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Synthetic and Structural Exploration of [2$_4$]Tetrathiacalix[2]arene[2]pyrimidines

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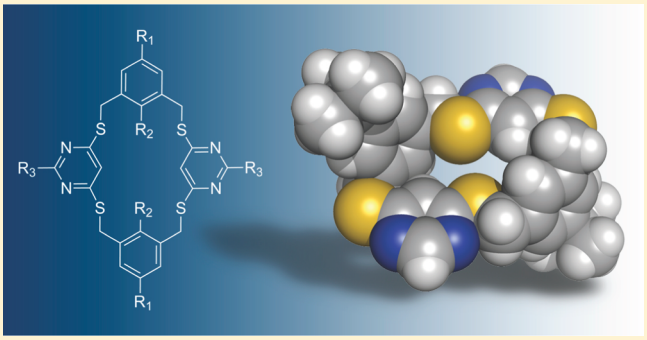
Supporting Information

ABSTRACT: A novel class of two atom bridged metacyclophanes—[2$_4$]thiacalix[2]arene[2]pyrimidines—has been synthesized via a straightforward S_NAr reaction. The conformational properties and intra-annular dimensions of the [2$_4$]-thiacalix[2]arene[2]pyrimidines were evaluated by X-ray structure analysis and compared with known homothia- and thiacalixarenes. Post-macrocyclization oxidation of the bridging sulfur moieties resulted in a [2$_4$]sulfonylcalix[2]arene[2]-pyrimidine, which gave access to an unexplored cavity size among sulfonylcalixarenes.



INTRODUCTION

Heteracalixarenes,[1] owing to their distinctive features compared to classical calixarenes, have become a subject of growing interest in recent years, among which thiacalixarenes in particular have been investigated the most. Notably, the presence of sulfur atoms instead of methylene bridges gives rise to dipole−dipole interactions between the sulfur atoms and guest species, which endows these macrocycles with many unique and interesting features lacking in the classical calixarene chemistry. Various reports have demonstrated that thiacalixarenes have high potency to act as efficient chelating agents for metal ions/clusters and to form nanoscale coordination cages.[1b−d,2] Oxidation of the bridging sulfur moiety to sulfoxides or sulfones is a modification unique to thiacalixarenes.[2b,3] Alteration of the interaction character between complexation of soft to hard metals after oxidation clearly elucidates the role of the bridging moiety on the supramolecular recognition pattern. Recently, the alkylation of the bridging sulfur atoms also was successfully demonstrated.[4]

Homothiacalixarenes are expanded analogues of thiacalixarenes in which CH_2SCH_2 bridges replace the sulfur atoms between the aromatic units.[5] The dimethylenehetero linkages impose an increased cavity size, conformational flexibility, and improved accessibility of the heteroatoms as binding site. Each of these features is beneficial to promote supramolecular interactions via induced-fit toward a certain guest molecule.

[2$_n$]Thiacalixarenes with CH_2S bridging moieties were initially reported to be formed in trace amounts by Vögtle et al.[6] However, up to the present date, it has been very quiet in this field. A recent revival in the [2$_n$](oxa/aza)calixarene chemistry was pursued by Wang and co-workers via preparation of several [2.2.1.1]- and [2.2.2.2]tetraheteracalix[2]arene[2]-triazines.[7] To clearly distinguish this class of metacyclophanes with monomethylenehetero linkages and to avoid confusion with the category of homoheteracalixarene with dimethylene-hetero bridges (Figure 1), we prefer the term [2$_n$]-heteracalixarenes. The introduction of heteroaromatic units in the calixarenoid framework allows a straightforward nucleophilic aromatic substitution (S_NAr) reaction as synthetic pathway toward these underexposed heterocalixarenes and the preparation of host systems with unique electronic features and different degrees of conjugation.[1] Recent studies show that these heterocalixarenes (owing to their multiple binding sites) act as efficient host systems with remarkable binding properties and selective molecular recognition.[8] Previously, we have optimized an one-pot procedure for homothia-[5d] and homoselenacalix[4]arenes[9] and have demonstrated their structural features. Moreover, the selective synthesis of selenacalix[3]triazines,[8n] heteracalix[2]arene[2]pyrimidines (with a direct O/S bridge),[10] and a fragment-coupling approach toward larger derivatives[11] have been established. The presence of pyrimidine moieties has allowed efficient post-macrocyclization modifications which have proven to be beneficial in various supramolecular applications.[12] This background in calixarene chemistry, together with the availability of dihalopyrimidine and 1,3-phenylenedimethanethiol building blocks, has now prompted us to explore the missing link

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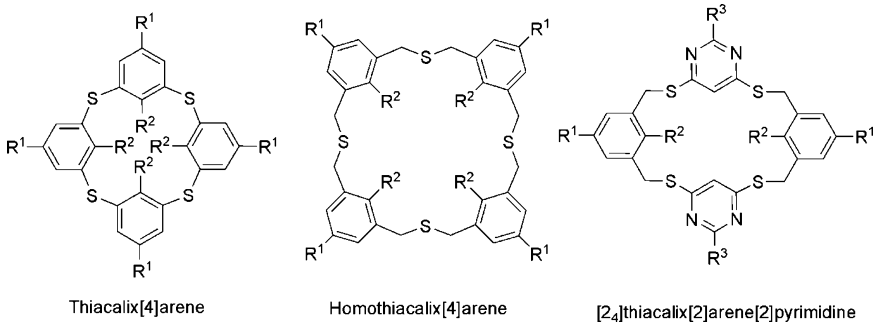


Figure 1. General representation of the thiacalixarene family with different bridging moieties.

