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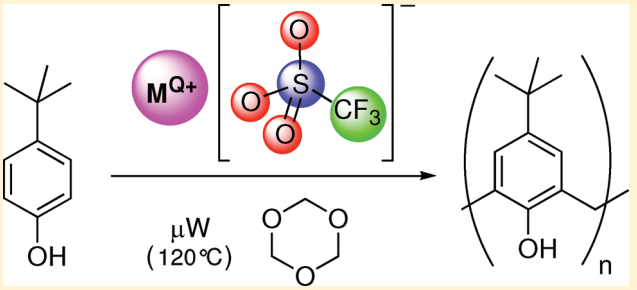
# Do Commercially Available Metal Salts Mediate Calixarene Formation via Hydrogen-Bonded Dimers?

Sean P. Bew* and Sunil V. Sharma

School of Chemistry, University of East Anglia, Norwich, NR4 7TJ, U.K.

Supporting Information

**ABSTRACT:** In this article we report the first example of a Lewis acid promoted, one-pot, Brønsted acid free, high-yielding synthesis of the calixarene macrocycle from the "monomer" *p-tert*-butylphenol. We report that when a commercially available metal salt (Lewis acid) is incorporated within the calixarene-forming reaction, a certain amount of control over the size of the calixarenes produced can be gained. Although a detailed mechanistic rationale on how the macrocycle is assembled is unclear, what is evident from this work is that the metal cation, the counteranion, and the oxidation state of the salt employed are all important contributors to the outcome of the reaction process. Indeed, evidence to date suggests that a subtle "symbiotic" relationship exists between the metal cation, its oxidation state, and the anion that allows the efficient transformation of the "monomeric" *p-tert*-butylphenol into linear oligomers and, ultimately, into macrocyclic calixarenes. Athough the metal salt mediated process described herein is efficient and high-yielding, what is also *fundamentally* important is that a comprehensive mechanistic understanding of how the calixarenes are assembled be accrued. Searching for possible indicators or clues, we propose that oligomeric methylene-linked phenolic entities are initially formed and that these, we tentatively suggest, generate metal and/or anion hydrogen-bonded supramolecular intermediates. It is possible that the preorganization of the linear polyphenolic oligomers allows the formation of hydrogen-bonded structures which, critically, result in the formation of supramolecular assemblies that are subsequently "stitched" together, generating the *p-tert*-butylcalix[*n*]arenes ($n$ = 4−9) in excellent yields. Substantiating the possibility that hydrogen-bonded entities are generated (and that these subsequently afford metal-templated assemblies), we make reference to a seldom cited 1962 *Nature* publication that reported the propensity of polyphenolic linear oligomers to form "well-defined intramolecularly hydrogen-bonded conformations".




## INTRODUCTION

The first most probable reported synthesis of the calixarene macrocycle was in 1872 by Albert von Baeyer[1] and later by Zinke in 1944.[2] Calixarenes are one of the most studied and widely utilized synthetic hosts, their interesting structures lending themselves to a plethora of applications in synthetic,[3] material,[4] analytical,[5] supramolecular,[6] and biological chemistries.[7] Furthermore, their use as a versatile platform is enhanced by the ability of *p-tert*-butylcalix[4]arene to be transformed, at will, into a *cone*, *partial cone*, or *1,3- or 1,2-alternate* conformation and also the ease with which it is possible to introduce diverse chemical functionality to either the lower rim or upper rim or both.

Given the importance of calixarenes, the time they have been known (viz. 139 years), and their widespread utility, it is interesting that there is considerable debate on *exactly* how the macrocyclic entities are assembled and the driving force for the chemoselective formation of certain ring sizes: i.e., *p-tert*-butylcalix[*n*]arenes ($n$ = 4, 6, 8) are often generated in preference to, for example, *p-tert*-butylcalix[*n*]arenes ($n$ = 7, 9, 10). Three protocols are available for calixarene synthesis, utilizing one of the following: (i) a Brønsted acid, (ii) an alkali-metal hydroxide, and (iii) a Lewis acid. The first two are one-pot procedures that require a sterically encumbered phenol (e.g. **1**), a source of formaldehyde, a suitable solvent, and a catalytic quantity of, for example, *p*-toluenesulfonic acid or hydrochloric acid in the case of (i) and an alkali-metal hydroxide, for example sodium hydroxide, for (ii).[8] Interestingly it was assumed until relatively recently (i.e. 1990) that the reaction between *p*-alkylphenols and formaldehyde afforded *only* high yields of *linear* oligomers under acidic conditions.[9] However, in a painstaking piece of groundbreaking research Gutsche et al. demonstrated that employing a Brønsted acid (PTSA) under specific reaction conditions afforded a high-yielding, complex mixture of *p-tert*-butylcalix[*n*]arenes ($n$ = 4−20).

Alternatively, depending on the size of the calixarene desired and utilizing a catalytic quantity of sodium or potassium hydroxide in conjunction with defined reaction conditions, the efficient, high-yielding synthesis of specific *p-tert*-butylcalix[*n*]arenes (i.e. $n$ = 4, 6, 8) is straightforward.[8,10]

As far as the author is aware, no mechanistic rationale has been forwarded that attempts to explain macrocycle formation under

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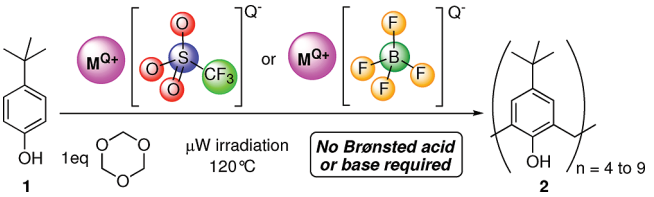
**Scheme 1. Synthesis of 2 without the Use of a Brønsted Acid or Alkali-Metal Hydroxide Salt**




Brønsted acid reaction conditions. Furthermore, although there is somewhat more of an understanding around the cyclooligomerization process using basic catalysts, this process is "far from being well understood"[11] with "metal cation template effects" or "molecular mitosis" assemblies being invoked to account for the formation of specific calix[n]arenes.

