Ferrocenium salts mediate *para-tert*-butylcalixarene synthesis†‡

Sean P. Bew,* Myles R. Cheesman and Sunil V. Sharma

Received (in Cambridge, UK) 11th August 2008, Accepted 12th September 2008
First published as an Advance Article on the web 1st October 2008
DOI: 10.1039/b813789g

Ferrocenium salts mediate high yielding one-pot and convergent syntheses of *para-tert*-butylcalixarenes in mild non-Lewis or Brønsted acidic reaction conditions; EPR indicates complex formation between the *s*-trioxane and the ferrocenium salt.

We report the first organometallic initiated synthesis of calixarenes. Ferrocenium salts ($[Fc]^+X^-$) are efficient, unique reagents that in combination with microwave irradiation afford calixarenes in high yields *via* a one-pot procedure (Scheme 1). Interestingly the ratio of *para-tert*-butylcalix[4]–[9]arenes synthesised *via* our ferrocenium salt protocol differs substantially from those using a conventional Brønsted acid. As far as we are aware, there are *no* reports of organometallic complexes being used to generate calixarenes.

Calix[4]arenes (first reported by von Baeyer in 1872 and subsequently by Alois Zinke in the 1940s[1]) are one of the most extensively studied and widely employed synthetic hosts. Indeed Seiji Shinkai referred to them as the '3rd generation' supramolecular host,[2] the 1st and 2nd being cyclodextrins and crown ethers, respectively. Their unique structures have lent themselves to a plethora of applications[3] in synthetic, material, analytical, supramolecular and biological chemistries. Given the importance and time that calixarenes have been known, it is remarkable that so few protocols exist for their synthesis. Thus Gutsche *et al.* reported a series of protocols for calixarene generation using *para*-substituted phenols, a source of formaldehyde, a suitable solvent and either: (i) tosic acid[4] or (ii) sodium or potassium hydroxide.[5] Alternatively Lewis acids afford unsymmetrical calix[4]arenes *via* [3 + 1] and/or [2 + 2] protocols.[6]

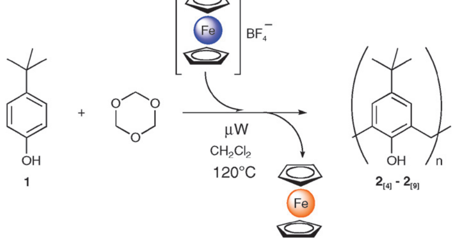
Ongoing interests in our laboratory focus on developing and investigating new calixarene syntheses and their applications.[7] In this context we considered the possibility that if a suitable and mild oxidising agent be utilised, it may be possible to chemoselectively oxidise the hydroxyl group on **1** such that an intermediary species is produced which may, *via* one or more of a series of radical and or condensation reactions, be transformed into calixarenes *i.e.* $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$.

The starting point for our study probed the use of silver triflate as a convenient oxidizing agent. Stirring a stoichiometric quantity of silver triflate, *s*-trioxane and **1** at ambient temperature afforded unreacted **1** in good mass balance. Repeating this reaction at 120 °C (6 h, oil bath) we isolated $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, in an excellent 95% yield (see ESI for $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, distribution†). Disappointingly when the heterogeneous reaction was microwave irradiated (120 °C) in an attempt to reduce the reaction time from hours to minutes the reaction tube exploded (deposited Ag° may have formed 'hot' spots).

Ferrocenium tetrafluoroborate ($[Fc]^+BF_4^-$) is a 17-electron, non-Lewis acidic metallocene. Due to its 17-electron status $[Fc]^+BF_4^-$ is not able to undergo Lewis acid mediated reactions but does instead proceed *via* single electron-transfer or one-electron oxidative processes that result in the formation of ferrocene (18-electron species). The capacity of $[Fc]^+BF_4^-$ to oxidize phenols to phenoxy radicals is known. Thus with the intention of developing an innovative synthesis of the calixarenes we undertook a focused preliminary study on the use of $[Fc]^+BF_4^-$ for their generation. The results of this initial study are the subject of this Communication.