Table 1. [2$_n$]Thiacalix[*m*]arene[*m*]pyrimidine Yield Optimization

entry	base	solvent	conc. (mM)	*T* (°C)	*t* (h)	**3a** (%)[a]	**4a** (%)[a]	**5a** (%)[a]
1	K_2CO_3	THF	6.4	50	15	–[b]	–[b]	–[b]
2	K_2CO_3	MeCN	6.4	50	15	19	19	41
3	K_2CO_3	DMSO	6.4	50	15	40	22	12
4	K_2CO_3	DMAc	6.4	50	15	33	23	13
5	K_2CO_3	EtOH	6.4	50	15	41	20	8
6	K_2CO_3	DMF	6.4	50	15	37	21	14
7	K_2CO_3	DMF	6.4	50	8	47	19	11
8	**K_2CO_3**	**DMF**	**6.4**	**50**	**4**	**60** (57[c])	**13** (10[c])	**9** (7[c])
9[d]	K_2CO_3	DMF	6.4	50	4	27	11	7
10	Cs_2CO_3	DMF	6.4	50	4	22	27	12
11	Na_2CO_3	DMF	6.4	50	4	13	3	--
12	Li_2CO_3	DMF	6.4	50	4	[b]	[b]	[b]

[a]Based on NMR analysis of the crude reaction mixture. [b]Inseparable oligomers. [c]Isolated yield, average of 3 runs. [d]5 mol % 18-crown-6 added as catalyst.

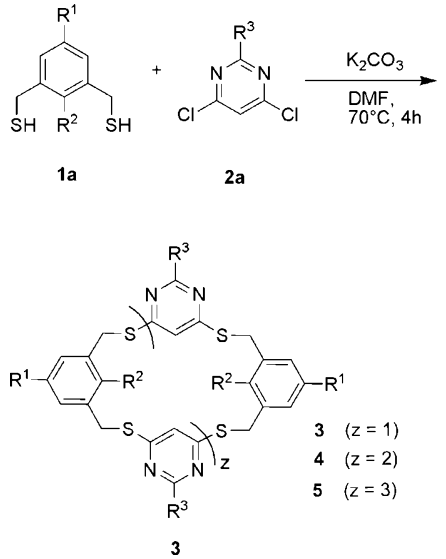
between the two classes of homothia- and thiacalixarenes, namely, [2$_n$]tetrathiacalix[*m*]arene[*m*]pyrimidines

RESULTS AND DISCUSSION

Initially, (5-*tert*-butyl-2-methoxy-1,3-phenylene)dimethanethiol (**1a**) and 4,6-dichloro-2-(*n*-propylsulfanyl)pyrimidine (**2a**) were combined in equimolar amounts with an excess of K_2CO_3 in THF at 50 °C during 15 h (Table 1, entry 1), similar to the S_NAr reaction conditions previously optimized for the homothiacalix[4]arenes.[5d] Unfortunately, mainly acyclic oligomers were observed in the mass spectrum of the reaction mixture and also reactions in NMP and 1,4-dioxane (not shown in Table 1) failed to yield cyclic products. Changing the solvent to MeCN resulted into a very different outcome.

After separation of the individual [2$_n$]thiacalix[*m*]arene[*m*]-pyrimidines ($n = 2m$), a comparison was made between their ^{1}H NMR spectra. This pointed out a distinct chemical shift for the proton in the C_5-position of the pyrimidine moieties, positions 29 and 31, when considering the calix[4]arene numbering scheme (see Supporting Information), that varies with the size of the macroring. A chemical shift of 6.90 ppm is observed for [2$_4$]thiacalix[4]arene **3a**, while for [2$_6$]thiacalix-[6]arene **4a** and [2$_8$]thiacalix[8]arene **5a**, a larger upfield shift to 6.48 ppm and 6.61 ppm is found, respectively. This kind of upfield shift for the interior protons of the electrophilic component has been observed before in oxa- and thiacalixarenes and can be attributed to anisotropic effects and conjugation of the S-bridging atoms into the electrophilic aromatic ring.[10] This peculiarity in chemical shift for the pyrimidine C_5-proton was further used as a probe to estimate the percentage of the different macrocycles from the ^{1}H NMR spectra of the crude reaction mixture while optimizing the reaction conditions.

Scheme 1. Synthesis of [2$_n$]thiacalix[*m*]arene[*m*]pyrimidine



The crude mixture after reaction in MeCN was estimated to consist of [2$_4$]thiacalix[4]arene **3a** (19%) and larger macrocyclic species **4a** (19%) and **5a** (41%) (Table 1, entry 2). Changing to more polar solvents favored the formation of **3a** at the expense of the larger oligomers (entries 3–6, Table 1). Since the smallest cyclic oligomer **3a** is likely to be the more interesting for application in supramolecular chemistry, the

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main focus of optimization was to improve the yield of this macrocycle.

Among the solvents screened (entries 3−6), the usage of more polar solvents like DMSO (entry 3), EtOH (entry 5), and DMF (entry 6) improved the yield for **3a** to 40%, 41%, and 37%, respectively. There, the outcome of the later reactions was very similar, and since in previous work DMF has given excellent results, it was opted to proceed with DMF as the optimal solvent.

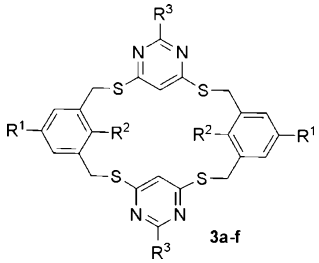
Extending the reaction time over 15 h hardly influenced the result, while a decrease in reaction time to 8 h resulted in a slight increase to 47% (entry 7). Further decrease to 4 h appeared to be even more beneficial for the selectivity toward **3a** with an additional increase of 13% (entry 8); a reaction time of less than 4 h led to incomplete conversion. The optimal concentration toward the largest amount of **3a** was found to be 6.4 mM. Changes in concentration of the reagents appeared to play a crucial role in the course of the reaction. Higher concentrations disfavored the formation of macrocycles, while higher dilution did not lead to higher yields. Addition of 5 mol % of 18-crown-6 as catalyst, which has proven before to be beneficial during oxacalix[2]arene[2]pyrimidine synthesis,[10] caused a substantial drop in the formation of cyclic oligomers (entry 9). This indicates the importance of a positively charged moiety in the reaction mixture, preorganizing the acyclic oligomers toward macrocyclization. To understand the effect and selectivity of different positively charged species on macrocyclization, different alkali carbonates like Cs_2CO_3, Na_2CO_3, and Li_2CO_3 were screened (entry 10−12), but lower yields were observed in the case of cesium and sodium carbonate whereas lithium carbonate failed to give any cyclic structure. This indicates that the K^+ cations act as a template to initiate the cyclization. Via chromatographic separation of the most optimal reaction (entry 8), the different [2_n]thiacalix[m]-arene[m]pyrimidines could be isolated giving pure [2_4]-thiacalix[4]arene **3a** (57%), [2_6]thiacalix[6]arene **4a** (10%), and [2_8]thiacalix[8]arene **5a** (7%) (average of 3 runs).

