ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue



Check for updates

Cite this: *Chem. Commun.*, 2021, **57**, 11045

Received 19th August 2021,
Accepted 29th September 2021

DOI: 10.1039/d1cc04607a

rsc.li/chemcomm

# Facile synthesis of a $C_4$-symmetrical inherently chiral calix[4]arene†

Luke Hodson, Kevin J. Visagie, Michael-Phillip Smith, Leigh Loots, David Kuter, Trégen M. Snayer and Gareth E. Arnott*

**Inherently chiral calix[4]arenes with $C_4$-symmetry are extremely rare and difficult to synthesise, severely hampering any effort to expand on their potential as chiral supramolecular catalysts and building blocks. Herein we report a reaction of a tetracarbamate calix[4]arene with NBS which results in a high yield of an inherently chiral calix[4]arenes with $C_4$-symmetry. Furthermore, employing a chiral *N*-Boc proline moiety allows for separation of the diastereomers formed, thus obtaining the pure enantiomers after hydrolysis. The enantiomers could be assigned based on the CD spectra and DFT calculated values.**

Calix[4]arenes have for many years drawn the attention of researchers owing to their defined three dimensional shape and ease of synthesis. An intriguing aspect of calixarenes is their modification to generate so-called inherently chiral structures, whose chirality is not associated with the more common point chirality of tetrahedral carbon atoms.[1,2] There are four main strategies that give rise to inherently chiral calix[4]arenes (see Fig. 1a), although combinations of these themes can also be employed.

For us, the *meta*-functionalization‡ strategy has resonated as it has flavors of planar chiral ferrocenes, which have been used extensively in asymmetric catalytic processes. The synthetic pathways to *meta*-functionalized calixarenes has recently been reviewed,[3] with the majority of these methods functionalizing only one or two of the aryl rings, resulting in chiral $C_1$- or $C_2$-symmetrical calix[4]arenes. The construction of chiral $C_4$-symmetrical calixarenes, *i.e.* where all four aryl rings have been *meta*-functionalized, has only ever been achieved through the so-called fragment condensation route, first described in the early 1990s.[4,5] The major problem with this method is that very low yields are obtained, typically less than 30% for the cyclisation step, notwithstanding the low yields for steps needed to synthesize the fragments themselves.

Functionalizing a calix[4]arene in the *meta*-position has been achieved in distinct ways such as intramolecular ring closing,[6–9] the *p*-bromodienone route[10] or directly using mercury(II) trifluoroacetate.[11,12] More commonly though this is achieved through the use of directing groups (DG) placed in the *para*-position (*i.e.* upper rim) of the calix[4]arene. In the literature, the DGs used include ethers,[13] amides,[14,15] oxazolines[16] and sulfoxides,[17,18] but in the majority of these cases only one DG was attached to the calix[4]arene. The number of potential compounds and side-products grows with each additional DG, becoming a rather daunting task (see Fig. 1b). The calix[4]arene is nevertheless unlikely to be functionalized at all eight positions at once, since steric and electronic factors would make this difficult. However, if tetra-*meta*-functionalization could be synthetically achieved (*i.e.* avoiding any mono, di and tri-functionalized side-products), then only four possible isomers are possible, with two of these being inherently chiral (Fig. 2). Of interest, is that there do not

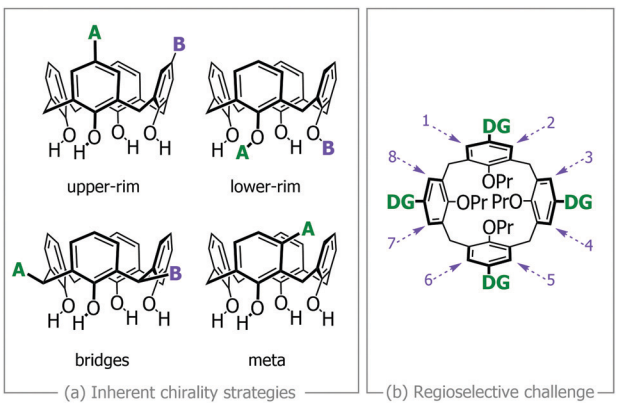



Fig. 1 Strategies for creating inherently chiral calix[4]arene: (a) the four main ways of generating inherent chirality (A and B may be any chemically distinct group),[2] (b) the regioselectivity challenge in functionalising multiple *meta*-positions (DG = any directing group).