Relative to the Brønsted acid or alkali-metal hydroxide methods recounted, the application of *Lewis acids* for *p-tert*-butylcalix[*n*]arene synthesis has remained relatively dormant, with the majority of protocols employing titanium(IV) chloride and directed toward convergent [2 + 2], [2 + 1 + 1], or [3 + 1] calix[4]arene syntheses. It is difficult to pinpoint exactly why convergent syntheses are seldom employed, but it may, in part, be due to the number of "preliminary" reactions required for constructing the starting materials and the often low to moderate yields of calixarenes that result.[12] Furthermore, similar to Brønsted acid mediated protocols and the results reported here (vide infra) a precise mechanistic rationale that fully explains, in detail, how titanium(IV) chloride mediates calixarene formation has yet to be reported/elucidated.

Calixarene research in our laboratory focuses on (i) generating new calixarene motifs with bespoke functionality[13] and (ii) dissecting and elucidating the mechanisms surrounding the construction of these fascinating macrocyclic entities assembled via "conventional" (i.e., those that employ alkali-metal hydroxides) and "nonconventional" procedures. We have, for example, recently reported that the Lewis acid tin(IV) chloride is a highly efficient reagent for the synthesis of *p-tert*-butylcalix[*n*]arenes (*n* = 8, 9) from *p-tert*-butylphenol.[13] In this high-yielding process these two calixarenes are the major constituents of the reaction mixture, with the hard to generate *p-tert*-butylcalix[9]arene being formed with exceptional ease. It is worth pointing out that in this one-pot reaction process 18 (for calix[9]arene) and 16 (for calix[8]arene) new C−C bonds are generated! Be that as it may, a mechanism that explains their formation has yet to be deciphered and is still an ongoing concern within our laboratory. Indeed, it was during our efforts at attempting to understand the mode of action of tin(IV) chloride, as well as alternative Lewis acids, in conjunction with our long-term goal of developing an efficient and generic non-Brønsted acid or non alkali-metal hydroxide mediated synthesis of entities based on **2** (Scheme 1) that the "metal salt effect" outlined here presented itself. Thus, using metal triflate or tetrafluoroborate salts, trioxane, and microwave irradiation, the efficient, high-yielding, and chemoselective cyclic oligomerization of **1** into macrocycles **2** has been achieved (Scheme 1) in the first example of a *Lewis acid promoted, one-pot, Brønsted acid free synthesis* of **2** from "monomer" **1**.

## RESULTS AND DISCUSSION

Initiating our work, we investigated the possibility that commercially available metal triflate salts such as zinc(II), ytterbium(III), and neodymium(III) triflates could mediate the reaction outlined in Scheme 1. We envisaged their application as being multifaceted, acting as bifunctional Lewis acids capable of, in the first instance, promoting the retrocyclization of trioxane (aiding in situ formation of formaldehyde) and subsequently as coordinating agents of the precursors to **2** or linear oligomers derived from **1**, allowing a "metal template"[14] effect to be established that aided the formation of **2**. Initial results were disappointing. Subjecting **1**, trioxane, and individual catalytic quantities of zinc(II), ytterbium(III), or neodymium(III) triflate (20 mol %) to microwave irradiation (120 °C) for 30 min in DCM returned *p-tert*-butylphenol (**1**) with good mass balances.[15] Furthermore, increasing the number of equivalents of trioxane (3 equiv) and Lewis acid (1 equiv), the temperature (from 80 to 150 °C), and the reaction time (up to 120 min) all resulted in no detectable formation of **2** or linear oligomers based on uncyclized **2**.

**Table 1. Investigation of Group 1A and Group IIA Triflate Salts for Their Ability To Afford Calixarenes**

| | amt, % | | |
|---|---|---|---|
| entry no., triflate salt | **1** | linear oligomers | calix[4−9]arene[c] |
| 1, $Li^{+a,b}$ | 100 | | |
| 2, $Na^{+a}$ | 96 | 4 | |
| 3, $Na^{+b}$ | 26.5 | 61.2 | 11.7 |
| 4, $K^{+b}$ | 69.5 | 15.1 | 15.4 |
| 5, $Rb^{+a,b}$ | 100 | | |
| 6, $Cs^{+a,b}$ | 100 | | |
| 7, $Mg^{2+a}$ | 13.4 | 1.9 | 84.0 |
| 8, $Mg^{2+b}$ | 3.0 | 6.5 | 90.4 |
| 9, $Ca^{2+b}$ | 5.5 | 2.9 | 90.2 |
| 10, $Ba^{2+a,b}$ | 100 | | |

[a] 20 mol % metal triflate. [b] 100 mol % metal triflate. [c] HPLC analysis is given in the Supporting Information.

Changing tack, we opted to investigate triflate salts derived from group IA metals, i.e. lithium, sodium, potassium, cesium, and rubidium (increasing metal radii and electropositive nature), and group IIA metals, i.e. calcium, magnesium, and barium (Table 1). It is known that $K^+$ and in particular $Na^+$ bind well to the phenolic hydroxyl groups on *p-tert*-butylcalix[4]arenes (cf. template effect[12]).

