Organic & Biomolecular Chemistry

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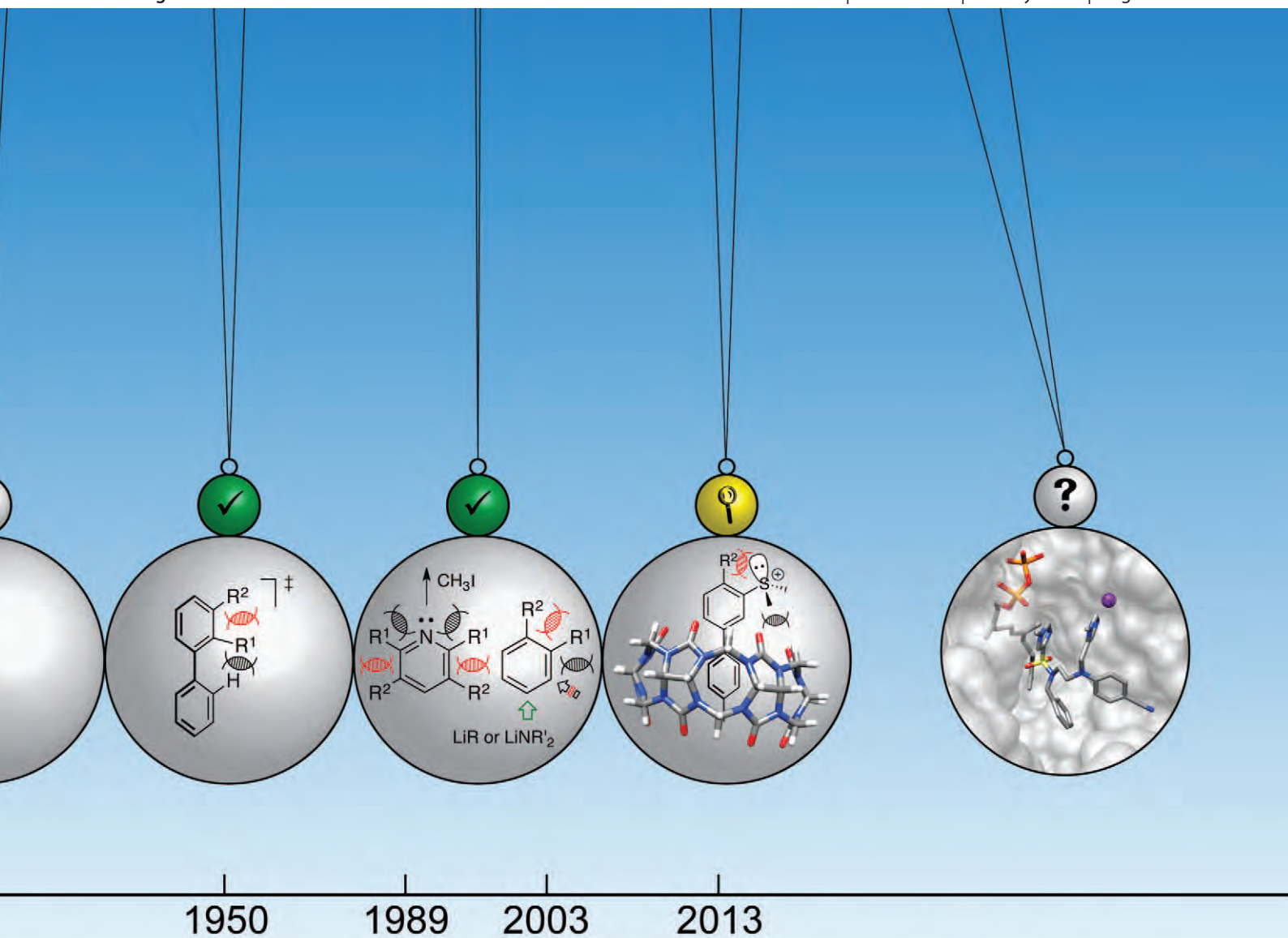
Volume 11 | Number 19 | 21 May 2013 | Pages 3075–3262



ISSN 1477-0520

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Subtle "supramolecular buttressing effects" in Cucurbit[7]uril/guest assemblies†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 3116