*Department of Chemistry and Polymer Science, Stellenbosch University, Private Bag X1, Matieland, 7602, South Africa. E-mail: arnott@sun.ac.za*

† Electronic supplementary information (ESI) available. CCDC 2104244. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc04607a

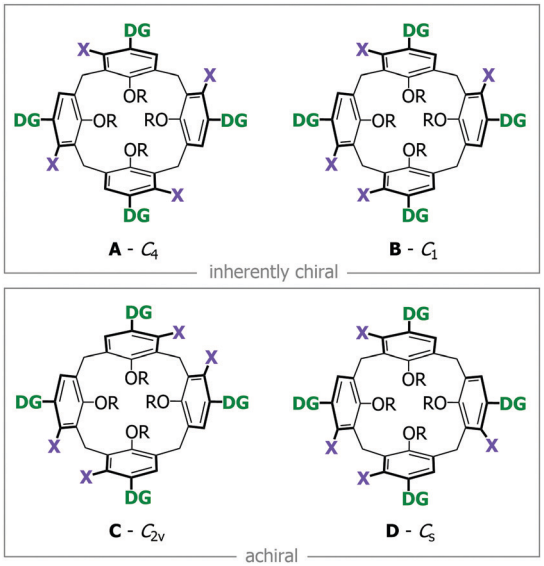
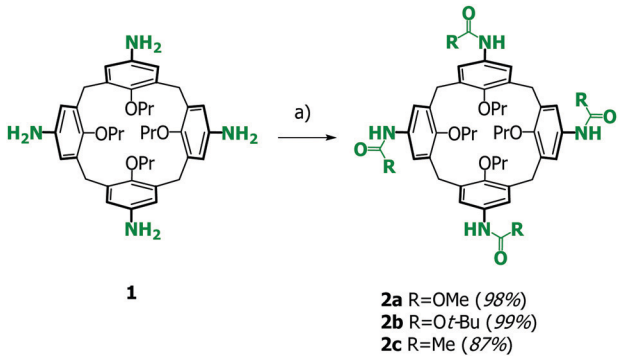



Fig. 2 The four possible isomers *via* tetra-*meta*-functionalisation. DG = directing group; X = any electrophilic group, *e.g.*, Br.

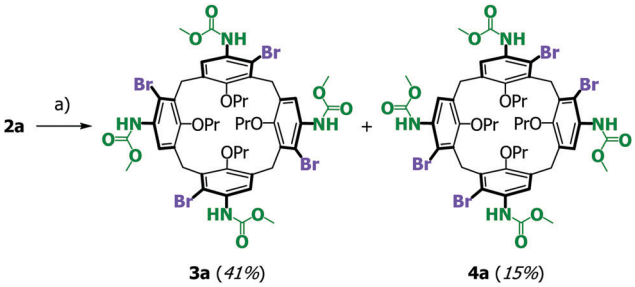
appear to be any reported attempts that try to tetra-*meta*-functionalize with four directing groups. At most only two directing groups (situated distally) have been used, which gave mixtures of products in all cases.[7,8,14] Our own research theme on inherently chiral calixarenes has had us looking for ways to generate these types of compounds. Our diastereoselective *ortho*-lithiation approaches are still the only successful direct method for stereoselectively forming *meta*-functionalized inherently chiral calix[4]arenes, but suffer from difficult synthetic protocols that do not scale up very well.[16,17] We have therefore avoided any attempt to tetra-lithiate a calix[4]arene, presuming it to be a battle with a low chance of success.

We have recently investigated a spuriously reported palladium catalysed C–H activation route employing a carbamate group and *N*-bromosuccinimide (NBS), but could show that this paper was actually overstated and incorrect on a number of levels.[19] Nevertheless, we wondered whether using a readily available tetra-carbamate as a directing group might allow for a facile synthesis of a $C_4$-symmetrical inherently chiral calix[4]arene.