Employing a catalytic quantity (20 mol %) of lithium triflate or sodium triflate or a stoichiometric quantity of lithium triflate with **1** and trioxane (1 equiv) afforded only starting material (30 min, 120 °C, microwave, entries 1 and 2, Table 1). When this reaction was repeated with 1 equiv of sodium triflate, **2** was generated in 11.7% yield (entry 3, Table 1). Although the yield of **2** was low, we were buoyed by this exciting preliminary result, which indicated for the first time that *p-tert*-butylcalix[*n*]arenes could indeed be generated in the *absence* of any Brønsted acid and in a one-pot reaction process. With a view to probing the mechanistic nature associated with the formation of **2** and the importance of the $Na^+$ cation within the condensation reaction, it was repeated (Scheme 1) using stoichiometric quantities of sodium triflate and the $Na^+$ complexing agent 15-crown-5. The reaction afforded only starting material **1**, in an almost quantitative yield. Thus, it seemed the complexing ability of 15-crown-5 for $Na^+$ effectively shut down the (presumably) initial condensation reaction between **1** and formaldehyde or its precursor. This being the case, it was perhaps not too unexpected that the linear oligomerization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and macrocyclization reaction products, i.e. **2**, were not observed. Repeating this reaction using more forcing conditions, i.e. 120 °C for an extended 60 min time period, did not afford **2**. We pondered the outcome that switching from $Na^+$ to $K^+$ (ionic radii 1.13 and 1.51 Å, respectively) would have not only on the yield of **2** but also on the ratios of individual *p-tert*-butylcalix[*n*]arenes within **2** (vide infra). Exchanging sodium triflate for potassium triflate (1 equiv) returned **2** in a disappointing 15.4% yield (entry 4) and a similarly low yield of linear oligomers (i.e. 15.1%. The mass balance of the reaction mixture comprised starting material **1**. From a mechanistic point of view it is interesting to note the 4:1 ratio difference between the linear oligomers in entries 3 and 4 (Table 1). Clearly, switching $K^+$ for $Na^+$ had a significant and detrimental effect on the ability of the reaction to generate linear oligomers and, presumably, **2**. Seeking an explanation that accounted for the ability of sodium triflate to generate 61% of linear oligomers (in contrast to potassium triflate) and the fact that water is generated in transforming **1** into **2** (Scheme 1), we considered the possibility that the $Na^+$ formed hydrated $Na^+$ cations which acted as supramolecular scaffolds or templates on which linear oligomers and/or calixarenes could form. The primary hydration numbers for $Li^+$, $Na^+$, and $K^+$ are all 4 (others are also possible), and the hydrated radii of the $Na^+$ and $K^+$ cations are 2.76 and 2.32 Å, respectively. Thus, given the fact that these cations have identical primary hydration numbers and similar hydrated radii, it seems unlikely that this could be invoked to explain the formation of differing ratios of linear oligomers and yields of calixarenes. Utilizing catalytic or stoichiometric quantities of rubidium or cesium triflate (entries 5 and 6, Table 1) returned starting material **1** in quantitative yields.

Switching to group IIA triflate salts ($M^{2+}$ ions are smaller and considerably less polarized than the isoelectronic $M^+$ ions), magnesium triflate (entry 7, Table 1, 20 mol %) afforded **2** in a significantly enhanced 84% yield, with only 1.9% of linear oligomers and 13% of **1**. Gratifyingly, increasing the amount of magnesium triflate still further to 1 equiv afforded an excellent 90% yield of **2** (entry 8, Table 1).

Similar to the case for magnesium triflate, switching to calcium triflate afforded **2** in an excellent 90% yield (entry 9, Table 1). Thus, it seemed that the $M^{2+}$ (M = group IIA) triflate salts (ionic radii of 0.71 Å for $Mg^{2+}$ and 1.14 Å for $Ca^{2+}$) are more effective than group IA triflate salts at generating macrocycles based on **2**. Barium triflate consistently returned starting material **1**.

Given that the solubility of magnesium or calcium triflate in dichloromethane is likely to be very low, even at 120 °C, it seems reasonable to assume that the reaction process which generates, very effectively, linear oligomers and **2** using these salts is heterogeneous in nature. Thus, the lack of barium triflate solubility in DCM does not appear to be a likely reason for the observed lack of reaction: i.e., no linear oligomers or **2** formed when barium triflate is employed. At this point in time it is unclear why barium triflate does not afford any linear oligomers or **2**. Furthermore, speculating that the lack of reaction can be attributed to the large ionic radius of $Ba^{2+}$ (i.e. 1.49 Å) makes it hard to explain why $K^+$, with a similar ionic radius (i.e. 1.51 Å), affords a reasonable yield of linear oligomer and **2**.

When **3**, **4**, and **7**−**9** were subjected to HPLC analysis (Table 2), several observations were evident.[16] Of particular note is the substantial difference in *p-tert*-butylcalix[*n*]arene (*n* = 4, 8) composition in entries 1 and 2 (derived from $Na^+$ and $K^+$ group IA salts, respectively; Table 2) and entries 3−5 ($Mg^{2+}$ and $Ca^{2+}$ group IIA salts; Table 2). Evidently in this

**Table 2. HPLC Analysis of 2 Synthesized using Group IA and IIA Metal Triflates**

| | amt, % | | | | | |
|---|---|---|---|---|---|---|
| entry no., triflate salt | [**4**][c] | [**5**][c] | [**6**][c] | [**7**][c] | [**8**][c] | [**9**][c] |
| 1, $Na^{+b}$ | 1.2 | 3.0 | 1.8 | 2.2 | 3.5 | |
| 2, $K^{+b}$ | 5.7 | 0.2 | 2.8 | 0.7 | 6.0 | |
| 3, $Mg^{2+a}$ | 32.8 | 1.2 | 6.6 | 4.2 | 39.2 | |
| 4, $Mg^{2+b}$ | 24.8 | 3.5 | 11.5 | 8.2 | 40.2 | 2.2 |
| 5, $Ca^{2+b}$ | 6.6 | 1.2 | 15.5 | 18.8 | 40.0 | 8.2 |

[a] 20 mol % metal triflate. [b] 100 mol % metal triflate. [c] HPLC analysis is given in the Supporting Information.

reaction the group IA $Na^+$ cation, which is generally considered a good "template" for *p-tert*-butylcalix[4]arene synthesis,[12] is inferior to a group IIA $Mg^{2+}$ cation, which affords substantially larger percentages of *p-tert*-butylcalix[4]arene within **2** (cf. 1.2% for $Na^+$). Worthy of particular note is the contrast between the hard, oxophilic $Mg^{2+}$ and the $Ca^{2+}$ cation. $Mg^{2+}$ (when present in catalytic or stoichiometric quantities; entries 3 and 4, respectively) affords substantially larger percentages of *p-tert*-butylcalix[4]arene within **2** than does $Ca^{2+}$ (cf. 6.6%). Indeed, under catalytic reaction conditions magnesium triflate afforded the highest percentage of *p-tert*-butylcalix[4]arene of any of the group IA and IIA salts. Furthermore, employing *either* catalytic (20 mol %) or stoichiometric quantities of magnesium triflate returned *p-tert*-butylcalix[8]arene in 39.2% and 40.2% yields, respectively, both of which are essentially identical with the percentage generated using calcium triflate. Worthy of note are the *increased* percentages of *p-tert*-butylcalix[*n*]arene (*n* = 7, 9; 18.8% and 8.2%, respectively, entry 5, Table 2) afforded using calcium triflate in comparison with the percentages generated using magnesium triflate (cf. entries 3 and 4, Table 2). It is interesting to contrast $Mg^{2+}$ with the more electro(di)positive and larger $Ca^{2+}$ (extra $3p^6$ and $4s^2$ shells) in their abilities to coordinate *longer* linear oligomers and thus afford (generally) larger percentages of *p-tert*-butylcalix[*n*]arenes (*n* = 6−9).