Roymon Joseph and Eric Masson*

Biphenyl derivatives bearing a dimethylsulfonium group at position 3 and three different substituents at position 4 (H, F and CH_3) have been prepared as probes to test the validity of the "supramolecular buttressing" concept. We define the latter as the alteration, by a neighboring unit, of a substituent effect on intermolecular recognition. In this case, the 4-substituents exert some pressure on the 3-dimethylsulfonium groups and control the ratio of their *syn* and *anti* conformations. As free species, biphenyls bearing 4-H and 4-F substituents are present as approximately equimolar mixtures of *syn* and *anti*-conformers, while the biphenyl scaffold with a 4-CH_3 group adopts the *anti*-conformation exclusively. The 3-dimethylsulfonium substituents then interact with one of the carbonylated portals of Cucurbit[7]uril (CB[7]), and their conformations affect the position of the guests inside the cavity of the macrocycle, thereby validating our "supramolecular buttressing" model. Surprisingly however, binding affinities towards CB[7] are barely affected by the nature of the 4-substituents and the conformations of the neighboring sulfonium groups, despite very different electronic densities presented to the CB[7] portal in their *syn* or *anti* conformations. Solvation was found to dramatically smoothen host–guest Columbic interactions, although the latter remain important in the recognition process. Replacing the positively charged 3-dimethylsulfonium unit with an isopropyl substituent decreases the affinity of the biphenyl guest by 1000-fold.

Received 3rd February 2013,
Accepted 26th March 2013

DOI: 10.1039/c3ob40250a

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Introduction

The term "buttressing effect" was proposed by Westheimer in 1950 to describe the impact of *meta*-substituents on the torsional barriers of substituted biphenyls along their aryl–aryl axis.[1] *meta*-Substituents were found to buttress (*i.e.* to support or strengthen) *ortho*-substituents, by limiting their ability to undergo distortion during the torsional isomerization process; the consequence was an increase of the torsional barrier (see Fig. 1a). A particularly spectacular example is the 6.8 kcal mol^{-1} penalty imposed by 3- and 3′-iodine atoms on the activation barrier of 2,2′,3,3′-tetraiodo-5,5′-dicarboxybiphenyl compared to its 2,2′-diiodo analog (30.2 *vs.* 23.4 kcal mol^{-1}).[1] Since then, buttressing effects have been invoked on numerous occasions to describe the alteration, by a neighboring or a more remote group, of a substituent effect on the mobility,[2] reactivity[3] and physical properties[4] of various structures. For example, Schlosser and co-workers showed that the metalation of arenes is blocked by *meta*-triethylsilyl groups (see substituent R^2 in Fig. 1b), which buttress *ortho*-substituents R^1 (Cl,[3a,b] Br[3c] and CF_3)[3d] and force them to shield the *ipso* position from the attacking base; metalation actually takes place *para* to the triethylsilyl substituent (see the green arrow in Fig. 1b).

To the best of our knowledge, the concept of chemical buttressing has never been extended to supramolecular systems. We propose to define "supramolecular buttressing" as the alteration, by a neighboring unit, of a substituent effect on *intermolecular recognition* (see Fig. 1c; remote group R^2 exerts pressure on substituent R^1, which is then forced to alter the interaction between units A and B). In this study, we present a

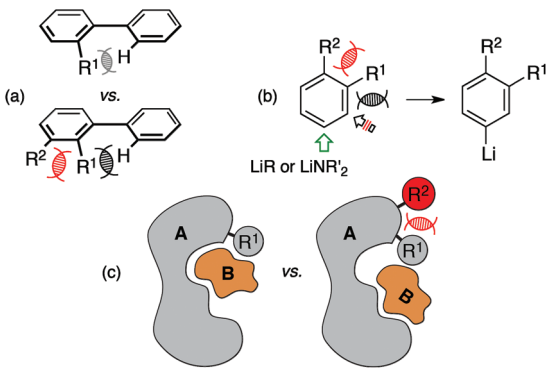

Fig. 1 (a) Barriers of torsional isomerisation of biphenyl scaffolds affected by buttressing. (b) Regioselectivity of arene metalation controlled by buttressing effects. (c) "Supramolecular buttressing".

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob40250a

case of supramolecular buttressing, and assess how the remote substituent (R^2 in Fig. 1c) affects the binding affinity between the two molecular partners A and B, and the structure of assembly A·B.