Our strategy involved using tetra-methylcarbamate calix[4]arene **2a** as the starting material for bromination at the calix[4]arene *meta*-positions. Whilst **2a** has been synthesized before using triphosgene,[20] we synthesized it following a different route from the known tetra-amino calix[4]arene **1**[20] and methyl chloroformate in an excellent yield (Scheme 1, R = Me). A preliminary selectivity experiment using tetra-methylcarbamate **2a**, five equivalents of NBS and two equivalents of *p*-toluene sulfonic acid (PTSA), returned a very interesting result by TLC, showing only two compounds in a roughly 2 : 1 ratio (Scheme 2). Isolation of these compounds was achieved by silica gel chromatography (41% & 15% yields); their isotopic distribution patterns in high-resolution mass spectra were identical and corresponded to the tetra-brominated targets. The room temperature $^1$H NMR spectrum of the more dominant product was difficult to interpret due to




Scheme 1 Synthesis of the tetra-acylated calix[4]arenes **2**. Reagents and conditions: for R = OMe: methyl chloroformate (8 equiv.), pyridine (8 equiv.), DCM, −10 °C – rt, 1 h; for R = O*t*-Bu: $Boc_2O$ (8 equiv.), $Et_3N$ (8 equiv.), THF, 0 °C – reflux, 2 h; for R = Me: $Ac_2O$ (8 equiv.), $Et_3N$ (8 equiv.), THF, rt – reflux, 2 h.




Scheme 2 Preliminary bromination of tetra-methyl carbamate calix[4]arene **2a**. Reagents and conditions: (a) NBS (5 equiv.), PTSA (2 equiv.), DCM, −35 °C, 5 h.

extremely broad signals but running the spectrum at 100 °C in DMSO-$d_6$ neatly resolved these, gratifyingly confirming an isomer that would be consistent with $C_{2v}$ (achiral) or $C_4$ (chiral) symmetry (see Fig. 3). One important feature of this $^1$H NMR spectrum is the two signals at $\delta$ 3.98 and 3.80 ppm corresponding to the (now) *diastereotopic* methylene signals on the lower rim propoxy groups (–$OCH_2CH_2CH_3$), supporting the evidence of an inherently chiral isomer **3a**.

The assignment of the minor product was more challenging. Its $^1$H NMR spectrum was consistent with an isomer with $C_2$ or $C_s$ symmetry, having two singlets each for the aromatic C–H, amide N–H and carbamate methyl protons (see Fig. 3). This eliminated the $C_1$ isomer as a possibility, since a considerably more complex spectrum would be expected. Eliminating $C_{2v}$ and $C_s$ was however not easy; The $C_{2v}$ isomer should have only one aromatic signal, but if the boat conformation was dominant, then one would expect to see two aromatic signals. To confirm this, the sample was heated to 100 °C, but still, two aromatic signals persisted. Although this suggested that this isomer could be the achiral $C_S$ symmetric calix[4]arene (**D** in Fig. 2), the calix[4]arene 'bridge' methylene signals appeared as a neat set of four doublets (a double AX system), which was inconsistent with the $C_s$ isomer (see, purple arrows). Fortunately, 2D NMR spectroscopy resolved this issue, with the gHMBCAD spectrum