At ambient temperature $[Fc]^+BF_4^-$ is only sparingly soluble in dichloromethane (affording a very pale green solution) however upon addition of **1** (1 equiv.) the solution immediately turns a clear dark blue (phenoxy radical formation[8] or formation of a charge transfer complex?, Scheme 2) with some (~50%) of the previously insoluble $[Fc]^+BF_4^-$ dissolving. Subsequent addition of *s*-trioxane (solution turns purple) and heating (μW, 30 min, no explosion) affords a clear green solution. Suspecting that the initial blue colour upon addition of $[Fc]^+BF_4^-$ to **1** was attributable to formation of a phenoxy radical raised concerns about the ability of phenoxy radicals to dimerise (reversibly) resulting in biaryl ether formation.[8] Scrutinising the reaction *via* ^{1}H-NMR after microwave irradiation but before purification we could find *no* evidence for the formation of any radical dimerisation adducts; furthermore purification (flash chromatography) and analysis (analytical HPLC and ^{1}H-NMR) confirmed the formation of $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, in an unoptimised 88% yield.

Gutsche *et al.* demonstrated that using a Brønsted acid (tosic acid, 3 mol%) afforded mixtures of the macrocycle that contained significant quantities *i.e.* ~20% of "large" calixarenes *i.e.* $\mathbf{2}_{[10]}$–$\mathbf{2}_{[20]}$, even when the reactions were undertaken



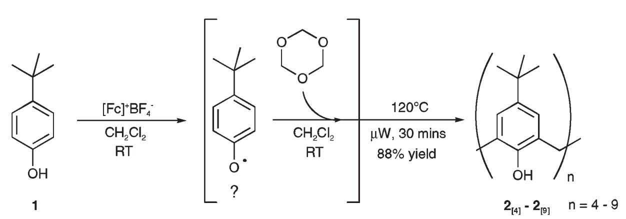
2	n	amount
$2_{[4]}$	4	14%
$2_{[5]}$	5	9%
$2_{[6]}$	6	18%
$2_{[7]}$	7	23%
$2_{[8]}$	8	16%
$2_{[9]}$	9	6%

Scheme 1 Synthesis of $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, using ferrocenium tetrafluoroborate.

School of Chemical Sciences & Pharmacy, University of East Anglia, Norwich, Norfolk, UK. E-mail: s.bew@uea.ac.uk;
Fax: +44(0)1603 592003; Tel: +44(0)1603 593142

† This Communication is dedicated to Professor Seiji Shinkai on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures, HPLC analysis and spectral data for **2**, **3**, **4**. See DOI: 10.1039/b813789g



Scheme 2 Ferrocenium tetrafluoroborate oxidation of **1**.

at low concentrations.[4] Interestingly analysing our $[Fc]^+BF_4^-$ mediated reaction (HPLC, Varian Pursuit RP C18, 4.6 mm × 250 mm) little evidence for any "large" calixarenes was found. Furthermore comparing the calixarene compositions afforded *via* the Brønsted acid and $[Fc]^+BF_4^-$ reactions a significant difference was noted. The $[Fc]^+BF_4^-$ mediated process comprised $\mathbf{2_{[4]}}$, $\mathbf{2_{[5]}}$, and $\mathbf{2_{[6]}}$, at 41% (14%, 9% and 18%, respectively); for the tosic acid reaction the same calixarenes amounted to only 14% *i.e.* 2.5%, 2% and 10% for $\mathbf{2_{[4]}}$, $\mathbf{2_{[5]}}$, and $\mathbf{2_{[6]}}$, respectively. The sizeable difference in product composition is tantalising evidence that these reactions may be following dissimilar mechanisms.

We sought evidence that the hydroxyl group of **1** was required for the formation of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$. Thus we attempted to synthesise *O*-alkylated calixarenes by substituting **1** for *O*-propyl-*para*-*tert*-butylphenol. Confirming the importance of a free phenolic hydroxyl for calixarene generation the reaction returned unreacted starting material in a good mass balance.

Probing the specific and key role of the $[Fc]^+BF_4^-$ (Scheme 2) it was switched for the reductant cobaltocenium hexafluorophosphate *i.e.* $[Co]^+PF_6^-$ ($[Co]^+BF_4^-$ was not commercially available). Our assumption was that the $[Co]^+PF_6^-$ would not be able to oxidise the phenolic hydroxyl or act as a Lewis acid and as a result the reaction would shut down. Gratifyingly, on incorporating $[Co]^+PF_6^-$ into our standard conditions (Scheme 1) no colour change was observed and, more importantly, analytical HPLC analysis confirmed that no linear oligomers or calixarenes had formed (a good mass balance of **1** was returned). This significant result substantiates the importance of employing a ferrocenium complex *i.e.* single-electron oxidant for the formation of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$. Although not a major concern we did consider the possibility that the PF_6^- counter-anion of the $[Co]^+PF_6^-$ was having a deleterious effect within the reaction. Investigating this we substituted $[Co]^+PF_6^-$ for $[Fc]^+PF_6^-$; $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$, were afforded in an 86% yield; thus confirming that the PF_6^- anion was not responsible for the failure of the $[Co]^+PF_6^-$ reaction.