Host–guest assemblies formed upon interaction between Cucurbit[7]uril (CB[7])[5,6] and positively charged guests are ideal A·B systems, since (1) binding affinities can be exceptionally high in aqueous medium (up to 5×10^{15} M^{-1}!),[7] (2) the structures of the assemblies are often very well defined, and (3) the position of the guest inside the cavity of the macrocycle can be readily assessed by ^1H NMR spectroscopy: hydrogen nuclei residing at the core of the hollow macrocycle are shifted upfield, and hydrogens outside the cavity undergo a downfield shift that weakens as the distance between the hydrogen atom and the carbonylated portal increases.[8] In order to test supramolecular buttressing, CB[7] guests (unit A in Fig. 1c) must bear (1) a hydrophobic moiety that is encapsulated by the macrocycle, (2) a positively charged substituent R^1 that interacts with the carbonyl portal of CB[7], and (3) a neighboring group R^2, which affects the geometry or the rigidity of substituent R^1. Biphenyls **1–3** (see Fig. 2a) satisfy these guidelines, since the nature of buttressing substituents R^2 is expected to control the conformation of the dimethylsulfonium group R^1 (*syn* or *anti*, see Fig. 2a), and consequently affect its interaction with CB[7].

Biphenyl **1** was prepared by diazotisation of 3-(methylthio)-aniline, followed by nucleophilic aromatic substitution with potassium iodide, Suzuki coupling with 4-tolylboronic acid and methylation of the thioether with trimethyloxonium tetrafluoroborate (see Schemes 1a and 1d). Biphenyl **2** was obtained by first converting 5-bromo-2-fluorophenol to the corresponding benzenethiol **2c** *via* carbamation, Newman–Kwart rearrangement[9] and decarbamation (see Scheme 1b); thiol **2c** was then methylated, and the resulting sulfide **2d** was coupled with 4-tolylboronic acid and methylated again to afford our target (Scheme 1d). 4-Bromo-2-nitrotoluene was converted to the corresponding benzenethiol **3c** *via* reduction to aniline **3a**, diazotisation, substitution with potassium ethyl xanthate and saponification. Thiol **3c** was then submitted to the same sequence of reactions as analog **2c** to afford biphenyl **3** (see Schemes 1c and 1d).

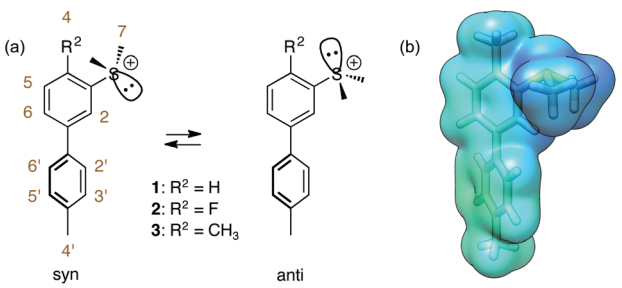
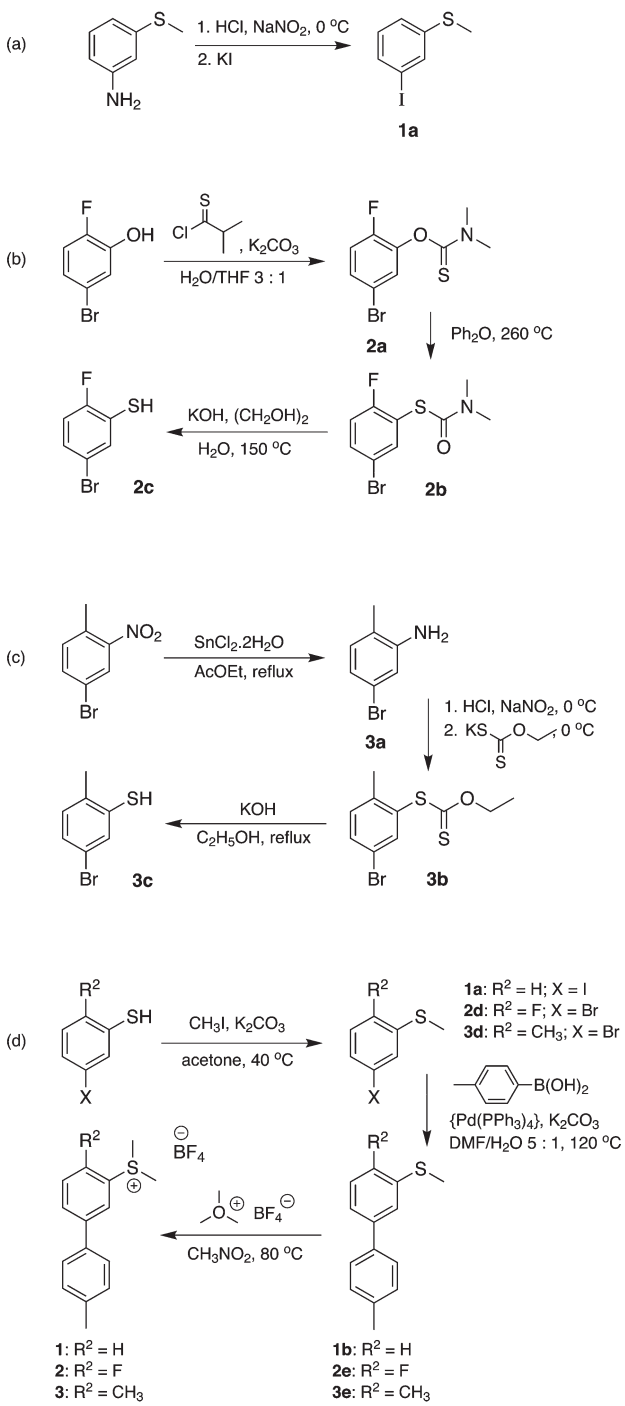