We were concerned that the hydrolysis of a triflate salt (perhaps via **1**) could afford triflic acid that may, via a Brønsted acid mediated process, afford **2**.[9] Investigating this, we reacted *p-tert*-butylphenol (**1**) and trioxane with (i) stoichiometric and (ii) catalytic quantities of triflic acid. Major decomposition was observed when a stoichiometric quantity of triflic acid was employed. Likewise, with 20 mol % of triflic acid a dark precipitate formed and significant decomposition was observed. Repeating the triflic acid mediated catalytic reaction (20 mol %) at *ambient* temperature (6 h) returned unreacted **1** in an 80% yield and *p-tert*-butylcalixarenes **2** in a poor 10% yield. Given these results, i.e. dark reaction mixtures, significant decomposition, copious amounts of precipitation, and low yields, it seemed unlikely that our efficient reaction process could be attributed to in situ triflic acid synthesis that, subsequently, mediates formation of **2**. Thus, the evidence to date seemed to suggest that the metal salt mediated process was proceeding via a template effect and that *different* metal cations derived from within group IA or IIA and between groups IA and IIA have a significant influence on the chemoselectivity of the reaction process that generates **2**.

Intrigued by these positive results, we felt compelled to explore alternative, readily available metal salts derived from copper, lanthanum, and the group IVb element tin. Of specific

**Table 3. Investigating Metal Triflate Salts 11−14 for Their Ability To Promote the Efficient Synthesis of 2**

| | | amt, % | | |
|---|---|---|---|---|
| entry no., triflate salt | ORP, e | **1** | linear oligomer [b] | calix[4−9]arene[b] |
| 11, CuOTf [a] | +0.52 | 7.3 | 7.5 | 84.3 |
| 12, $Cu(OTf)_2$ [a] | +0.15 | 10.4 | 4.2 | 84.5 |
| 13, $Sn(OTf)_2$ [a] | −0.24 | 5.6 | 0.6 | 93.6 |
| 14, $La(OTf)_3$ [a] | −2.52 | 3.0 | 2.5 | 94.7 |

[a] 20 mol % metal triflate. [b] HPLC analysis is given in the Supporting Information.

**Table 4. HPLC Analysis of 2 Synthesized using Metal Triflate Salts 11−14**

| | amt, % | | | | | |
|---|---|---|---|---|---|---|
| entry no., triflate salt | [**4**][b] | [**5**][b] | [**6**][b] | [**7**][b] | [**8**][b] | [**9**][b] |
| 1, $Cu^{+a}$ | 29.2 | 4.8 | 12.2 | 7.6 | 29.5 | 1.0 |
| 2, $Cu^{2+a}$ | 32.4 | 3.2 | 6.4 | 4.0 | 38.5 | |
| 3, $Sn^{2+a}$ | 21.4 | 4.7 | 13.9 | 9.6 | 42.0 | 2.0 |
| 4, $La^{3+a}$ | 21.7 | 3.8 | 10.9 | 9.1 | 47.0 | 2.2 |

[a] 20 mol % metal triflate. [b] HPLC analysis is given in the Supporting Information.

interest was the feasibility of increasing any chemoselective nature displayed by these salts such that we enhance the formation of specific *p-tert*-butylcalix[*n*]arenes: cf. our previous report using tin(IV) chloride for the synthesis of *p-tert*-butylcalix[*n*]arene (*n* = 8, 9).[13c] Thus far, all successful applications had explored the use of single metal salt species in only *one* oxidation state: i.e., +1 (group 1A) or +2 (group IIA). Changing tack, we considered the possibility of incorporating *one metal salt* that was readily available in *two oxidation states.* Copper(I) and copper(II) triflates are both commercially available and are ideally suited to probing the effect that a decreasing ionic radius ($Cu^+$ (0.74 Å) to $Cu^{2+}$ (0.71 Å)) and different oxidation states would have, if any, on the formation of **2**. Gratifyingly, catalytic quantities of either copper(I) or copper(II) triflate afforded essentially identical yields of **2**: i.e. 83.3% and 84.5% (entries 11 and 12, respectively, Table 3). Similarly, tin(II) triflate (ionic radius 1.12 Å) returned a 93.6% yield of **2** (entry 13), while lanthanum triflate (ionic radius 1.17Å) returned **2** in an excellent 94.7% yield (entry 14, Table 3). Worthy of note is the fact that, broadly speaking, the ionic radii of these metal salts are similar to those of $Mg^{2+}$ and $Ca^{2+}$ and that collectively all of these salts afforded excellent yields of **2**. Furthermore, as the redox potentials (ORP) of the metal salts in **11**−**14** decrease, i.e. Cu(I) +0.52e, Cu(II) +0.15e, Sn(II) −0.24e, and La(III) −2.52e (Table 3), the yields of **2** steadily *increase* from ∼84% to ∼95%. These interesting and unoptimized results suggest that perhaps the size of the metal cation and its oxidation state play a key role in the efficient formation of **2**.

HPLC analysis of **11**−**14** ($Cu^+$, $Cu^{2+}$, $Sn^{2+}$, and $La^{3+}$, respectively) are outlined in Table 4. As a first observation, it is interesting to note the difference in the percentages of *p-tert*-butylcalix[*n*]arene (*n* = 6, 7) when stoichiometric quantities of copper(I) and copper(II) triflate are employed. The copper(I) triflate afforded approximately twice as much *p-tert*-butylcalix[*n*]arene (*n* = 6, 7) as the copper(II) triflate, while the percentage of *p-tert*-butylcalix[4]arene generated was, more or less, the same for both copper(I) and copper(II) triflates (compare entries 1 and 2, Table 4). Second, of *all* the salts tested, lanthanum(III) triflate returned the largest percentage, i.e., 47% of *p-tert*-butylcalix[8]arene, via a reaction that afforded the highest yield of **2**, i.e. 95% (entry 4, Table 4). With this latter observation in mind, it is worth noting the general trend for larger amounts of *p-tert*-butylcalix[8]arenes (entries 1−4, Table 4, descending order observed for the [**8**] column) as the redox potentials of the metal triflate salts decrease, i.e. 29.5% $Cu^+$ +0.52e, 38.5% $Cu^{2+}$ +0.15e, 42% $Sn^{2+}$ −0.24e, and 47% $La^{3+}$ −2.52e, as well as for the formation of smaller percentages of *p-tert*-butylcalix[4]arene.