As previous studies on homoselenacalix[4]arenes[9] and homothiacalix[4]arenes[10] revealed the crucial role of inner rim methoxy group on the macrocyclization, it was thought to study the effect of intra- and extra-annular aryl substituents on the macrocyclization outcome. A major advantage of the pyrimidine moiety as electrophilic building block is the ease in which a diverse substitution pattern can be obtained.[13] A number of 4,6-dichloropyrimidines were reacted with various phenylenedimethanethiol units under the reaction conditions (DMF, K_2CO_3, 50 °C, 4 h) previously optimized for [2_4]thiacalix[4]arene **3a** (Table 2).

Hence, reaction of (5-*tert*-butyl-2-methoxy1,3-phenylene)-dimethanethiol (**1a**) with 4,6-dichloropyrimidine (**2b**), lacking the *n*-propylsulfanyl group, resulted in only 15% of tetramer **3b** and 12% of hexamer **4b** after chromatographic purification (entry 2). This may be due to the loss of product upon purification, which can be attributed to the lower solubility of the product. In fact, we failed to get a sample of **4b** that was completely free of traces of higher oligomers. Similar losses of valuable compound during purification have recently been reported for diazadioxacalix[4]arenes.[14] Using 4,6-dichloro-2-methylsulfanylpyrimidine (**2c**) or 4,6-dichloro-2-benzylsulfanyl-pyrimidine (**2d**) even failed to produce any cyclic compound (entry 3, 4).

Combining (5-*tert*-butyl-1,3-phenylene)dimethanethiol (**1b**), lacking the methoxy group, and pyrimidine building blocks **2a**−**d** gave considerably diminished yields for the [2_4]thiacalix[4]-arene **3c**−**3f** (15−26%; entries 5−8). Especially, the collation between cases **1a** with **2a** (57%) and **1b** with **2a** (25%) suggests that the methoxy group plays a crucial role during the macrocyclization, possibly due to a templating effect. For the reaction of (1,3-phenylene)dimethanethiol (**1c**), a nucleophilic building block lacking both methoxy and *tert*-butyl group, with **2a**, no cyclic oligomers were observed (Table 2, entry 9). Upon combining (2-methoxy-1,3-phenylene)dimethanethiol (**1d**), lacking just the *tert*-butyl moiety, with **2a**, a trace amount of product was observed, suggesting that the methoxy group appears to promote the formation of cyclic oligomers. However, due to the low solubility no substantial amount of calixarene could be formed (Table 2, entry 10).

Table 2. Scope of Synthesized [2_4]Thiacalix[2]arene[2]pyrimidines 3a−f



3a-f

entry	nucleophile	pyrimidine	**3** (%)[a]
1	**1a** (R^1 = *t*-Bu, R^2 = OMe)	**2a** (R^3 = SC_3H_7)	**3a** (57)
2	**1a**	**2b** (R^3 = H)	**3b** (15)
3	**1a**	**2c** (R^3 = SMe)	[b]
4	**1a**	**2d** (R^3 = SBz)	[b]
5	**1b** (R^1 = *t*-Bu, R^2 = H)	**2a**	**3c** (25)
6	**1b**	**2b**	**3d** (21)
7	**1b**	**2c**	**3e** (26)
8	**1b**	**2d**	**3f** (15)
9	**1c** (R^1, R^2 = H)	**2a**	[b]
10	**1d** (R^1 = H, R^2 = OMe)	**2a**	[c]

[a]Isolated yields. [b]Only acyclic oligomers were observed. [c]Only a trace amount of [2_4]thiacalix[2]arene[2]pyrimidine was observed.

A specific feature attributed to thiacalixarenes is the oxidation of the bridging sulfur atom to sulfoxide and sulfonyl units.[1b−d,3] The sulfonylcalixarenes are known to act as multinucleating or cluster-forming ligands due to their oxygen donors,[15] which have attracted considerable attention in inner transition metal binding studies due to the promising properties[16] of their complexes. The presence of the CH_2S linkages and the unique cavity size allowed us to oxidize the [2_4]thiacalix[4]arene **3d** to the [2_4]sulfonylcalix[2]arene-[2]pyrimidine **6** (71%) using *m*-CPBA/$MgSO_4$ in dry dichloromethane at ambient temperature during 15 h.