Fig. 2 (a) Equilibrium between *syn* and *anti* conformations of biphenyls **1–3**. (b) Electrostatic potential map superimposed on the isodensity surface of biphenyl *anti*-**3** (isovalue 0.004); rainbow color coding, with dark blue indicating particularly positive regions and yellow neutral regions.



Scheme 1 (a) Preparation of sulfide **1a**; preparation of key thiol intermediates (b) **2c** and (c) **3c**; (d) preparation of biphenyls **1–3** from the corresponding thiols.

The very low rotation barriers along the C_{aryl}–S bond of derivatives **1–3** (2.1, 3.8 and 6.9 kcal mol^{-1}, respectively)[10] render the accurate determination of the *syn*/*anti* ratio by NMR experiments at low temperature impossible.[11] Therefore, we decided to extract the information by using density functional theory (DFT) as well as Hartree–Fock and second order Møller–Plesset perturbation (MP2). The geometries of the three pairs

Table 1 Calculated stabilities $\Delta G_{syn\rightarrow anti}$ of *anti*-conformers relative to *syn* conformers in aqueous medium and, between parentheses, in the gas phase[a]

	B3LYP-D	B97-D	B97-D3-(BJ)	PW6B95-D3-(BJ)	MP2
1	−0.2 (−0.1)	−0.2 (−0.1)	−0.2 (−0.1)	−0.2 (−0.1)	−0.2 (−0.1)
2	+0.8 (+2.3)	+0.2 (+1.7)	−0.3 (+1.2)	+0.4 (+1.9)	0.0 (+1.5)
3	−2.4 (−2.0)	−2.5 (−2.1)	−3.2 (−2.7)	−3.2 (−2.8)	−3.5 (−3.1)

[a] In kcal mol^{-1}; negative values indicate *anti*-preference.

of *syn* and *anti*-conformers were optimized using the B3LYP-D[12,13] hybrid and triple-ζ, doubly polarized def2-TZVPP basis sets.[14] Single-point calculations were then carried out using the B97-D,[13,15] B97-D3(BJ)[15,16] and PW6B95-D3(BJ)[16,17] functionals to refine the electronic contributions to the *syn*/*anti* preferences, and vibrational analysis was performed with the B3LYP-D hybrid to extract Gibbs free energies at 25 °C (see Table 1). Energies were finally corrected with a solvation term, calculated using the polarizable continuum solvation model (IEFPCM)[18] at the B97-D level. Since the interaction between substituents R[2] and the methyl groups of the dimethylsulfonium unit (or its opposite lone pair of electrons) operates essentially through space, with interatomic distances ranging from 2 to 5 Å, all tested functionals have been corrected for medium and long-range dispersive interactions using Grimme's DFT-D[13] or DFT-D3(BJ)[16] methods (the latter being the most recent version). These corrections are especially important since dispersive interactions are maximal at approximately 3 Å.[19] The choice of the four functionals was based in part on one of our recent studies, where we showed that the B3LYP-D and B97-D hybrids afforded highly accurate barriers of torsional isomerisation for a 46-member set of substituted biphenyls,[20] and on Grimme's recent thorough benchmark,[21] which recommends the use of the B97-D3(BJ) GGA and the PW6B95-D3(BJ) hybrid. Some six years ago, the B97-D functional had also been shown to accurately evaluate interaction energies in supramolecular assemblies.[19] Finally, we carried out optimizations and vibrational analysis at the MP2/def2-TZVPP level to compare this widely used method with DFT-D.