**Table 5. Investigation of Salts 15−17 for Their Ability To Promote the Synthesis of 2**

| | amt, % | | |
|---|---|---|---|
| entry no., salt | **1** | linear oligomer [b] | calix[4−9]arene[b] |
| 15, $Zn(BF_4)_2$ [a] | 1.0 | 23.0 | 75 |
| 16, $CuBF_4$ [a] | 3.8 | 17.4 | 77.6 |
| 17, $Pb(BF_4)_2$ [a] | 7.8 | 46.5 | 45.5 |

[a] 100 mol % metal triflate. [b] HPLC analysis is given in the Supporting Information.

**Table 6. HPLC Analysis of 2 Synthesized via Metal Tetrafluoroborate Salts 15−17**

| | amt, % | | | | | |
|---|---|---|---|---|---|---|
| entry no., $BF_4$ salt | [**4**] | [**5**] | [**6**] | [**7**] | [**8**] | [**9**] |
| 1, $Zn^{2+}$ | 7.7 | 5.7 | 15.1 | 21.9 | 15.9 | 6.7 |
| 2, $Cu^+$ | 8.3 | 4.8 | 16.2 | 21.6 | 17.5 | 9.2 |
| 3, $Pb^{2+}$ | 16.8 | 0.5 | 7.2 | 1.6 | 19.4 | |

Repeating our standard reaction (Scheme 1) with a stoichiometric quantity of zinc(II), copper(I), or lead(II) tetrafluoroborate (Table 5) afforded **2** in moderate (i.e. ∼45%) to good (i.e. ∼77%) yields. Of the three tetrafluoroborate salts tested, copper(I) tetrafluoroborate (entry 16, Table 5) afforded the highest yield of **2** and lowest percentage yield of linear oligomers. Furthermore, of particular note is the aptitude of zinc(II) (**15**) and lead(II) tetrafluoroborate (**17**) to afford **2** at all. Indeed, the ability of **15** and **17** (Table 5) to afford **2**, albeit both in lower yield than when **16** was employed, was in sharp contrast to the case for zinc(II) triflate, which afforded only starting material **1**. Intriguingly, this observation suggests the possibility that a subtle *anion* recognition effect is operating, with a successful reaction dependent on not only the type of cation employed but also the anion associated with the cation. It is interesting to note the difference in yields between zinc(II) triflate (cf. 0%) and zinc(II) tetrafluoroborate which, under otherwise identical reaction conditions, afford **2** in 75% yield.

HPLC analysis of the calixarenes resulting from **15**−**17** are outlined in Table 6. On comparison of these results with those in Table 4 derived from the triflate salts it is evident that zinc(II) or copper(I) tetrafluoroborate (Table 6, entries 1 and 2, respectively) afford a near 3- to 4-fold *decrease* in the percentage of *p-tert*-butylcalix[4]arene generated when **11**−**14** (stoichiometric quantities) were employed. This is in stark contrast to the significant 2.5−5.5-fold increase in *p-tert*-butylcalix[7]arene generated


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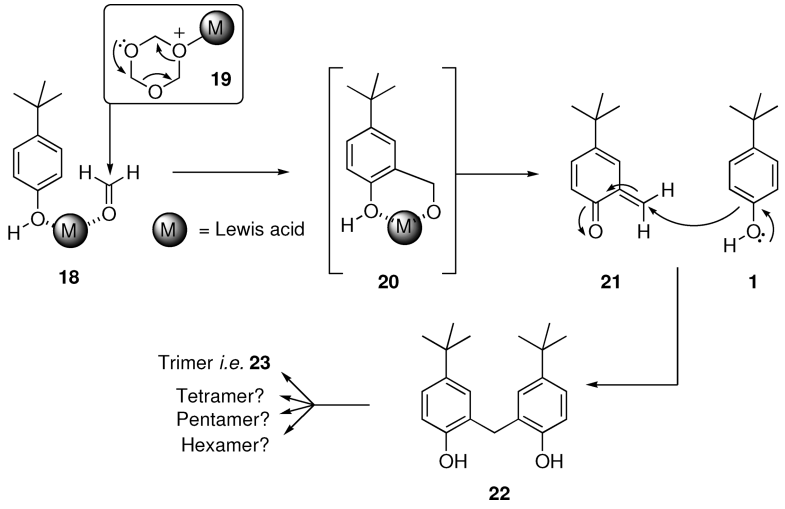
**Scheme 2. Possible Synthesis of "Dimer" 22 via a Lewis Acid Assisted Reaction Process**




using zinc(II) tetrafluoroborate **15** (i.e. 21.9%; entry 1, Table 6) or copper(I) tetrafluoroborate **16** (i.e. 21.6%; entry 2, Table 6): cf. 4% using copper(II) triflate (entry 2, Table 4). Furthermore, there is a 6−9-fold *increase* in *p-tert*-butylcalix[9]arene when **15** or **16** is used: i.e., compare entries 1 and 2 in Table 4 with entries 1 and 2 in Table 6. Turning our attention to lead(II) tetrafluoroborate, **17** mediated the formation of a very low percentage of *p-tert*-butylcalix[*n*]arene (*n* = 5, 7), i.e. 0.5 and 1.6% (entry 3, Table 6); furthermore, in comparison to **15** and **16**, **17** generated a significantly higher 16.8% of *p-tert*-butylcalix[4]arene.