Solid State Structural Elucidation. Single crystals of compounds **3d** and **3f** suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of petroleum ether/ethyl acetate and dichloromethane/methanol, respectively. Earlier, it was reported that thiacalix[2]arene[2]-pyrimidines in solid state adopt a 1,3-alternate conformation.[12c] The introduction of methylene units into the bridging linkages adversely causes both [2_4]thiacalix[4]arenes **3d** and **3f** to adopt a 1,2-alternate conformation (see Figure 2 for **3d** and Supporting Information for **3f**). In both molecular structures, the opposing aryl rings as well as the pyrimidine moieties are aligned in parallel planes. In **3d**, the pyrimidine units are

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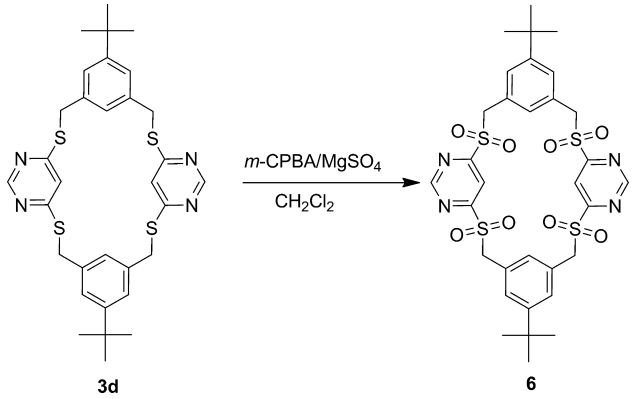
Scheme 2. Synthesis of [2$_4$]Sulfonylcalix[2]arene[2]pyrimidine



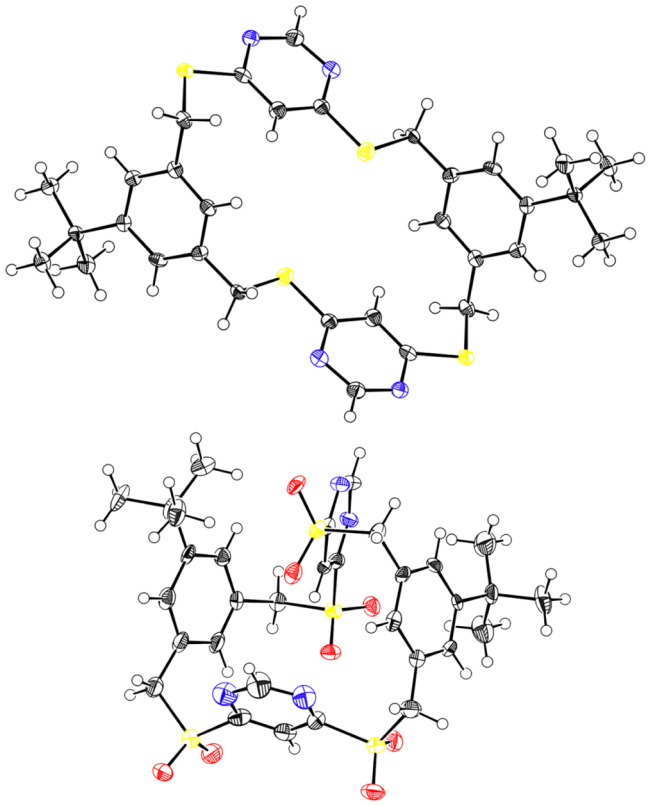


Figure 2. ORTEP representation of [2$_4$]calix[4]arenes **3d** (top) and **6** (bottom, only half of the asymmetric unit is shown) showing thermal ellipsoids at 50% probability.

pointing outward, while for **3f**, they are pointing inward towards the cavity, but in both cases, all four bridging heteroatoms are located on the same plane. More interestingly, for **3d** and **3f** the aryl and pyrimidine ring centroids form a quadrangle with side lengths of 5.30 × 6.66 Å^2 and 5.61 × 5.71 Å^2, respectively (see Supporting Information). These dimensions are notably smaller compared to a homothiacalix[4]arene (6.99 × 6.99 Å^2 on average) but larger in comparison to these of a thiacalix[2]arene[2]pyrimidine with single atom linkages (5.02 × 4.99 Å^2).[5d,12c] This underexplored cavity size can be applied as a new tool toward the selective inclusion of guest molecules. The oxidized analogue **6** adopts in solid state a strongly distorted 1,2-alternate conformation with the pyrimidine rings turning perpendicular to each other while the aryl rings are aligned almost parallel to one another. To the best of our knowledge, these dimensions are unknown among sulfonylcalixarenes,[1b−d,3] opening new possibilities for selective guest inclusion.

CONCLUSIONS

[2$_4$]Tetrathiacalix[2]arene[2]pyrimidines, a new class of two atom bridged metacyclophanes, were synthesized via an one-pot S$_N$Ar reaction. Single-crystal analysis confirmed an, until now, unexplored size among thia- and homothiacalixarenes. Oxidation of the CH_2S bridge to a CH_2SO_2 unit gave access to a new sulfonylcalixarene with unique dimensions which might introduce unknown metal inclusion aspects to the field of supramolecular chemistry. Both soft and hard metal binding studies are the subject of ongoing research.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were acquired on commercial instruments, and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (^{1}H) or the internal (NMR) solvent signals (^{13}C).[17] NMR peak assignments were performed based on DEPT and standard 2D NMR methods (HSQC and HMBC). Exact mass measurements were acquired in the EI (at a resolution of 10 000) or ESI (at a resolution of 60 000) mode. Melting points were determined by using a Reichert Thermovar apparatus and were not corrected. For column chromatography, 70−230 mesh silica 60 was used as the stationary phase. Chemicals received from commercial sources were used without further purification. K_2CO_3 (anhydrous, granulated) was finely ground (with mortar and pestle) and dried overnight in an oven at 200 °C prior to use.

(5-*tert*-Butyl-2-methoxy-1,3-phenylene)dimethanethiol (1a). This compound has been prepared according to the procedure reported by Tashiro et al.[18] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

(5-*tert*-Butyl-1,3-phenylene)dimethanethiol (1b). This compound has been prepared according to the procedure reported by Sander et al.[19] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

(2-Methoxy-1,3-phenylene)dimethanethiol (1c). This compound has been prepared according to the procedure reported by Krajulj et al.[20] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

(1,3-Phenylene)dimethanethiol (1d). This compound has been prepared according to the procedure reported before Ashram et al.[21] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

