

# An expedient one-pot synthesis of *para-tert*-butylcalix[8]- and [9]arene†

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We report the first efficient synthesis of *para-tert*-butylcalix[8]-arene and -[9]arene via an exceptionally straightforward innovative protocol that takes place at ambient temperature, employing readily available tin(IV) chloride and s-trioxane.

Calixarenes have attracted substantial attention in recent years. This can be attributed to their unique structural/chemical properties allowing their use in the synthesis of diverse molecular architectures. The 'calix family' comprises the 'major', where  $n = 4, 6$  or  $8$ , the 'minor', where  $n = 5$  or  $7$ , and the 'large', where  $n = 9-20$ . Within these 'families' only the 'major' are readily available.

We now report the first example of a straightforward Lewis acid mediated synthesis of the previously very difficult to procure *para-tert*-butylcalix[9]arene which, in conjunction with *para-tert*-butylcalix[8]arene, is generated via a one-pot reaction in excellent yield. This innovative reaction proceeds readily at ambient temperature, yields the calixarenes in exceptionally high yields, uses cheap starting materials and is amenable to multi-gram scale. Scheme 1 demonstrates the remarkable nature of this reaction and its ability to synthesise complex macrocyclic entities via multiple carbon-carbon bond forming reactions at ambient temperature.

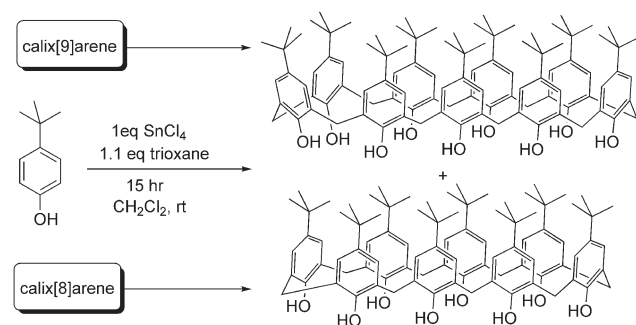
Gutsche *et al.* reported an elegant series of protocols for synthesising multi-gram quantities of the 'major' calix[ $n$ ]arenes, *i.e.*  $n = 4$  (49%),  $6$  (80%) or  $8$  (60%).<sup>1</sup> Generating substantial quantities of these calixarenes in high purity was, undoubtedly, the milestone that allowed their diverse and widespread use. For discussions on 'major' calixarene use readers are directed to a number of excellent reviews<sup>2</sup> and monographs.<sup>3</sup>

Although the prospective applications of the 'large' calixarenes are evident,<sup>4</sup> their current lack of availability is severely impeding

their potential. Presently calix[9]arene is isolated as a minor product during base promoted syntheses of calixarenes.<sup>5</sup> Separation of the calix[9]arene from the 'broth' is tedious, inefficient and time consuming, a fact that is reflected in the very poor 1–8% yields reported.<sup>5</sup> Titanium(IV) chloride has been employed for the synthesis of calix[4]arene:<sup>6</sup> furthermore, until recently it was assumed that only linear oligomers were returned from acid-catalysed reactions between *para*-substituted phenols and formaldehyde.<sup>7</sup> Unique to the work reported here, there are no reports, as far as we are aware, of any one-pot Lewis acid mediated 'large' calixarene syntheses.

We have ongoing interests in developing calix[9]arene derived species and their potential as molecular recognition agents. Recent research in our group suggests catalytic amounts of specific Lewis acids improve the yields of acid-catalysed calixarenes. It was during these studies that the strategy reported here suggested itself.

Reacting a *para-tert*-butylphenol/tin(IV) chloride (10 mol%) dichloromethane solution with s-trioxane (33 mol%) for 180 min afforded a mixture of cyclic calix[4]- to calix[9]arenes in 45% yield (Table 1) together with linear oligomers (43%). Curious about the rate of this reaction it was repeated but terminated after 30 min. HPLC analysis revealed that significant, but smaller, amounts of calix[ $n$ ]arenes [ $n = 5-7$  (6.9%) and  $8$  (5%)] had formed with calix[4]arene the major component at 14%. That 92% of the *para-tert*-butylphenol had been consumed within 30 min indicated to us the efficiency of the reaction and, potentially, calixarene synthesis. Table 1 outlines how increasing the tin(IV) chloride influences the resulting calixarene concentrations. It is not surprising, given the efficiency of the reaction, that as the tin(IV) chloride concentration is increased from 2, 10, 25, 50 and 100 mol% the *para-tert*-butylphenol is steadily consumed, *i.e.*, 88% to <1%. Interestingly, a simultaneous gradual decline in calix[4]arene concentration is also observed, *i.e.*, peaking at 14% (10 mol% SnCl<sub>4</sub>) but dropping to 1% at 50 mol% SnCl<sub>4</sub>. In contrast, our attention was drawn to the calix[8]- and [9]arene concentrations that, quite remarkably, gradually increased, *i.e.*, 5% to 55.3% and 2.4% to 29.8%,