Ferrocene (generated from the reduction of $[Fc]^+BF_4^-$) is a poor Lewis acid. Although ferrocene was not thought to play a critical role (perhaps acting as a weak Lewis acid) in the generation of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$, it was considered important to test for any effect the 18-electron species may be having. Substituting $[Fc]^+BF_4^-$ for ferrocene (stoichiometric quantity) afforded no reaction or colour change (either before or after heating).

If the $[Fc]^+BF_4^-$ were acting simply as a catalytic or stoichiometric source of Brønsted acid then, similar to conventional Gutsche *et al.* tosic acid mediated calixarene syntheses, we would expect sub-stoichiometric quantities of $[Fc]^+BF_4^-$ to return $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$. Anticipating that 20 or 50 mol% quantities of $[Fc]^+BF_4^-$ would afford, if not good yields (*viz.* 88%) of calixarenes, then at the very least levels of calixarenes commensurate with the quantity of $[Fc]^+BF_4^-$ employed we were surprised that starting material **1** was returned in 98% and 97% yields respectively. These results provide evidence for an inextricable link between the quantity of $[Fc]^+BF_4^-$employed and the possibility that a non-Brønsted or Lewis acid mechanism is operating, that requires equimolar quantities of $[Fc]^+BF_4^-$ for the synthesis of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$.

Discounting the possibility that *in situ* generated ferrocene was acting as a Lewis acid, our attention again focused on the possibility that an *in situ* generated Brønsted acid *i.e.* tetrafluoroboric acid could be responsible for the formation of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$, *via* a mechanism akin to that reported by Gutsche and Stewart.[4] Probing this theory we substituted $[Fc]^+BF_4^-$ for an aqueous or an ethereal solution of tetrafluoroboric acid. Substantiating our theory that the reaction proceeds *via* a single-electron transfer process both these Brønsted acid reactions afforded significantly inferior 57% and 65% yields of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$, (*viz.* $[Fc]^+$ salts ~90%) with 39% and 31% of linear oligomers formed respectively. Clearly the inferior yields of $\mathbf{2_{[4]}}$–$\mathbf{2_{[9]}}$, obtained with the tetrafluoroboric acids indicate that the $[Fc]^+BF_4^-$ salts are not acting simply as a source of Brønsted acid; if this was the case then it is difficult to explain the observed excellent yields obtained with $[Fc]^+BF_4^-$. Furthermore the non-Lewis acidic nature of the ferrocenium salts make it improbable that the reaction proceeds *via* a 19-electron complex comprising the $[Fc]^+BF_4^-$ and either the *para*-*tert*-butylphenol or *s*-trioxane.

Using NMR as our investigative tool and within the detection limits of ^{1}H-NMR (300 MHz) we found no evidence for the formation of any new species (*viz.* blue colour) when equimolar quantities of $[Fc]^+BF_4^-$ and *s*-trioxane or *para*-*tert*-butylphenol were mixed (independently) both at ambient temperature (60 min) and subsequently after microwave irradiation (120 °C, 30 min). Intrigued by the possibility that a radical species was generated we employed EPR to probe the reaction (Scheme 1). Freezing (liquid nitrogen) a mixture of $[Fc]^+BF_4^-$ and **1** (after µW, 120 °C, 30 min) allowed the EPR spectra (9.7 GHz) to be recorded (Fig. 1a). The features labelled with their *g*-values are consistent with the highly anisotropic spectra previously reported for ferrocenium.[9]

No additional features were observed at temperatures up to 40 K. Importantly no sharp features at ~2.001 characteristic of radical species were observed. We cannot, however, rule out

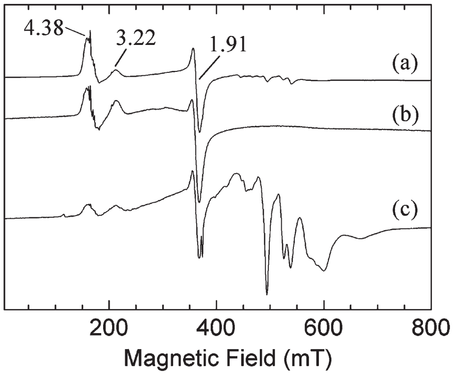
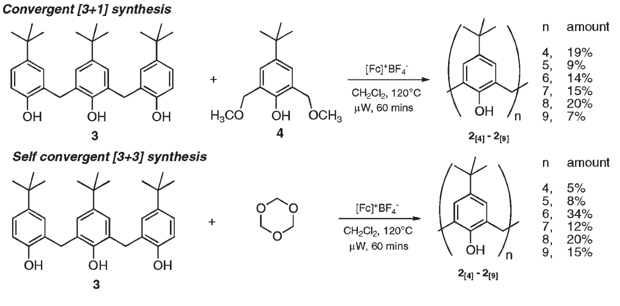