4,6-Dichloro-2-(propylsulfanyl)pyrimidine (2a). Thiobarbituric acid (5.0 g, 34 mmol) and triethylamine (4.8 mL, 34 mmol) were dissolved in methanol (20 mL) and allowed to stir for 5 min. 1-Bromopropane (3.15 mL, 34 mmol) was added dropwise and the mixture was refluxed for 18 h. The reaction mixture was cooled to room temperature and poured into ice−water. The pH was adjusted to 1 with 1 M HCl. A pale yellow precipitate was formed, filtered, washed several times with 1 M HCl, and dried under vacuum at 40 °C (yield 61%, mp >350 °C). The obtained compound was dissolved in $POCl_3$ (60 mL) and refluxed for 12 h. The reaction mixture was cooled to rt, and the excess of $POCl_3$ was removed under reduced vacuum. The residue was poured into ice−water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated under vacuum. After purification by column chromatography (silica, eluent CH_2Cl_2−hexane, 3−7), the desired pyrimidine **2b** was obtained as a colorless liquid (1.3 g, 17%); MS (EI+) m/z 223 [M+H]; HRMS (EI) calcd for $C_7H_8Cl_2N_2S$: 221.9785; found: m/z 221.9783; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H; 5-pyrim), 3.19 (t, ^3J = 7.2 Hz, 2H; CH_2), 1.81−1.72 (m, 2H; CH_2), 1.04 (t, ^3J = 7.1 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C; 2-pyrim), 161.3 (C; 4,6-pyrim), 115.7 (CH; 5-pyrim), 33.4 (CH_2), 22.2 (CH_2), 13.4 (CH_3).

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4,6-Dichloro-2-(methylsulfanyl)pyrimidine (2c). This compound has been prepared before by Nugent et al.[22] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

2-(Benzylsulfanyl)-4,6-dichloropyrimidine (2d). This compound has been prepared before by Nugent et al.[22] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

4,6-Dichloro-2-(methylsulfanyl)pyrimidine-5-carbaldehyde (2e). This compound has been prepared before by Gupton et al.[23] Material identity was confirmed by MS and ^{1}H and ^{13}C NMR.

5,7,19,21-Tetraaza-13,27-di-*tert*-butyl-30,32-dimethoxy-6,20-dipropylsulfanyl-2,10,16,24-tetrahomo-3,9,17,23-tetrathiacalix[4]arene (3a). General procedure 1: (5-*tert*-Butyl-2-methoxy-1,3-phenylene)dimethanethiol (**1a**) (100 mg, 0.39 mmol, 1 equiv), 4,6-dichloro-2-(propylsulfanyl)pyrimidine (**2a**) (87 mg, 0.39 mmol, 1 equiv) and K_2CO_3 (135 mg, 0.97 mmol, 2.5 equiv) were combined in DMF (70 mL) and the solution was degassed by a strong argon flow during 15 min. The mixture was stirred at 50 °C under an argon atmosphere during 4 h and subsequently evaporated to dryness. The crude residue was redissolved in a mixture of CH_2Cl_2 and water. The organic fraction was separated, washed with water, dried with $MgSO_4$, filtered, and concentrated under vacuum. After purification by column chromatography (silica, MPLC, eluent CH_2Cl_2–hexane, 8–2), the desired [2$_4$]thiacalix[4]arene was obtained as an off-white solid (105 mg, 57%); mp >300 °C; MS (ESI+) *m*/*z* 814.4 [MH+]; HRMS (EI) calcd for $C_{40}H_{53}N_4O_2S_6$: 813.2493 [M+H]; found: *m*/*z* 813.2460; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 4H; Ph), 6.90 (s, 2H; 5-pyrim), 4.18 (s, 8H; CH_2), 3.81 (s, 6H; CH_3–O), 3.08 (t, ^3J = 7.2 Hz, 4H; CH_2-propyl), 1.77–1.70 (m, 4H; CH_2-propyl), 1.26 (s, 18H, *t*-Bu), 1.02 (t, ^3J = 7.2 Hz, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C; 2-pyrim), 169.3 (C; 4,6-pyrim), 153.9 (C; 5-Ph), 148.1 (C; 1,3-Ph), 129.5 (C; 2-Ph). 127.7 (CH; 4,6-Ph), 107.8 (CH; 5-pyrim), 62.94 (CH_3–O), 34.6 (C; *t*-Bu), 32.9 (CH_2), 31.5 (CH_3; *t*-Bu), 28.3 (CH_2), 22.8 (CH_2), 13.6 (CH_3). During the synthesis of thiacalix[4]arene **3a**, the thiacalix[6]arene **4a** and thiacalix[8]arene **5a** analogue were formed as well.

5,7,19,21,33,35-Hexaaza-13,27,41-tri-*tert*-butyl-43,45,47-trimethoxy-6,20,34-tripropylsulfanyl-2,10,16,24,30,38-hexahomo-3,9,17,23,31,37-hexathiacalix[6]arene (4a). Yield (8 mg, 10%); mp: 190–191 °C; MS (ESI+) *m*/*z* 1243.2 [M+Na]; HRMS (ESI+) calcd for $C_{60}H_{79}N_6O_3S_9$ 1219.3695 [M+H$^+$]; found: *m*/*z* 1219.3690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 6H; Ph), 6.48 (s, 3H; 5-pyrim), 4.33 (s, 12H; CH_2), 3.79 (s, 9H; CH_3–O), 3.15 (t, ^3J = 7.1 Hz, 6H; CH_2), 1.84–1.71 (m, 6H; CH_2), 1.23 (s, 27H; *t*-Bu), 1.02 (t, ^3J = 7.1 Hz, 9H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1 (C; 2-pyrim), 169.3 (C; 4,6-pyrim), 153.9, (C; 5-Ph), 148.0 (C; 1,3-Ph), 127.7 (CH; 2,4,6-Ph), 107.8 (CH; 5-pyrim), 62.9 (CH_3–O), 34.6 (C, *t*-Bu), 32.8 (CH_2), 31.5 (CH_3; *t*-Bu), 28.3 (CH_2), 22.8 (CH_2), 13.6 (CH_3).