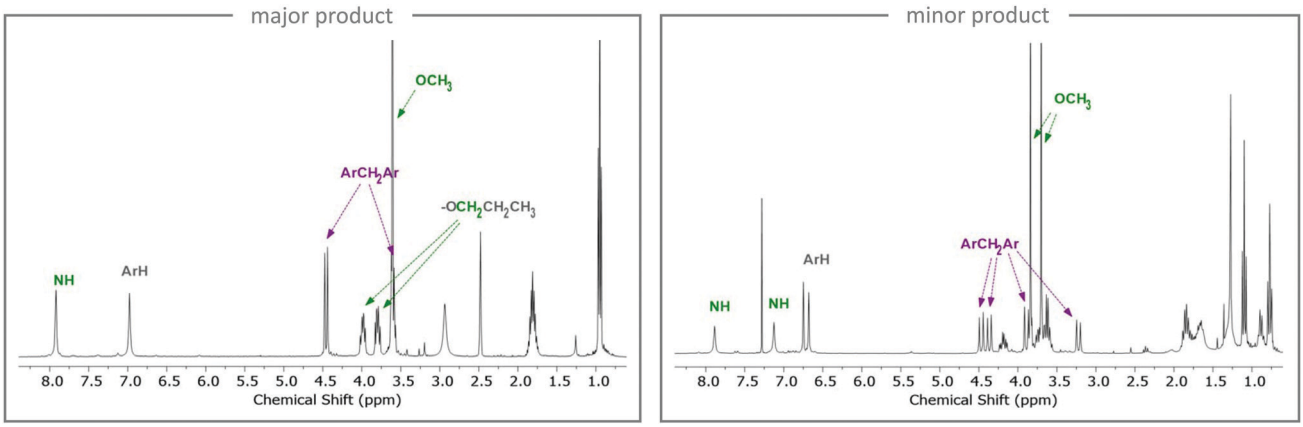


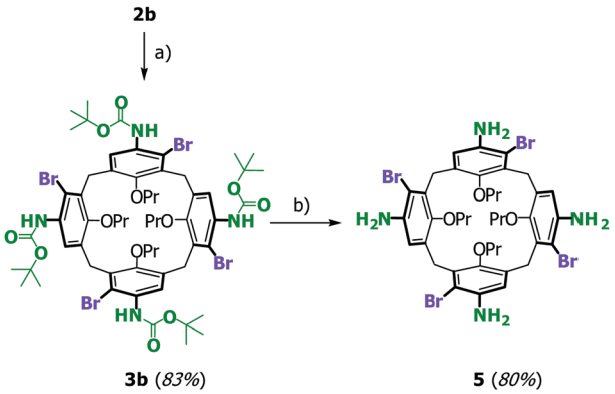

Fig. 3 $^1$H NMR spectra for compounds **3a** (major product, 400 MHz, DMSO-d$_6$, 100 °C) and **4a** (minor product, 300 MHz, CDCl$_3$, 25 °C).

revealing a clear connection between the one AX system and both $C_{Ar}$–H carbon atoms and the other AX system and both $C_{Ar}$–Br carbon atoms (see ESI† page S13 for full assignments), confirming the $C_2$-symmetric compound **4a**.

The synthesis of a $C_4$-symmetric inherently chiral calixarene in one step was an important result and prompted us to investigate this reaction further. We reasoned that changing the methyl carbamate to a *tert*-butyl carbamate (Boc group), would introduce a greater steric effect that might improve the selectivity of this reaction. Tetra-Boc calix[4]arene **2b** was therefore synthesised under optimum conditions, returning a quantitative yield of the desired tetracarbamate (Scheme 1, R = *t*-Bu). Running the bromination reaction under the same conditions gave a slightly improved yield of the major $C_4$ isomer **3b**, which nevertheless encouraged us to undertake a small optimisation study (see ESI† for full details of optimisation). In the optimisation study we found that the acid (PTSA) could be reduced to 0.2 equivalents, the optimum temperature was −42 °C and the bromine source needed to be NBS. The solvent was screened, but methylene chloride remained the preferred choice, although butanone gave similar results and could thus be considered an alternative, more environmentally friendly option. An experiment using chiral camphorsulfonic acid, unfortunately returned racemic product. Using the optimised conditions (see Scheme 3 and ESI†), a one gram scale reaction returned an 83% yield of the inherently chiral $C_4$-symmetric calix[4]arene **3b**. The method was reapplied to the tetramethylcarbamate calix[4]arene **2a** where the yield obtained was **3a**:**4a** = 51%:24%.

Whilst this was an improvement on our starting point, the result still suggested that the Boc-group was more important for both yield and ratio of products. Three procedures for the removal of the Boc-groups were then examined (see ESI†), with HCl giving yields of 80–85% for tetra-bromo-tetra-amino calix[4]arene **5**.

We attempted several crystallisation experiments to gain concrete evidence for the structural assignment of the $C_4$-isomer. Fortuitously, **3b** gave crystals suitable for diffraction. The solved structure (see Fig. 4 and ESI†) proved that the chiral $C_4$-symmetric isomer **3b** was the major product in these reactions. Whilst the crystal structure is in the so-called boat conformation,




Scheme 3 Optimised synthesis of an inherently chiral calixarene. Reagents and conditions: (a) NBS (5 equiv.), PTSA (0.2 equiv.), $CH_2Cl_2$, −42 °C, 6 h; (b) conc. HCl (10%), THF, reflux, 3 h.