**Scheme 1** Lewis acid mediated synthesis of calix[8]- and [9]arene.

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**Table 1** Effect of tin(IV) chloride concentration on the yields of calix[ $n$ ]arenes

Conc. (%)	Time/min	s/m	Oligo (%)	[4]%	[5]-[7]%	[8]%	[9]%
2 mol	30	88	11	0.5	—	—	—
2 mol	180	36	58	5	0.4	—	—
10 mol	30	8	63	14	6.9	5	2.4
10 mol	180	2.1	43	5.3	21	13.4	6.2
25 mol	30	1.8	15	1.7	33.2	26.3	11.8
25 mol	180	1.4	13	2.7	29.2	25.2	9.9
50 mol	30	1.4	13	0.9	19.9	35.3	12.4
100 mol	60	<1	3	1.6	4.9	55.3	29.8
200 mol	60	Black precipitate formed: no analysis undertaken					

**Table 2** Yields of calix[4]–[9]arene using microwave irradiation and varying concentrations of tin(IV) chloride

2 mol% SnCl <sub>4</sub> , microwave irradiation at 120 °C for 30 min					
Calix[4]	Calix[5]	Calix[6]	Calix[7]	Calix[8]	Calix[9]
5.3%	4.7%	14.8%	25.1%	24.2%	12.3%
10 mol% SnCl <sub>4</sub> , microwave irradiation at 75 °C for 15 min					
Calix[4]	Calix[5]	Calix[6]	Calix[7]	Calix[8]	Calix[9]
2.7%	2.9%	10.8%	20.1%	22.8%	9.9%
100 mol% SnCl <sub>4</sub> , microwave irradiation at 60 °C for 1 min					
Calix[4]	Calix[5]	Calix[6]	Calix[7]	Calix[8]	Calix[9]
4.2%	0.5%	7.9%	5.2%	54.7%	17.0%

respectively, as the tin(IV) chloride increased from 10 mol% to 100 mol%. Anticipating 200 mol% of tin(IV) chloride may enhance the yields of calix[8]- and [9]arene we were disappointed that decomposition resulted. These preliminary results suggest that an increase in the yield of calix[8]- and [9]arenes seems inextricably linked to the quantity of Lewis acid employed which, in turn, may be affording the calixarenes *via* a unique mechanism.

We pondered over the possibility that increasing the temperature may not only afford a faster reaction but also a more selective one. Following Scheme 1, utilising 2 mol% of tin(IV) chloride at ambient temperatures, no calix[5]–[9]arene formation was observed (Table 1). Remarkably, repeating this reaction at 120 °C under microwave irradiation afforded an 86% yield of calix[4]–[9]arenes (Table 2), with substantial amounts of calix[6]- to [8]arene (14.8%, 25.1% and 24.2%, respectively). As was previously observed (Table 1), as the concentration of the tin(IV) chloride increases so does the yield of calix[8]- and, to a more limited extent, calix[9]arene, *i.e.* 24.2% to 54.7% and 12.3% to 17%, respectively. These preliminary results indicate that the temperature/catalyst concentration has a substantial effect on the yield of calix[8]- and [9]arene. Interestingly, the composition of the reaction mixture when tin(IV) chloride (2 mol%) was employed mirrors those reported by Gutsche *et al.* for their acid-catalysed protocol.<sup>7</sup> Presumably the 2 mol% of tin(IV) chloride is hydrolysed by the *para-tert*-butylphenol, generating *in situ* HCl that subsequently catalyses calixarene formation in a process similar to that reported by Gutsche *et al.*

We deliberated on the possibility that the tin(IV) chloride could be acting as a macrocycle template. Following a protocol based on that outlined in Scheme 1, anhydrous iron(III) chloride or tin(II) chloride returned linear oligomers only. Zinc chloride and aluminium trichloride, under microwave irradiation (120 °C, 30 min) but not ambient temperature, afforded complex mixtures of calixarenes, linear oligomers and retro-Friedel–Crafts products. Titanium(IV) ethoxide afforded no calixarene products. With titanium(IV) chloride the reaction went black and decomposition took place. This again suggested that macrocycle formation was proceeding *via* a unique mechanism that was intimately linked to the Lewis acid employed, *i.e.*, tin(IV) chloride.