5,7,19,21,33,35,47,49-Octaaza-13,27,41,55-tetra-*tert*-butyl-43,45,47,49-quadramethoxy-6,20,34,48-tetrapropylsulfanyl-2,10,16,24,30,38,44,52-octahomo-3,9,17,23,31,37,45,51-octathiacalix[8]arene (5a). Yield (4 mg, 7%), mp: 209–210 °C; MS (ESI+) *m*/*z* 1648.3 [MH+Na]; HRMS (ESI+) calcd for $C_{80}H_{105}N_8NaO_4S_{12}$ 1648.4805 [MH+Na]; found: *m*/*z* 1648.4809; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 8H; Ph), 6.61 (s, 4H; 5-pyrim), 4.39 (s, 16H; CH_2), 3.82 (s, 12H; CH_3–O), 3.13 (t, ^3J = 7.1 Hz, 8H; CH_2), 1.82–1.70 (m, 8H; CH_2), 1.23 (s, 36H; *t*-Bu), 1.00 (t, ^3J = 7.1 Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8/170.5 (C; 2-pyrim), 167.7/167.2 (C; 4,6-pyrim), 154.6/154.5 (C; 5-Ph), 147.6/147.4 (C; 1,3-Ph), 129.8/129.7 (C; 2-Ph), 127.8 (CH; 4,6-Ph), 110.1/109.7 (CH; 5-pyrim), 62.4 (CH_3–O), 34.5 (C; *t*-Bu), 33.0 (CH_2), 31.4 (CH_3; *t*-Bu), 28.5 (CH_2), 22.9 (CH_2), 13.6 (CH_3).

5,7,19,21-Tetraaza-13,27-di-*tert*-butyl-30,32-dimethoxy-2,10,16,24-tetrahomo-3,9,17,23-tetrathiacalix[4]arene (3b). Synthesis according to general procedure 1; (5-*tert*-butyl-1,3-phenylene)dimethanedithiol (**1a**) (100 mg, 0.389 mmol), 4,6-dichloro-2-(propylsulfanyl)pyrimidine (**2b**) (58.09 mg, 0.389 mmol); purification by column chromatography (silica, eluent CH_2Cl_2–hexane, 8–2); Yield: 15% (20 mg); mp >300 °C; MS (ESI+) *m*/*z* 665.0 [MH+]; HRMS (ESI+) calcd for $C_{34}H_{41}N_4O_2S_4$: 665.2112 [M+H]; found: *m*/*z* 665.2078; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 2H; 2-pyrim), 7.40 (s, 4H; Ph), 7.23 (s, 2H; 5-pyrim), 4.22 (s, 8H; CH_2), 3.83 (s, 6H; CH_3–O), 1.25 (s, 18H; *t*-Bu). The poor solubility of this compound prevented further characterization by ^{13}C NMR. During the synthesis of thiacalix[4]arene **3b**, the thiacalix[6]arene **4b** analogue was formed as well.

5,7,19,21,33,35-Hexaaza-13,27,41-tri-*tert*-butyl-43,45,47-trimethoxy-2,10,16,24,30,38-hexahomo-3,9,17,23,31,37-hexathiacalix[6]arene (4b). Yield (15 mg, 12%); mp: 115–116 °C; MS (ESI+) *m*/*z* 1020.4 [M+Na]; HRMS (ESI+) calcd for $C_{51}H_{61}N_6O_3S_6$: 997.3121 [M+H]; found: *m*/*z* 997.3119; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 3H; 2-pyrim), 7.37 (s, 6H; Ph), 6.78 (s, 3H; 5-pyrim), 4.32 (s, 12H; CH_2), 3.82 (s, 9H; CH_3–O), 1.22 (s, 27H; *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (C; 4,6-pyrim), 156.7 (CH; 2-pyrim), 154.5 (C; 2-Ph), 147.7 (C; 5-Ph), 129.3 (C; 1,3 Ph), 127.9 (CH; 4,6-Ph), 114.1 (CH; 5-pyrim), 62.5 (CH_3–O), 34.5 (C; *t*-Bu), 31.4 (CH_3; *t*-Bu), 28.8 (CH_2).

5,7,19,21-Tetraaza-13,27-di-*tert*-butyl-6,20-dipropylsulfanyl-2,10,16,24-tetrahomo-3,9,17,23-tetrathiacalix[4]arene (3c). Synthesis according to general procedure 1; (5-*tert*-butyl-1,3-phenylene)dimethanedithiol (**1b**) (100 mg, 0.44 mmol), 4,6-dichloro-2-(propylsulf-any)pyrimidine (**2a**) (0.98 mg, 0.44 mmol); purification by column chromatography (silica, eluent petroleum ether–CH_2Cl_2, 6–4); Yield: 25% (42 mg); mp: 249–250 °C. MS (ESI+) *m*/*z* 753.4 [M+H]; HRMS (ESI+) calcd for $C_{38}H_{49}N_4S_6$: 753.2281 [M+H]; found: *m*/*z* 753.2261; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 2H; 2-Ph), 7.16 (s, 4H; 4,6-Ph), 6.58 (s, 2H; 5-pyrim), 4.32 (s, 8H; CH_2), 2.93 (t, ^3J = 7.2 Hz, 4H; CH_2), 1.64–1.59 (m, 4H; CH_2), 1.30 (s, 18H; *t*-Bu), 0.88 (t, ^3J = 7.3 Hz, 6H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C; 2-pyrim), 167.1 (C; 4,6-pyrim), 151.4 (C; 5-Ph), 138.5 (C; 1,3-Ph), 126.0 (CH; 2-Ph), 124.5 (CH; 4,6-Ph), 110.2 (CH; 5-pyrim), 34.7 (C; *t*-Bu), 33.2 (CH_2), 33.0 (CH_2), 31.4 (CH_3; *t*-Bu), 22.8 (CH_2), 13.5 (CH_3). During the synthesis of thiacalix[4]arene **3c**, the thiacalix[6]arene **4c** analogue was formed as well.