Fig. 1 X-Band EPR of $[Fc]^+BF_4^-$ complexes (2 mW, 10 K).

the presence of an EPR silent Fe^{III}-phenoxy radical complex. EPR of a mixture of $[Fc]^+BF_4^-$ and *s*-trioxane (60 min, rt) similarly detected no radical species (Fig. 1b). Subsequent μW irradiation and EPR analysis did not afford any evidence for the formation of an *s*-trioxane radical complexed to an Fe^{II} species. It did however reveal a new set of signals at high-field (400–700 mT, Fig. 1c). These we attribute to the formation of a new metal species, presumably formed between the *s*-trioxane and the Fe^{III} metal center of $[Fc]^+BF_4^-$.

Advocating innovative applications of $[Fc]^+BF_4^-$ (1 equiv.) we considered its use as a mild and efficient reagent for promoting a [3 + 1] convergent synthesis of calixarenes. In general convergent [3 + 1] syntheses of calixarenes employ multiple equivalents of strong Lewis acids *i.e.* titanium(IV) chloride and afford very poor to moderate yields *i.e.* 15–38%.[6] Previous work in our laboratory indicated **4** to be a "problematic" substrate for inclusion within a tin(IV) chloride mediated [3 + 1] convergent synthesis.[7] Thus attempting to use **4** and $[Fc]^+BF_4^-$ within a convergent (chemoselective?) calixarene synthesis it was not clear that the reaction would work. Gratifyingly heating a solution of **3**, **4** and $[Fc]^+BF_4^-$ afforded an excellent 90% yield of $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, (Scheme 3). Furthermore HPLC analysis confirmed the percentage of $\mathbf{2}_{[4]}$ had increased, as anticipated, by 36% to 19% (relative to $\mathbf{2}_{[4]}$ generated in Scheme 1). This result is even more remarkable when compared to the percentages of $\mathbf{2}_{[4]}$ generated within Gutsche's "conventional" tosic acid procedure,[4] with an 87% increase *i.e.* 2.5% to 19% of $\mathbf{2}_{[4]}$.

The exciting and interesting prospect of "chemically tuning" the $[Fc]^+BF_4^-$ mediated protocol such that increased quantities of specific calixarenes were formed merited further investigation. The increased percentage of $\mathbf{2}_{[4]}$ arising from **3** and **4** suggested the possibility that in the absence of **4** the reaction between **3**, *s*-trioxane and $[Fc]^+BF_4^-$ may afford increased quantities of $\mathbf{2}_{[6]}$ *via* a previously unknown *self*-convergent [3 + 3] protocol (Scheme 3). Reacting **3**, *s*-trioxane and $[Fc]^+BF_4^-$ afforded $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, in an excellent 93% yield. Gratifyingly, HPLC analysis confirmed, as predicted, the major product at 34% to be $\mathbf{2}_{[6]}$, (*viz.* Gutsche *et al.* 10%[4] and 14% Scheme 3), whilst the amount of $\mathbf{2}_{[4]}$ present *i.e.* 5% (Scheme 3) had undergone a 4-fold reduction.



Scheme 3 Convergent syntheses of $\mathbf{2}_{[4]}$–$\mathbf{2}_{[9]}$, using $[Fc]^+BF_4^-$.

In summary, we report the unique application of $[Fc]^+BF_4^-$ for the synthesis of calixarenes *via* an exceptionally mild, high yielding and time-efficient protocol that proceeds *via* a one-pot or convergent strategy. A particularly exciting aspect of our preliminary results suggests that application of $[Fc^+]BF_4^-$ to previously unreactive convergent strategies to be an innovative, chemoselective route capable of generating specific calixarenes. The minutiae of the reaction including mechanistic features, a full investigation into the scope, the use of catalytic quantities of ferrocenium salts and possible alternative applications are currently under investigation.