A study was undertaken to probe for any solvent effects. Employing toluene as the solvent, *para-tert*-butylphenol, *s*-trioxane and tin(IV) chloride (all 1 eq<sup>n</sup>) at ambient temperature afforded only linear oligomers. Interestingly, when toluene was substituted for a more polar, potentially co-ordinating Lewis basic solvent, *i.e.* acetonitrile, THF, dioxane or diglyme, no reaction was observed. This lack of reaction contrasted sharply with that when halogenated solvents were employed. Chloro/bromobenzene, carbon tetrachloride and chloroform all afforded calix[*n*]arenes

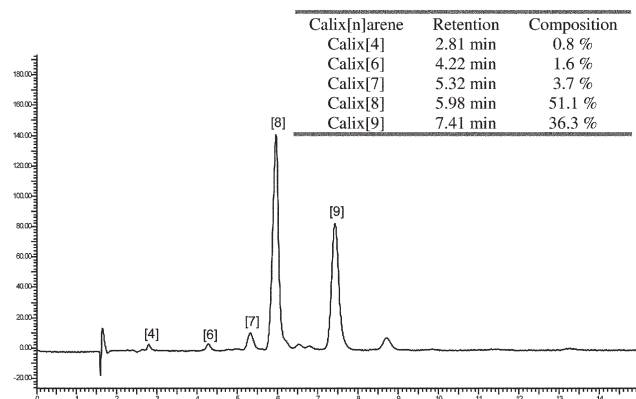
**Table 3** Chlorinated solvents utilized for calix[*n*]arene synthesis

Solvent	Time/h	[4]%	[5]–[6]%	[7]%	[8]%	[9]%
C <sub>6</sub> H <sub>5</sub> Cl	1	0.9	9.0	10.2	19.7	5.8
C <sub>6</sub> H <sub>5</sub> Cl	15	5.6	18.7	12.2	43.4	9.2
C <sub>6</sub> H <sub>5</sub> Br	1	2.8	9.9	12.3	20.9	6.2
C <sub>6</sub> H <sub>5</sub> Br	15	5.7	18.1	14.9	46.2	10.8
CCl <sub>4</sub>	1	5.0	4.1	5.7	7.9	1.9
CCl <sub>4</sub>	15	7.0	4.2	8.1	11.4	2.8
CHCl <sub>3</sub>	1	—	6.2	6.4	12.1	3.2
CHCl <sub>3</sub>	15	5.2	14.1	8.9	52.8	11.2
(CH <sub>2</sub> Cl) <sub>2</sub>	1	—	1.8	3.7	57.8	28.1
(CH <sub>2</sub> Cl) <sub>2</sub>	15	—	—	6.8	58.1	32.7
CH <sub>2</sub> Cl <sub>2</sub>	1	1.8	7.1	4.9	46.1	24.2
CH <sub>2</sub> Cl <sub>2</sub>	15	0.8	1.6	3.7	51.1	36.3

after 15 h with calix[8]arene predominating in each case (Table 3). Interestingly, when DCM and 1,2-DCE were utilised calix[8]arene was returned in 51.1% and 58.1% yields, respectively, whilst calix[9]arene was afforded in an exceptionally high 36% (Fig. 1) and 33% yields, respectively. Employing the alternative Lewis acids mentioned above in chlorinated solvents failed to return any substantial amounts of calixarenes.

Separation and purification of calix[9]arene, a minor product of the Gutsche acid catalysed procedure, is complicated and time consuming (the Gutsche procedure affords mixtures of calix[*n*]arenes *n* = 9–11).<sup>7</sup> Presumably for this reason the realisation of calix[9]arenes' full potential has been severely impeded. The straightforward and uncomplicated nature of our protocol affording excellent yields of calix[8]- and [9]arene suggested itself as a possible solution. Gratifyingly, quenching a reaction performed on 3 g of *para-tert*-butylphenol with aqueous acid (1 M HCl), extraction of the calixarenes into dichloromethane and filtration of the solution through silica afforded, after solvent removal, 2.1 g of calix[8] and [9]arenes.<sup>8</sup> Refluxing (2 h) this pale yellow solid with *n*-hexane (15 mg mL<sup>-1</sup>) and cooling to ambient temperature precipitated calix[8]arene (95% pure by HPLC, Fig. 2).