5,7,19,21,33,35-Hexaaza-13,27,41-tri-*tert*-butyl-6,20,34-tripropylsulfanyl-2,10,16,24,30,38-hexahomo-3,9,17,23,31,37-hexathiacalix[6]arene (4c). Yield (22 mg, 13%), mp: 120–121 °C; MS (ESI+) *m*/*z* 1129.5 [M+H]; HRMS (ESI+) calcd for $C_{57}H_{73}N_6S_9$: 1129.3378 [M+H$^+$]; found: *m*/*z* 1129.3349; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 9H; Ph), 6.60 (s, 3H; 5-pyrim), 4.33 (s, 12H; CH_2), 3.01 (t, ^3J = 7.2 Hz, 6H; CH_2), 1.73–1.63 (m, 6H; CH_2), 1.28 (s, 27H; *t*-Bu), 0.90 (t, ^3J = 7.3 Hz, 9H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C; 2-pyrim), 167.4 (C; 4,6-pyrim), 151.9 (C; 5-Ph), 137.3 (C; 1,3-Ph), 126.7 (CH; 2-Ph), 125.1 (CH; 4,6-Ph), 110.3 (CH; 5-pyrim), 34.8 (C; *t*-Bu), 33.7 (CH_2), 32.9 (CH_2), 31.4 (CH_3; *t*-Bu), 29.8 (CH_2), 22.9 (CH_2), 13.5 (CH_3).

5,7,19,21-Tetraaza-13,27-di-*tert*-butyl-2,10,16,24-tetrahomo-3,9,17,23-tetrathiacalix[4]arene (3d). Synthesis according to general procedure 1; (5-*tert*-butyl-1,3-phenylene)dimethanedithiol (**1b**) (100 mg, 0.44 mmol), 4,6-dichloropyrimidine (**2b**) (0.65 mg, 0.44 mmol); purification by column chromatography (silica, eluent petroleum ether–ethyl acetate, 7–3); Yield: 26% (35 mg); mp: 249–250 °C; MS (ESI+) *m*/*z* 605.3 [M+H]; HRMS (ESI+) calcd for $C_{32}H_{37}N_4S_4$: 605.1901 [M+H]; found: *m*/*z* 605.1901; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 2H; 2-pyrim), 7.46 (s, 2H; 2-Ph), 7.19 (s, 4H; 4,6-Ph), 6.78 (s, 2H; 5-pyrim), 4.29 (s, 8H; CH_2), 1.28 (s, 18H; *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4 (C; 4,6-pyrim), 156.6 (C; 2-pyrim), 151.9 (C; 5-Ph), 138.0 (C; 1,3-Ph), 126.8 (CH; 2-Ph), 125.0 (CH; 4,6-Ph), 115.0 (CH; 5-pyrim), 34.8 (C; *t*-Bu), 33.2 (CH_2), 31.4 (CH_3; *t*-Bu). During the synthesis of thiacalix[4]arene **3d**, the thiacalix[6]arene **4d** analogue was formed as well.

5,7,19,21,33,35-Hexaaza-13,27,41-tri-*tert*-butyl-2,10,16,24,30,38-hexahomo-3,9,17,23,31,37-hexathiacalix[6]-arene (4d). Yield (45 mg, 34%); mp: 107–108 °C; MS (ESI+) *m*/*z* 930.6 [M+Na]; HRMS (ESI+) calcd for $C_{48}H_{55}N_6S_6$: 907.2812 [M+H]; found: *m*/*z* 907.2801; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 3H; 2-pyrim), 7.25 (s, 9H; Ph), 6.89 (s, 3H; 5-pyrim), 4.33 (s, 12H; CH_2), 1.28 (s, 27H; *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8/167.7 (C; 4,6-pyrim), 157.0 (CH; 2-pyrim), 152.0 (C; 5-Ph), 137.14/137.11 (C; 1,3-Ph), 126.7 (CH; 2-Ph), 125.4/125.3 (CH; 4,6-Ph), 115.1 (CH; 5-pyrim), 34.7 (C; *t*-Bu), 33.9 (CH_2), 31.3 (CH_3; *t*-Bu).

5,7,19,21-Tetraaaza-13,27-di-*tert*-butyl-6,20-dimethylsulfanyl-2,10,16,24-tetrahomo-3,9,17,23-tetrathiacalix[4]arene (3e). Synthesis according to general procedure 1; (5-*tert*-butyl-1,3-phenylene)dimethanedithiol (**1b**) (100 mg, 0.44 mmol), 4,6-dichloro-2-(methylsulfanyl)pyrimidine (**2c**) (0.86 mg, 0.44 mmol); purification by column chromatography (silica, eluent petroleum ether−CH_2Cl_2, 7−3); Yield: 26% (40 mg); mp: 264−265 °C; MS (ESI+) *m*/*z* 697.9 [M+H]; HRMS (ESI+) calcd for $C_{34}H_{41}N_4S_6$: 697.1655 [M+H]; found: *m*/*z* 697.1680; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 2H; 2-Ph), 7.15 (s, 4H; 4,6-Ph), 6.58 (s, 2H; 5-pyrim), 4.33 (s, 8H; CH_2), 2.38 (s, 6H; CH_3), 1.30 (s, 18H; *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (2-pyrim), 167.1 (C; 4,6-pyrim), 151.4 (C; 5-Ph), 138.6 (C; 1,3-Ph), 126.0 (CH; 2-Ph), 124.5 (CH; 4,6-Ph), 110.2 (CH; 5-pyrim), 34.7 (C; *t*-Bu), 33.2 (CH_2), 31.5 (CH_3; *t*-Bu), 14.2 (CH_3−S). During the synthesis of thiacalix[4]arene **3e**, the thiacalix[6]arene **4e** analogue was formed as well.