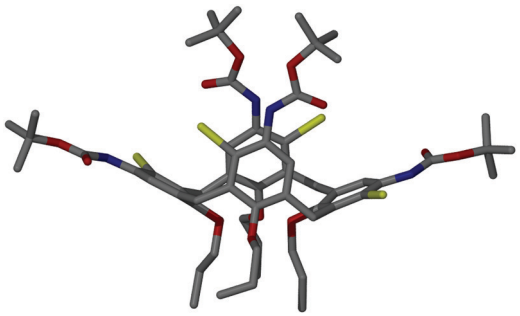
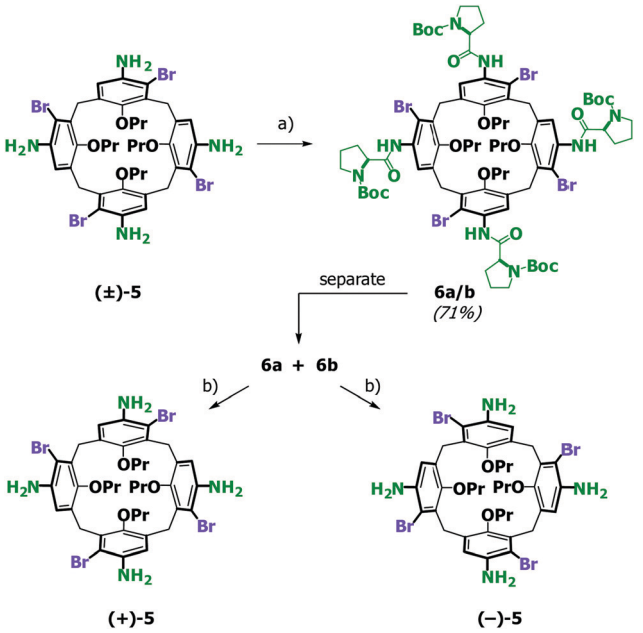


Fig. 4 Crystal data for **3b**: Side view; hydrogen atoms and solvent molecules omitted for clarity (see ESI† for more clarity).

the high symmetry of the NMR spectra is due to the dynamic equilibrium at 100 °C.

To establish the necessity for a carbamate directing group, the tetra acetamide calixarene analogue **2c** was synthesized (Scheme 1, R = Me) using a different procedure than that reported[21] giving an 87% yield (*vs.* 43% previously reported). For the ortho bromination reactions, solubility issues restricted the use of methylene chloride, but several reactions were carried out using both butanone and DMF with the optimised conditions.




Scheme 4 Separation of calixarene enantiomers. Reagents and conditions: (a) N-Boc-proline (6 equiv.), DCC (6 equiv.), DMAP (0.5 equiv.), $CH_2Cl_2$, rt, 13 h; (b) $Ba(OH)_2{\cdot}8H_2O$ (xs), *t*BuOH, reflux, 48 h.

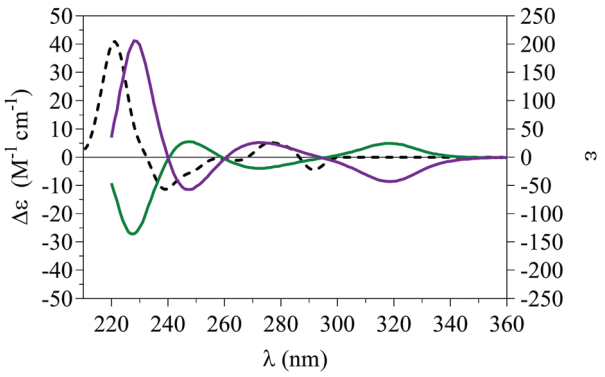



Fig. 5 ECD spectra of (+)-**5** (purple line) and (−)-**5** (green line) showing the opposite cotton-effect and the computed spectrum of (***M***)-**5** (black dashed line) corresponding to (+)-**5** obtained from the diastereomer **6a** (top spot).

Unfortunately, all reactions resulted in the formation of several brominated products, that were difficult to isolate or characterise.

Finally, we attempted to separate the enantiomers using classical diastereomeric techniques. In this case we found that coupling the racemic calix[4]arene **5** to *N*-Boc-(L)-proline under standard conditions (DCC, DMAP) gave a mixture of diastereomers (top spot = **6a** & bottom spot = **6b**) in good yield, which could be adequately separated *via* preparative thin layer chromatography (Scheme 4).

Removal of the chiral Boc-protected amino acid groups with barium hydroxide in *tert*-butanol under reflux[15] returned the two separate enantiomers of **5** (Scheme 4) whose ECD spectra were obtained in acetonitrile confirming their enantiomeric nature (Fig. 5). Furthermore, an ECD spectrum for **(M)-5** was calculated using DFT (PBE0/TZVP see ESI† for full details)[22–24] and corresponded to the enantiomer obtained from hydrolysis of diastereomer **6a** (top spot), confirming its assignment.

In conclusion, we have demonstrated a scalable method for synthesising racemic $C_4$-symmetrical inherently chiral calix[4]arenes and a preliminary method on obtaining the pure enantiomeric forms. Future work will involve further developing the method to separate the enantiomers, investigating the potential for diastereoselectivity in the reaction and further functionalisation of the inherently chiral backbone to create chiral ligand-like materials suitable for asymmetric catalysis.