In the gas phase, all functionals as well as MP2 calculations indicate that (1) biphenyl **1** is present as a 1 : 1 mixture of *syn* and *anti*-conformers ($\Delta G_{syn\rightarrow anti}$ −0.08 kcal mol^{-1} on average), (2) the *syn* conformation of fluorinated biphenyl **2** is clearly favored ($\Delta G_{syn\rightarrow anti}$ +1.7 ± 0.4 kcal mol^{-1} on average, corresponding to a 95 : 5 *syn*/*anti* ratio), and (3) biphenyl **3** adopts almost exclusively the *anti*-conformation ($\Delta G_{syn\rightarrow anti}$ −2.5 ± 0.5 kcal mol^{-1}; *syn*/*anti* ratio 1 : 99; see Table 1). We should note that although favorable Columbic and van der Waals interactions between the 4-fluoro-substituent of biphenyl **2** and the two methyl groups of the sulfonium unit are certainly responsible for the observed *syn* preference, the presence of the fluorine atom is overall destabilizing, regardless of the conformation of the sulfonium group: in a virtual equilibrium, biphenyl **1** and fluorobenzene are favored over biphenyl **2** and benzene, by 3.1 and 5.1 kcal mol^{-1} with *syn* and *anti* conformers, respectively.[10] The destabilization is most likely due to steric congestion when the fluoro and dimethylsulfonium groups are vicinal.

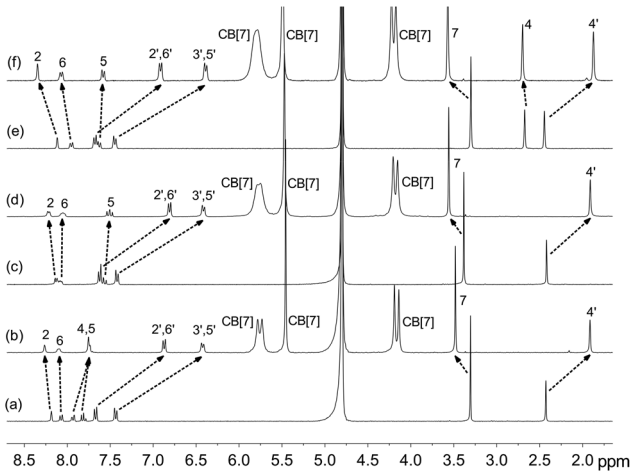


Fig. 3 ^{1}H NMR spectra of (a) biphenyl **1** and (b) its inclusion complex with CB[7]; (c) biphenyl **2**, (d) assembly **2**·CB[7], (e) biphenyl **3** and (f) assembly **3**·CB[7]. Measurements carried out in deuterium oxide. See Fig. 2 for numbering.

In aqueous solution however, the *syn* preference of biphenyl **2** is almost entirely counterbalanced by stronger solvation of the *anti*-conformer (−44.8 *vs.* −43.3 kcal mol^{-1}). This effect is likely due to the concomitant shielding of a large surface surrounding the positively charged sulfonium unit and of one side of the fluorine substituent from solvent interactions. A similar preference is observed with biphenyl **3**, albeit weaker. According to calculations, *syn* and *anti*-conformers of biphenyls **1** and **2** co-exist in 42 : 58 and 60 : 40 ratios, respectively ($\Delta G_{syn\rightarrow anti}$ −0.18 ± 0.03 and +0.2 ± 0.4 kcal mol^{-1}), and biphenyl **3** is present exclusively in its *anti*-conformation ($\Delta G_{syn\rightarrow anti}$ −3.0 ± 0.5 kcal mol^{-1}; *syn*/*anti* ratio > 1 : 99). Experimentally, we can confirm the trends in *syn*/*anti* selectivities by NOESY experiments. In the case of biphenyl **1**, volume integrals of NOESY cross-peaks between H(7)/H(2) and H(7)/H(4) (see Fig. 2 for numbering) are of similar magnitude, and confirm the presence of an approximately equimolar ratio of *syn* and *anti*-conformers. An intense H(7)/H(2) cross-peak and the absence of H(7)/4-CH_3 cross-peaks indicate that biphenyl **3** adopts exclusively the *anti*-conformation. A moderate H(7)/H(2) cross-peak is also observed with biphenyl **2**, approximately half as intense as the H(7)/H(2) signal of biphenyl **3** (the volume integrals of H(3′)/4′-CH_3 and H(5′)/4′-CH_3 cross-peaks are used as reference in both cases). This again suggests the presence of approximately equimolar amounts of *syn* and *anti*-conformers in biphenyl **2**.