5,7,19,21,33,35-Hexaaza-13,27,41-tri-*tert*-butyl-6,20,34-trimethylsulfanyl-2,10,16,24,30,38-hexahomo-3,9,17,23,31,37-hexathiacalix[6]arene (4e). Yield (10 mg, 7%); mp: 87−88 °C; MS (ESI+) *m*/*z* 1047.1 [MH+], 1068.4 [M+Na]; HRMS (ESI+) calcd for $C_{51}H_{60}N_6NaS_9$: 1067.2264 [M+Na]; found: *m*/*z* 1067.2244; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.18 (s, 3H; 2-Ph), 7.16 (s, 6H; 4,6-Ph), 6.56 (s, 3H; 5-pyrim), 4.27 (s, 12H; CH_2), 2.34 (s, 9H; CH_3), 1.20 (s, 18H; *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (C; 2,4,6-pyrim), 151.9 (C; 5-Ph), 137.5 (C; 1,3-Ph), 126.6 (CH; 2-Ph), 125.1 (CH; 4,6-Ph), 110.3 (CH; 5-pyrim), 34.8 (C; *t*-Bu), 33.7 (CH_2), 31.4 (CH_3; *t*-Bu), 14.2 (CH_3−S).

5,7,19,21-Tetraaza-13,27-di-*tert*-butyl-6,20-diphenylsulfanyl-2,10,16,24-tetrahomo-3,9,17,23-tetrathiacalix[4]arene (3f). Synthesis according to general procedure 1; (5-*tert*-butyl-1,3-phenylene)dimethanedithiol (**1b**) (100 mg, 0.44 mmol), 2-(benzylsulfanyl)-4,6-dich-loropyrimidine (**2d**) (119 mg, 0.44 mmol); purification by column chromatography (silica, eluent petroleum ether−CH_2Cl_2, 7−3); Yield: 40% (70 mg); mp: 210−211 °C; MS (ESI+) *m*/*z* 850.8 [M+H]; HRMS (ESI+) calcd for $C_{46}H_{49}N_4S_6$: 849.2281 [M+H]; found: *m*/*z* 849.2248; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 2H; 2-Ph), 7.24−7.19 (m, 10H; benzyl), 7.14 (s, 4H; 4,6-Ph), 6.64 (s, 2H; 5-pyrim), 4.27 (s, 8H; CH_2), 4.18 (s, 4H; CH_2), 1.26 (s, 18H; *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C; 2-pyrim), 167.3 (C; 4,6-pyrim), 151.5 (C; 5-Ph), 138.5 (C; 1,3-Ph), 137.4 (C; *ipso*-benz), 128.9 (C; *m*-benz), 128.5 (C; *o*-benz), 127.1 (C; *p*-benz), 126.1 (CH; 2-Ph), 124.5 (CH; 4,6-Ph), 110.6 (CH; 5-pyrim), 35.4 (CH_2-benz), 34.7 (C; *t*-Bu), 33.4 (CH_2), 31.4 (CH_3; *t*-Bu). During the synthesis of thiacalix[4]arene **3f**, the thiacalix[6]arene **4f** analogue was formed as well.

5,7,19,21,33,35-Hexaaza-13,27,41-tri-*tert*-buty-6,20,34-triphenylsulfanyl-2,10,16,24,30,38-hexahomo-3,9,17,23,31,37-hexathiacalix[6]arene (4f). Yield (10 mg, 5%); mp: 104−105 °C; MS (ESI+) *m*/*z* 1312 [M+K]; HRMS (ESI+) *m*/*z* calcd for $C_{69}H_{73}N_6S_9$: 1273.3383 [M+H]; found: *m*/*z*; 1273.3380; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 3H), 7.28 (s, 3H), 7.22 (s,12H), 7.20−7.14 (m, 6H), 6.57 (s, 3H; 5-pyrim), 4.31 (s, 6H; CH_2), 4.27 (s, 12H; CH_2), 1.26 (s, 27H; *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C; 2-pyrim), 167.6 (C; 4,6-pyrim), 151.9 (C; 5-Ph), 137.4 (C; *ipso*-benz), 137.2 (C; 1,3-Ph), 128.9 (C; *m*-benz), 128.6 (C; *o*-benz), 127.2 (C; *p*-benz), 126.7 (CH; 2-Ph), 125.2 (CH; 4,6-Ph), 110.5 (CH; 5-pyrim), 35.4 (CH_2-benz), 34.8 (C; *t*-Bu), 33.8 (CH_2), 31.4 (CH_3; *t*-Bu).

5,7,19,21-Tetraaza-13,27-di-*tert*-butyl-2,10,16,24-tetrahomo-3,9,17,23-tetrasulfonylcalix[4]arene (6). *m*-CPBA (356 mg, 2.06 mmol, 12 equiv) and $MgSO_4$ (248 mg, 2.06 mmol) were mixed together in CH_2Cl_2 (10 mL) and stirred for 1 h at RT. Subsequently, thiacalix[4]arene **3d** (100 mg, 0.17 mmol, 1 equiv) was added and the mixture was stirred at RT for 12 h (under Ar). The resulting solution was filtered, diluted with MeOH (20 mL), and CH_2Cl_2 was carefully evaporated in vacuum, resulting in the formation of a white crystalline solid, which was filtered off and washed with MeOH to afford calix[4]arene **6** as an off-white solid. Yield: 71% (90 mg); mp: 304−305 °C; MS (ESI+) *m*/*z* 755 [M+Na]; HRMS (ESI+) calcd for $C_{32}H_{37}N_4O_8S_4$: 733.1494; found: *m*/*z* 733.1481; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 2H; 2-pyrim), 7.63 (s, 2H; 2-Ph), 7.15 (s, 2H; 5-pyrim), 7.09 ppm (s, 4H; 4,6-Ph), 4.60 (s, 8H; CH_2), 1.14 (s, 18H; *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C; 4,6-pyrim), 159.1 (CH; 2-pyrim), 153.2 (C; 5-Ph), 130.4 (CH; 2-Ph), 128.8 (CH; 4,6-Ph), 127.3 (C; 1,3-Ph), 116.0 (CH; 5-pyrim), 58.3 (CH_2), 34.7 (C; *t*-Bu), 31.1 (CH_3; *t*-Bu).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional X-ray data (CIF), copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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