Filtering the precipitated calix[8]arene off and removal of the *n*-hexane *in vacuo* afforded a solid significantly enriched in calix[9]arene. Subjecting this crude calix[9]arene containing mixture to flash chromatography afforded analytically pure calix[9]arene in an isolated 23% yield based on 2.1 g of crude material (99% pure by HPLC, Fig. 3). The corresponding calix[8]arene was afforded in an isolated 55% yield (total yield 78%) with the remaining mass

**Fig. 1** HPLC chromatogram of the reaction mixture using CH<sub>2</sub>Cl<sub>2</sub> solvent after 15 h.

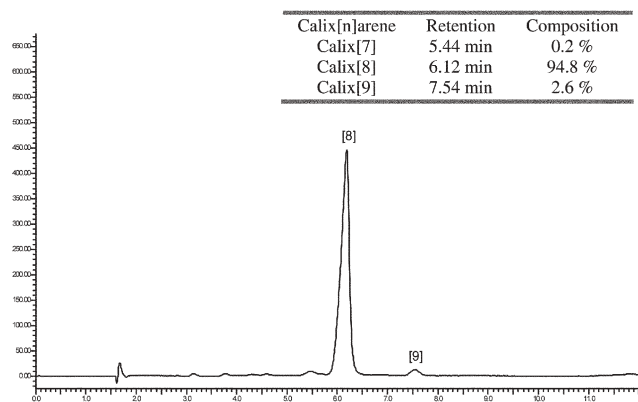


Fig. 2 HPLC chromatogram of the n-hexane insoluble precipitate.

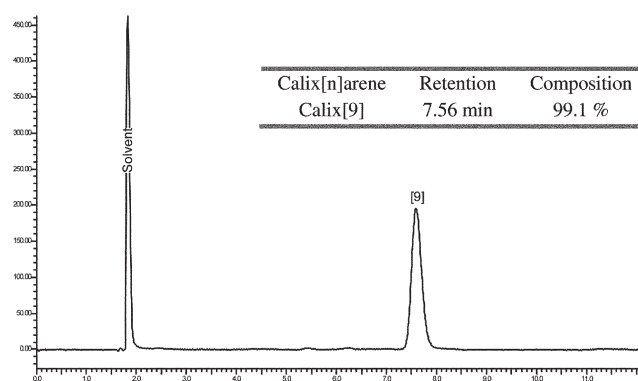


Fig. 3 HPLC chromatogram of the fractions containing pure calix[9]arene after column chromatography.

balance (22%) comprising a mixture of the two calixarenes which could, if desired, be purified *via* further chromatography. It is worthy of note that the reported isolated yields by Lamartine *et al.*<sup>5b</sup> and Gutsche *et al.*<sup>7</sup> are 1.26% and 8.6%, respectively, and in this respect our Lewis acid mediated procedure represents a significant advance. Furthermore, and worthy of note, is the fact that our purification protocol<sup>8</sup> affords, if desired, calix[6]–[9]arenes *via* a procedure that is considerably simpler than current literature protocols and importantly does not require the use of the extremely flammable and highly toxic carbon disulfide as the chromatography solvent.<sup>7</sup>

Conventional base promoted syntheses of calix[4]-, -[6] and -[8]arene are amenable to their production in multi-gram

quantities. We are currently exploring the synthesis of multi-gram quantities of calix[9]arene using the tin(IV) chloride protocol outlined here: initial results are encouraging, both the mass balance and ratio of calix[8]- and -[9]arene (60:30 respectively) were unaffected when performed on a 24 g scale.

In conclusion, we have identified an innovative tin(IV) chloride mediated reaction that is a highly efficient, one-pot synthesis of calix[8]- and -[9]arene.<sup>9</sup> This is the first metal-mediated synthesis of ‘large’ calixarenes; although further work is required it is feasible that they are synthesised *via* a *unique* metal-template mechanism. We have also developed a straightforward purification procedure that affords analytically pure calix[8]- and -[9]arene. The protocol outlined here has significant potential, further augmenting the calixarene ‘tool-box’ and extending the useful range of calixarenes beyond calix[8]arene such that calix[9]arene can now be considered part of the ‘family’.

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- See the ESI for representative synthetic procedures as well as analytical/characterisation data, *i.e.*, <sup>1</sup>H, <sup>13</sup>C, MALDI mass spectra, FT-IR, mp and analytical HPLC data associated with the synthesis and purification of calix[8]arene and calix[9]arene.
- A mechanistic study based on the work reported here for calix[8]- and -[9]arene will be the subject of a forthcoming paper.