At the present time it is unclear exactly how the calixarenes are assembled. However, clues can be gleaned from the literature on the synthesis and properties of methylene-linked polyphenols. Of particular relevance, Casnati et al. has reported the regioselective synthesis of *o*-hydroxymethylene-substituted phenols via a template-driven reaction between aryloxymagnesium bromides and formaldehyde.[17] With this and the work of Casiraghi et al.[18] in mind, it seems likely the first step toward generating **2** is the synthesis of a linear "dimer" and "trimer" based on **22** and **23** (Scheme 2). Presumably the Lewis acid acts as a bifunctional catalyst, facilitating in situ formaldehyde synthesis via activation and retrocyclization of trioxane (**19**, boxed part in Scheme 2), but also enables subsequent coordination of the formaldehyde *and* the *p-tert*-butylphenol, allowing them to react and generate a metal chelate complex similar to **20** (Scheme 2). Subsequent rearrangement of **20** affords a reactive *o*-quinone methide species (i.e. **21**) that reacts with **1**, generating dimer **22**. Utilizing **22** as the "core oligomer" starting material and repeating this sequence of reaction events allows the formation of homologated trimers: i.e., **23**, tetramer, pentamer, etc. With these "core" building blocks in place, their subsequent transformation into calixarenes based on **2** can occur.

Eglinton and Cairns[19] have described how oligomeric methylene-linked phenolic species based on **22** and **23** generate intramolecular hydrogen-bonded complexes: i.e., **24** and **25** (Figure 1). Similarly, Yamagishi et al. reported that entities similar to **22** and **23** self-assemble via intramolecular and intermolecular hydrogen bonds, generating bimolecular aggregates that assume "pseudo-cyclic conformations analogous to *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[6]arenes". Thus, in the absence of structural data we propose the preorganization of **22** and **23** into hydrogen-bonded dimers **24** and **25**, respectively, to be a viable, potentially important process that in conjunction with cationic and or anionic recognition processes (vide infra) may offer a possible rationale for the formation of **2**.

Our preliminary results suggest that the efficient formation of **2** is dependent on the metal cationic center and to a certain extent the anion associated with the cation of the Lewis acid employed. Searching for a possible mechanistic rationale for the formation of **2**, it is interesting to note that single and multiple cationic metal centers are known to coordinate with phenols such as **22** and **23**. For example Vicens and Masci et al. have reported[21] that multiphenolic ligands similar to **22** and **23** efficiently bind, in some cases multiple, metal cations, affording large cyclic complexes that are held together via hydrogen bonding and metal−heteroatom coordination (see Figure 5 in ref 21).

With the propensity for oligomeric phenols to undergo hydrogen bond dimerization (cf. Figure 1) as well as their ability to efficiently coordinate cationic metals in mind, it seems plausible that if these two processes were combined, then a possible explanation for the efficient formation of **2** could be invoked. By way of example, incorporating **22** or its ortho-bis(hydroxymethylated) analogue may result in a [2 + 2] metal-chelated/hydrogen-bonded complex similar to **26** (Figure 3). The formation of a complex based on **26** allows the proposed and important "methylene stitching" event that joins the four hydrogen-bonded metal-coordinated spatially constrained aryl groups into close proximity, thus allowing *p-tert*-butylcalix[4]arene formation. Invoking a similar intramolecular hydrogen bond, metal-mediated self-assembly process, the synthesis of *p-tert*-butylcalix[*n*]arenes (*n* = 5, 6) via [2 + 3] and [3 + 3] assemblies: i.e., **27** and **28** respectively could be envisaged (Figure 3).

The synthesis of *p-tert*-butylcalix[*n*]arenes (*n* = 6−8) can be accommodated by invoking a broadly similar but *multimetal* mediated reaction process. Thuéry and Nierlich reported that a hexameric *o*-methylene-linked phenolic species effectively coordinated *two* uranyl ions ($UO^{2+}$), each one to a trimeric phenol component within a hexameric phenol; it is interesting to note (given our observed triflate and tetrafluoroborate anion effect, vide supra) that the assembly is held in place via a central double chelated $NO_3^-$ anion (Figure 2).[22] Invoking a similar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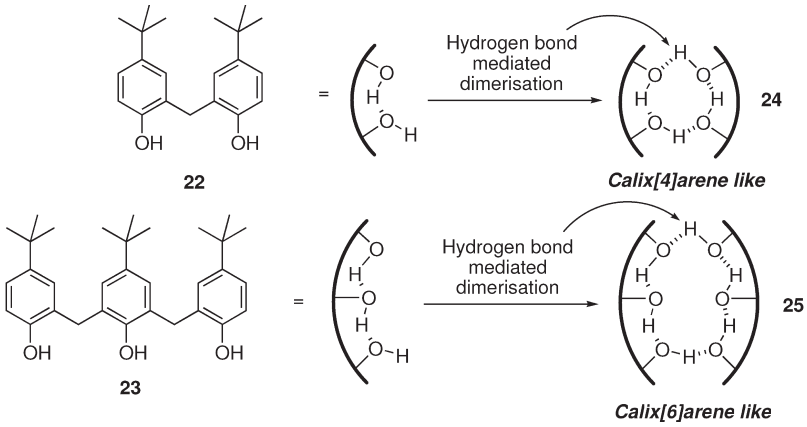


**Figure 1.** Dimerization of **22** and **23** generates calixarene like supramolecular architectures *i.e.* **24** and **25**.

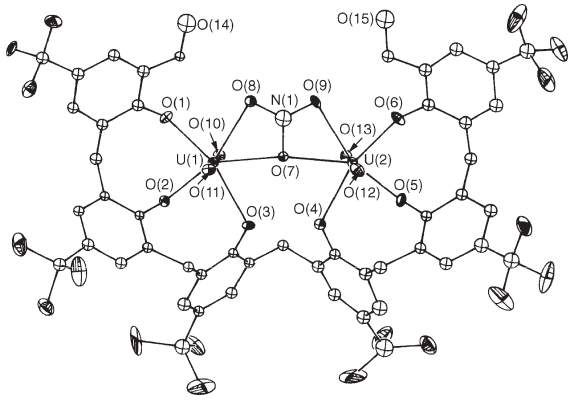


**Figure 2.** X-ray crystal structure of a uranyl ($UO^{2+}$) complex that incorporates an acyclic bis(hydroxymethyl)phenolic hexamer and an unusual bridging nitrate anion.[22]

assembly/reaction process, the formation of [3 + 3], [3 + 4], and [4 + 4] complexes (i.e. **15**−**17**) would afford, after macrocyclization via "methylene" stitching, the desired *p-tert*-butylcalix[*n*]arenes ($n = 6-8$).