This work was supported by the National Research Foundation (CPRR160428163281).

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

‡ The term *meta*-functionalization may appear odd to general practitioners, but it is a convention in the calixarene community to group functionalizations of this type together under this term.

1 A. Szumna, *Chem. Soc. Rev.*, 2010, **39**, 4274–4285.
2 G. E. Arnott, *Chem. – Eur. J.*, 2018, **24**, 1744–1754.
3 O. Kundrat and P. Lhoták, in *Calixarenes and Beyond*, Springer International Publishing, Cham, 2016, pp. 43–73.
4 G. D. Andreetti, V. Böhmer, J. G. Jordon, M. Tabatabai, F. Ugozzoli, W. Vogt and A. Wolff, *J. Org. Chem.*, 1993, **58**, 4023–4032.
5 D. K. Fu, B. Xu and T. M. Swager, *J. Org. Chem.*, 1996, **61**, 802–804.
6 R. Miao, Q.-Y. Zheng, C.-F. Chen and Z.-T. Huang, *J. Org. Chem.*, 2005, **70**, 7662–7671.
7 O. G. Barton, B. Neumann, H.-G. Stammler and J. Mattay, *Org. Biomol. Chem.*, 2008, **6**, 104–111.
8 W. Hüggenberg, A. Seper, I. M. Oppel and G. Dyker, *Eur. J. Org. Chem.*, 2010, 6786–6797.
9 M. Tlustý, H. Dvořáková, J. Čejka, M. Kohout and P. Lhoták, *New J. Chem.*, 2020, **44**, 6490–6500.
10 C. Gaeta, F. Troisi, C. Talotta, T. Pierro and P. Neri, *J. Org. Chem.*, 2012, **77**, 3634–3639.
11 M. Tlustý, P. Slavík, M. Kohout, V. Eigner and P. Lhoták, *Org. Lett.*, 2017, **19**, 2933–2936.
12 M. Tlustý, D. Spálovská, M. Kohout, V. Eigner and P. Lhoták, *Chem. Commun.*, 2020, **56**, 12773–12776.
13 M. Mascal, R. T. Naven and R. Warmuth, *Tetrahedron Lett.*, 1995, **36**, 9361–9364.
14 W. Verboom, P. J. Bodewes, G. van Essen, P. Timmerman, G. J. van Hummel, S. Harkema and D. N. Reinhoudt, *Tetrahedron*, 1995, **51**, 499–512.
15 Z.-X. Xu, C. Zhang, Q.-Y. Zheng, C.-F. Chen and Z.-T. Huang, *Org. Lett.*, 2007, **9**, 4447–4450.
16 S. A. Herbert and G. E. Arnott, *Org. Lett.*, 2010, **12**, 4600–4603.
17 D. C. Castell, N. Lesotho, V. I. Nikolayenko and G. E. Arnott, *Eur. J. Org. Chem.*, 2017, 4328–4333.
18 J. Holub, V. Eigner, L. Vrzal, H. Dvořáková and P. Lhoták, *Chem. Commun.*, 2013, **49**, 2798–2800.
19 K. J. Visagie, L. Hodson and G. E. Arnott, *S. Afr. J. Chem.*, 2020, **73**, 15–21.
20 A. M. A. Van Wageningen, E. Snip, W. Verboom, D. N. Reinhoudt and H. Boerrigter, *Liebigs Ann.*, 1997, **11**, 2235–2245.
21 S. Tommasone, C. Talotta, C. Gaeta, L. Margarucci, M. C. Monti, A. Casapullo, B. MacChi, S. P. Prete, A. Ladeiradearaujo and P. Neri, *Angew. Chem., Int. Ed.*, 2015, **54**, 15405–15409.
22 C. Schiel, G. A. Hembury, V. V. Borovkov, M. Klaes, C. Agena, T. Wada, S. Grimme, Y. Inoue and J. Mattay, *J. Org. Chem.*, 2006, **71**, 976–982.
23 C. Talotta, C. Gaeta, F. Troisi, G. Monaco, R. Zanasi, G. Mazzeo, C. Rosini and P. Neri, *Org. Lett.*, 2010, **12**, 2912–2915.
24 G. Concilio, C. Talotta, C. Gaeta, P. Neri, G. Monaco, R. Zanasi, D. Tedesco and C. Bertucci, *J. Org. Chem.*, 2017, **82**, 202–210.