Upon interaction with CB[7], the terminal 4′-CH_3 group, as well as hydrogens H(2′), H(3′), H(5′) and H(6′) from the neighboring aryl unit, undergo strong upfield shifts (0.53, 1.02 and 0.79 ppm on average in the case of 4′-CH_3 hydrogens, *meta*'- and *ortho*'-hydrogens, respectively); to the contrary, dimethylsulfonium hydrogens H(7) are shifted upfield (0.21 ppm on average; see Fig. 3). These shifts indicate that the 4′-tolyl

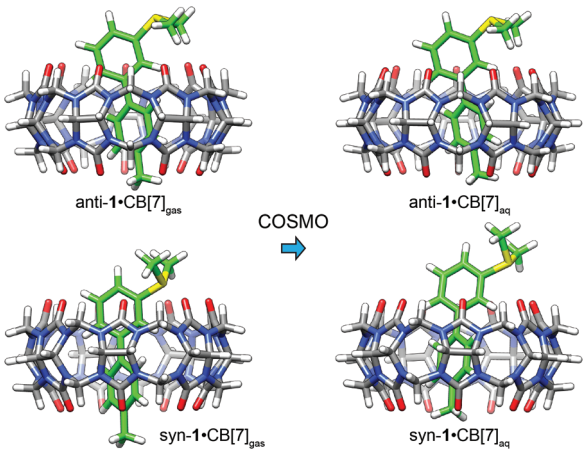


Fig. 4 Optimized structures of assemblies *syn*-**1**·CB[7] and *anti*-**1**·CB[7] in the "gas phase" and in "aqueous medium", calculated at the B97-D/SVP level without and with the COSMO solvation model, respectively.

moieties of biphenyls **1–3** are located inside the cavity of the macrocycle, and the dimethylsulfonium groups are dominating one of the portals.

The modelling of the interaction between CB[7] and biphenyls **1–3** is challenging. All tested optimization methods (force fields, semi-empirical and DFT-D) propose that CB[7] is sitting between the two aryl units, with 4′-CH_3 substituents located outside the macrocycle (see complexes *anti*-**1**·CB[7]$_{gas}$ and *syn*-**1**·CB[7]$_{gas}$, Fig. 4), in stark contrast with experimental results. Such an arrangement may well be valid in the gas phase to maximize dispersive interactions between the 4′-CH_3 substituent (as well as hydrogens H(3′) and H(5′)) and the carbonylated portal of CB[7]. Only when DFT-D optimizations (at the B97-D/SVP level) are carried out with corrections for solvation (either by using IEFPCM or the conductor-like screening model COSMO),[22] the 4′-CH_3 group translates further inside the cavity of CB[7] to allow proper solvation of the carbonylated rim (see assemblies *anti*-**1**·CB[7]$_{aq}$ and *syn*-**1**·CB[7]$_{aq}$, Fig. 4). Although improved compared to "gas phase" optimizations, the "solvated" assemblies are still not satisfactory, since hydrogens H(2) and 4′-CH_3 are located at the level of the CB[7] portal, while experimentally, they undergo contrasted chemical shifts (+0.09 and −0.52 ppm, respectively, in the case of biphenyl **1**; see Table 2). We suspect that solvation effects are still underestimated during optimizations, and thus the 4′-CH_3 substituent should sit further inside the cavity of CB[7]. However, one should note that the exchange rates between CB[7] and biphenyls **1–3** are fast on the NMR time scale, and thus energy profiles describing the binding processes are inevitably shallow and difficult to model accurately.