After a relatively slow start, the use of synthetic hosts for anion recognition/complexation is becoming an increasingly important theme in chemistry. Nabeshima and co-workers[23] have recently described a *p-tert*-butylcalix[4]arene motif capable of binding a cation (i.e. $Na^+$ or $Ag^+$) *and* either a $CF_3SO_2^-$ or $BF_4^-$ anion; furthermore, Ito et al. has described a 2,2′-dihydroxy-1,1′-dinaphthyl-1-methane species (similar to **22**) that has an affinity for anions such as $HSO_4^-$, $NO_3^-$, $H_2PO_4^-$, and $CH_3CO_2^-$.[24] With this in mind, it seems plausible that a hydrogen-bond-mediated self-assembly process (Figure 1) in conjunction with $CF_3SO_3^-$ or $BF_4^-$ coordination may be a driver for macrocyclization of oligomers based on **22** or **23** and their subsequent transformation into calixarenes **2**.

Thus, encapsulation of the $CF_3SO_3^-$ anion within a hydrogen-bonded [2 + 2] dimer would afford a self-assembled supramolecular complex based on **27** (presumably anion complexes based on **28** and **29** are also possible; not shown) which is analogous to the cationic dimer **26** (Figure 3). Following a similar macrocyclization pathway (outlined for **26**), subsequent "$CH_2$ stitching" generates the desired *p-tert*-butylcalix[4]arene. Again, using similar molecular recognition events such as anion

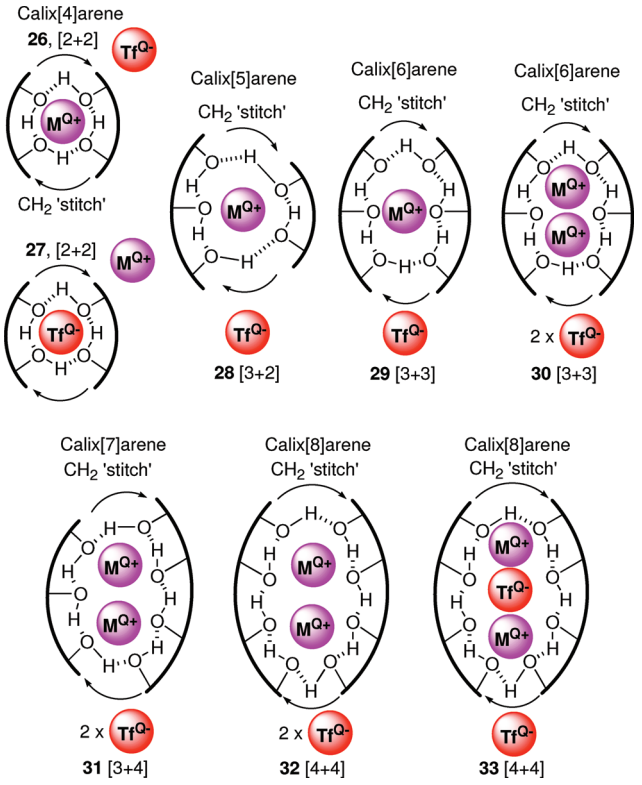


**Figure 3.** Proposed supramolecular assemblies for *p-tert*-butylcalix[*n*]arene ($n = 4-8$) **26**−**33** synthesis.

or cation coordination and trimeric, tetrameric, etc. phenol systems allows the supramolecular assembly of differently sized calixarenes to be envisaged.

With the work of Thuéry and Nierlich[22] in mind, an alternative route for the formation of the larger calixarenes appears viable. Thus, generating a supramolecular complex that incorporates multiple cationic centers, i.e. $Cu^{2+}$, $Sn^{2+}$, or $La^{3+}$ (for example **30**−**32**, Figure 3), and one anionic species encapsulated by two ortho-linked methylene tetrameric phenols affords a supramolecular complex based on **33** (Figure 3). It is interesting to note that in a recent full paper Shibasaki et al. reported[25] the formation of a novel binuclear $[La_2Li_4(binaphthoxide)_5]$ complex that incorporates five (*R*)-BINOL motifs (structural similarities to


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**22**), thus demonstrating the feasibility of the $La^{3+}$ cation to acccomodate large numbers of multicyclic phenol motifs. Subsequent "$CH_2$ stitching" of a complex based on **33** should result in a *p-tert*-butylcalix[8]arene macrocycle. The formation and possible intermediacy of an entity based on **33** could help explain the symbiotic relationship observed between certain metal centers and the anion of the salt and their preference for the formation of larger *p-tert*-butylcalixarenes.

## CONCLUSION

In summary, we report the first and only example of a one-pot calixarene synthesis from a 'monomeric' phenol that does *not* utilize base or acid. Although an exact mechanistic rationale for the generation of **2** is unclear, it may be possible that hydrogen-bonded dimers are formed and that these encapsulate cationic and or anionic species and may play an important role in calixarene formation. By way of substantiating the possibility that the formation of a supramolecular assembly be important, we refer to a 1962 *Nature* publication by Cairns and Eglinton (cited 18 times). Interestingly, given the continued debate on calixarene formation, this communication has, by and large, been overlooked by the calixarene chemistry community; it may be the case that hydrogen bond entities are formed and their involvement in calixarene synthesis is more important than might be apparent at first. This and other additional mechanistic features of the reaction are currently under investigation in our laboratories. The possibility of "fine-tuning' our metal salt mediated reaction such that the inclusion of a simple metal salt affords a specific *p-tert*-butylcalix[*n*]arene is of significant interest and promise. Results from these studies will be published in due course.

## EXPERIMENTAL SECTION

**General Protocols.** All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of argon. All commercially available chemicals, reagents, and salts were used as supplied. Microwave syntheses were performed on an Emrys Creator.

