\text{CH}_2\text{Cl}_2$ /hexanes 9:1 to pack/elute. The solvent was removed under high vacuum to obtain the product (**9**) as a yellow, viscous oil (0.068 g, 0.261 mmol, 73%). NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$ : 7.29–7.12 (m, 5H, aromatic), 4.83–4.79 (m, 1H, OCH), 2.18–2.15 (m, 1H, CH), 1.79–1.71 (m, 2H,  $\text{CH}_2$ ), 1.59–1.42 (m, 4H,  $2\text{CH}_2$ ), 1.34–1.18 (m, 9H,  $\text{CH} + 4\text{CH}_2$ ), 0.85–0.82 (m, 6H,  $2\text{CH}_3$ ).  $^{13}\text{C}\{^1\text{H}\}$ : 143.5 (s, aromatic), 128.3 (s, aromatic), 127.2 (s, aromatic), 125.9 (s, aromatic), 85.8 (s, CO), 80.5 (CO), 39.3 (s,  $\text{CH}_2$ ), 38.8 (s,  $\text{CH}_2$ ), 35.9 (s,  $\text{CH}_2$ ), 35.9 (s,  $\text{CH}_2$ ), 26.7 (s,  $\text{CH}_2$ ), 26.6 (s,  $\text{CH}_2$ ), 23.5 (s,  $\text{CH}_3$ ), 14.3 (s,  $\text{CH}_3$ ). IR (ATR, neat):  $\nu$  3052 (vw), 3026 (vw), 2952 (s), 2929 (s), 2858 (s)  $\text{cm}^{-1}$ .

2,2-dibutyl-5-methyltetrahydrofuran (**10**):



In a 7 mL vial with Teflon screw cup, the diol **6** (0.100 g, 0.500 mmol) and  $[\text{FeCp}_2]\text{BF}_4$  (0.013 g, 0.005 mmol) were combined and kept at 70 °C for 64 h. The crude product was purified by filtration over  $1.5 \times 5$  cm  $\text{Al}_2\text{O}_3$ , using  $\text{CH}_2\text{Cl}_2$ /hexanes 9:1 to pack/elute. The solvent was removed under high vacuum to obtain the product (**10**) as a yellow, viscous oil (0.083 g, 0.418 mmol, 84%). NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$ : 3.98–3.88 (m, 1H, OCH), 1.90–1.82 (m, 1H, CHH), 1.67–1.59 (m, 2H,  $\text{CH}_2$ ), 1.43–1.30 (m, 4H,  $2\text{CH}_2$ ), 1.21–1.18 (m, 9H, CHH,  $4\text{CH}_2$ ), 1.14 (t, 3H,  $J_{\text{HH}} = 6$  Hz,  $\text{CH}_3$ ), 0.83 (t,  $J_{\text{HH}} = 6$  Hz, 6H,  $2\text{CH}_3$ ).  $^{13}\text{C}\{^1\text{H}\}$ : 85.1 (s, CO), 74.4 (s, CO), 39.5 (s,  $\text{CH}_2$ ), 39.2 (s,  $\text{CH}_2$ ), 35.5 (s,  $\text{CH}_2$ ), 34.1 (s,  $\text{CH}_2$ ), 26.6 (s,  $\text{CH}_2$ ), 26.5 (s,  $\text{CH}_2$ ), 23.43 (s,  $\text{CH}_2$ ), 23.39 (s,  $\text{CH}_2$ ), 21.5 (s,  $\text{CH}_3$ ), 14.2 (s,  $\text{CH}_3$ ). IR (ATR, neat):  $\nu$  2980 (s), 2960 (s), 2910 (s)  $\text{cm}^{-1}$ .

## 4. Conclusions

In summary, we demonstrated for the first time that ferrocenium cations cyclize substituted 1,4-butanediols to afford 2,2,5-trisubstituted tetrahydrofuran derivatives. The isolation of the products is straightforward by filtration through aluminum oxide, as the polarity of the diols is much higher than that of the products. The protocol allows for access to the trisubstituted tetrahydrofurans in a two-step procedure from commercial or easily accessible starting materials. We propose a reaction mechanism involving either a carbocation intermediate or a species in which the ferrocenium cation polarizes the C–OH bond. This method aligns with the principles of green chemistry, as it utilizes an iron-based catalyst and produces only water as a byproduct.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/inorganics13020059/s1>,  $^1\text{H}$ ,  $^{13}\text{C}\{^1\text{H}\}$  NMR, and IR spectra of the diols and the catalysis products in Schemes 1 and 2 as well as  $^1\text{H}$  NMR spectra of some reactions in Scheme 3 catalyzed by  $\text{FeCl}_3$  and  $\text{KPF}_6$ .

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