Notes and references

1 C. D. Gutsche, in *Calixarenes—Mongraphs in Supramolecular Chemistry*, Royal Society of Chemistry, Cambridge, 1989.

2 S. Shinkai, *Tetrahedron*, 1993, **49**, 8933.

3 (*a*) M. X. Wang and H. B. Yang, *J. Am. Chem. Soc.*, 2004, **126**, 15412; (*b*) U. Darbost, M. N. Rager, S. Petit, I. Jabin and O. Reinaud, *J. Am. Chem. Soc.*, 2005, **127**, 8517; (*c*) K. Moon and A. E. Kaifer, *J. Am. Chem. Soc.*, 2004, **126**, 15016; (*d*) C. Hippius, F. Schlosser, M. O. Vysotsky, V. Böhmer and F. Wurthner, *J. Am. Chem. Soc.*, 2006, **128**, 3870; (*e*) J. L. Atwood, G. A. Koutsantonis and C. L. Raston, *Nature*, 1994, **368**, 229; (*f*) P. K. Thallapally, L. Dobrzanska, T. R. Gingrich, T. B. Wirsig, L. B. Barbour and J. L. Atwood, *Angew. Chem., Int. Ed.*, 2006, **45**, 6506; (*g*) R. Zadmard and T. Schrader, *Angew. Chem., Int. Ed.*, 2006, **45**, 2703; (*h*) D. L. Dermody, R. M. Crooks and T. Kim, *J. Am. Chem. Soc.*, 1996, **118**, 11912; (*i*) Y. Kubo, S. Maeda and S. Tokita, *Nature*, 1996, **382**, 522; (*j*) R. K. Castellano, B. H. Kim and J. Rebek, *J. Am. Chem. Soc.*, 1997, **119**, 12671; (*k*) A. Wu and L. Isaacs, *J. Am. Chem. Soc.*, 2003, **125**, 4831; (*l*) A. M. Rincon, P. Prados and J. de Mendoza, *J. Am. Chem. Soc.*, 2001, **123**, 3493; (*m*) L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469; (*n*) Y. Rondelez, M.-N. Rager, A. Duprat and O. Reinaud, *J. Am. Chem. Soc.*, 2002, **124**, 1334; (*o*) A. Casnati, S. Cellai and R. Ungaro, *J. Am. Chem. Soc.*, 2006, **128**, 14528; (*p*) L. Baldini, A. Casnati, F. Sansone and R. Ungaro, *Chem. Soc. Rev.*, 2007, **36**, 254; (*q*) K. D. Shimizu and J. Rebek, *Proc. Natl. Acad. Sci. U. S. A.*, 1995, **92**, 12403; (*r*) D. Buccella and G. Parkin, *J. Am. Chem. Soc.*, 2006, **128**, 16358; (*s*) H.-H. Yu, A. E. Pullen, M. G. Büschel and T. M. Swager, *Angew. Chem., Int. Ed.*, 2004, **43**, 3700; (*t*) M. A. McKervey and D. Diamond, *Chem. Soc. Rev.*, 1996, **25**, 15; (*u*) I. Vatsouro, V. Rudzevich and V. Böhmer, *Org. Lett.*, 2007, **9**, 1375; (*v*) L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469; (*w*) F. Szemes, M. G. B. Drew and P. D. Beer, *Chem. Commun.*, 2002, **111**, 1228; (*x*) P. D. Beer and J. Cadman, *Coord. Chem. Rev.*, 2000, **205**, 131.

4 D. R. Stewart and C. D. Gutsche, *J. Am. Chem. Soc.*, 1999, **121**, 4136.

5 (*a*) C. D. Gutsche and M. Iqbal, *Org. Synth.*, 1990, **68**, 234; (*b*) M. Makha, C. L. Raston, B. W. Skelton and A. H. White, *Green Chem.*, 2004, **6**, 158.

6 (*a*) V. Böhmer, L. Merkel and U. Kunz, *J. Chem. Soc., Chem. Commun.*, 1987, 896; (*b*) M. Backes, V. Böhmer, G. Ferguson, C. Gruttner, C. Schmidt, W. Vogt and F. Ugozzoli, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1193.

7 (*a*) S. P. Bew and S. V. Sharma, *Chem. Commun.*, 2007, 975; (*b*) S. P. Bew, R. A. Brimage, N. L'Hermite and S. V. Sharma, *Org. Lett.*, 2007, **9**, 3713.

8 E. R. Altwicker, *Chem. Rev.*, 1967, **67**, 475.

9 (*a*) R. Prins, *Mol. Phys.*, 1970, **19**, 603; (*b*) C. Elschenbroich, E. Bilger, R. D. Ernst, D. R. Wilson and M. S. Kralik, *Organometallics*, 1985, **4**, 2068; (*c*) T. Sixt, J. Fiedler and W. Kaim, *Inorg. Chem. Commun.*, 2000, **3**, 80.