**General Procedure.** *p-tert*-Butylphenol (PTBP, 150 mg, 1 mmol), trioxane (90 mg, 1 mmol), and magnesium triflate (1 mmol) were added to dichloromethane (4 mL) in a microwave vial of 2.0−5.0 mL capacity. This heterogeneous mixture was heated (after sealing with an aluminum crimp cap with a PTFE-lined rubber seal) in the microwave synthesizer at 120 °C for 30 min. After this time, HPLC analysis of the reaction mixture indicated complete consumption of the starting material (PTBP) and the formation of a mixture of *p-tert*-butylcalix[*n*]arenes (90%). The reaction mixture was diluted with dichloromethane (10 mL) and filtered to remove solid magnesium sulfate. The insoluble solid was washed with dichloromethane (5 mL). The combined organic extracts were washed with dilute sodium bicarbonate solution (5 mL, 10%) and brine, respectively. The organic layer was dried using anhydrous magnesium sulfate and filtered and the solvent removed under reduced pressure, affording a white solid. The individual calix[*n*]arenes ($n$ = 4−9) were isolated (in 85−99% HPLC purity) by gradient flash chromatography using a cyclohexane−toluene−ethanol (90:10:00 to 60:48:2 in 120 min using 2 mL/min flow rate) solvent system (monitored by HPLC).

**HPLC Procedure.** HPLC analysis was performed on a Pursuit RP C18 column (4.6 mm i.d., 250 mm) packed with 5 $\mu$m reverse-phase silica. The analysis procedure followed was similar to that reported by Gutsche et al.[9a] The HPLC separation of calix[*n*]arenes ($n$ = 4−9) was achieved using a mixture of two eluents (at 280 nm), A and B, at a flow rate of 2 mL/min. Eluent A was MeCN with 1% AcOH, and eluent B was a mixture of $CH_2Cl_2$ and *tert*-butyl methyl ether (12:9 ratio) with 1% AcOH. An isocratic run using an 80:20 mixture of A and B for 15 min was found suitable for separation of calix[*n*]arenes ($n$ = 4−12). (Note: a significant shift in retention times was observed as a function of the variable room temperature; higher retention times were noticed under cold conditions.)

**5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene:[8].** mp 335−340 °C; FT-IR 3152, 2953, 2864, 1479, 1199 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 10.33 (br s, 1H), 7.03 (s, 2H), 4.22 (d, 1H, $J$ = 14.0 Hz), 3.46 (d, 1H, $J$ = 14.0 Hz), 1.23 (s, 9H); MS (APCI) $m/z$ calcd for $C_{44}H_{56}O_4$ 648.9, found 649.3.

**5,11,17,23,29-Pentakis(1,1-dimethylethyl)-35,36,37,38,39-pentahydroxycalix[5]arene:[8].** mp 285−288 °C; FT-IR 3262, 2957, 2868, 1484, 1201 $cm^{-1}$; $^1H$ NMR ($CDCl_3$−pyridine-$d_5$, 10%, 400 MHz) $\delta$ 8.64 (br s, 1H), 7.15 (s, 2H), 3.75 (br s, 2H), 1.18 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$ 147.8, 144.2, 128.0, 125.9, 34.1, 31.7, 31.6; MS (APCI) $m/z$ calcd for $C_{55}H_{70}O_5$ 811.1, found 811.2.

**5,11,17,23,29,35-Hexakis(1,1-dimethylethyl)-37,38,39,40,41,42-hexahydroxycalix[6]arene:[8].** mp >350 °C; FT-IR 3134, 2957, 2866, 1482, 1200 $cm^{-1}$; $^1H$ NMR ($CDCl_3$−pyridine-$d_5$, 10%, 400 MHz) $\delta$ 10.44 (br s, 1H), 7.10 (s, 2H), 3.82 (br s, 2H), 1.20 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$ 147.5, 144.5, 127.2, 126.4, 34.2, 33.5, 31.7; MS (APCI) $m/z$ calcd for $C_{66}H_{84}O_6$ 973.4, found 973.4.

**5,11,17,23,29,35,41-Heptakis(1,1-dimethylethyl)-43,44,45,46,47,48,49-heptahydroxy calix[7]arene:[8].** mp 235−238 °C (reported 249−251 °C); FT-IR 3143, 2956, 2883, 1483, 1200 $cm^{-1}$; $^1H$ NMR ($CDCl_3$−pyridine-$d_5$, 10%, 400 MHz) $\delta$ 7.15 (s, 2H), 3.88 (br s, 2H), 1.24 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$ 147.5, 144.6, 127.6, 126.3, 34.2, 33.1, 31.7; MS (APCI) $m/z$ calcd for $C_{77}H_{98}O_7$ 1135.5, found 1135.5.

**5,11,17,23,29,35,41,47-Octakis(1,1-dimethylethyl)-49,50,51,52,53,54,55,56-octahydroxy calix[8]arene:[8].** mp >360 °C; FT-IR 3191, 2953, 2348, 1485, 1201; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 9.62 (br s, 1H), 7.17 (s, 2H), 4.35 (d, 1H, $J$ = 12.8 Hz), 3.48 (d, 1H, $J$ = 12.8 Hz), 1.24 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$ 146.8, 144.9, 128.9, 125.7, 34.2, 32.5, 31.7; MS (MALDI) $m/z$ calcd for $C_{88}H_{112}O_8Na$ 1320.8, found 1320.8.

**5,11,17,23,29,35,41,47,53-Nonakis(1,1-dimethylethyl)-55,56,57,58,59,60,61,62,63-nonahydroxycalix[9]arene:** mp 302−304 °C; FT-IR 3194, 2955, 2360, 1484, 1202; $^1H$ NMR ($CDCl_3$−pyridine-$d_5$, 10%) $\delta$ 7.09 (d, 2H, $J$ = 3.3), 3.84 (br s, 2H), 1.17 (s, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 147.2, 144.5, 128.0, 125.9, 34.2, 32.6, 31.5; MS (MALDI) $m/z$ calcd for $C_{99}H_{126}O_9Na$ 1482.9, found 1483.0.

## ASSOCIATED CONTENT

**Supporting Information.** Analytical HPLC and NMR spectra for the compounds discussed in this manuscript can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

**Corresponding Author**
*E-mail: s.bew@uea.ac.uk.

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(15) All reactions were repeated two to three times to ensure consistent results.

(16) See the Supporting Information for HPLC analyses.

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