Binding affinities between CB[7] and biphenyls **1–3** were subsequently determined by isothermal titration calorimetry (ITC). Surprisingly, they were very similar, with binding constants equal to 1.3×10^6, 1.8×10^6 and 1.1×10^6 M^{-1}, respectively. A barely significant increase in binding enthalpies is measured with increasingly electron-donating 4-substituents, ranging from −8.3 kcal mol^{-1} in the case of fluorobiphenyl **2** to −8.9 kcal mol^{-1} with methylated biphenyl **3** (see Table 3); this enthalpic improvement is counterbalanced by an increasingly high entropic penalty along the same sequence ($T\Delta S$ ranging from +0.20 kcal mol^{-1} with biphenyl **2** to −0.67 kcal/mol for biphenyl **3**), thereby reversing the trend in affinity. We should note however, that this possible enthalpy–entropy compensation spans a very narrow range of enthalpies and entropies, compared to the uniquely wide distributions of these two parameters observed with CB[7]/guest complexes; with binding affinities of approximately 10^6 M^{-1}, enthalpy contributions have been measured between −14 and −2 kcal mol^{-1}, and entropy between −7 and +6 kcal mol^{-1}, respectively![6e] Therefore, we will not attempt to justify the minor variations described above.

Table 2 Chemical shifts measured upon CB[7] encapsulation[a]

	H(4′)	H(3′), H(5′)	H(2′), H(6′)	H(2)	H(6)	H(7)
1	−0.52	−1.01	−0.80	+0.09	+0.03	+0.18
2	−0.51	−1.00	−0.81	+0.09	−0.02	+0.18
3	−0.57	−1.06	−0.77	+0.23	+0.11	+0.27

[a] In ppm; negative values indicate upfield shifts. See Fig. 2 for numbering.

Table 3 Thermodynamic parameters describing the interaction between guests **1–5** and CB[7], as determined by ITC

	ΔH^a	ΔS^b	$T\Delta S^c$	ΔG^d	K^e
1	−8.7 (± 0.1)	−1.2 (± 0.1)	−0.4 (± 0.1)	−8.4 (± 0.1)	1.3 (± 0.1) × 10^6
2	−8.3 (± 0.1)	0.7 (± 0.2)	0.2 (± 0.1)	−8.6 (± 0.1)	1.8 (± 0.1) × 10^6
3	−8.9 (± 0.1)	−2.2 (± 0.1)	−0.7 (± 0.1)	−8.2 (± 0.1)	1.1 (± 0.1) × 10^6
4	−6.2 (± 0.1)	−6.6 (± 0.3)	−2.0 (± 0.1)	−4.2 (± 0.1)	1.2 (± 0.1) × 10^3
5	−8.8 (± 0.3)	−6.9 (± 1.0)	−2.1 (± 0.3)	−6.8 (± 0.3)	8.9 (± 0.5) × 10^4

[a] Binding enthalpy [kcal mol^{-1}]. [b] Binding entropies [cal mol K^{-1}]. [c] Entropic component to the interaction [kcal mol^{-1}]. [d] Free energy of binding [kcal mol^{-1}]. [e] Binding affinity [M^{-1}]. Errors between parentheses.

Relative binding affinities between pairs of biphenyls obtained by competitive ^{1}H NMR titrations in the presence of CB[7] afford similar results; a minor discrepancy was obtained for the binding affinity of biphenyl **2** relative to biphenyl **1** (a 2.3-fold difference was determined by NMR experiments, compared to a 1.4-fold preference by ITC).

These unexpectedly similar binding affinities let us envision two borderline scenarios when biphenyls **1** and **2** interact with CB[7]: (1) *anti* conformers may undergo torsional isomerisation along their C_{aryl}–S axis to afford complexes *syn*-**1**·CB[7] and *syn*-**2**·CB[7] exclusively. However, if the latter option were favorable, biphenyl **3**, which is forced to remain in its *anti*-conformation, would display a much weaker affinity for CB[7] compared to biphenyls **1** and **2** (the 2.8 kcal mol^{-1} penalty for *anti* → *syn* isomerisation would translate into an approximately 600-fold decrease in binding affinity). (2) On the opposite side of the continuum, *syn*-conformers may isomerize upon encapsulation with CB[7], thereby affording assemblies *anti*-**1**·CB[7] and *anti*-**2**·CB[7] exclusively. This option is plausible since

electrostatic potential maps of the biphenyls in their *anti* conformation show an electron-deficient area surrounding the two methyl groups of the sulfonium unit exposed to the CB[7] portal (see Fig. 2b). However, if this scenario were correct, the dimethylsulfonium hydrogens H(7) of biphenyls **1** and **3** would undergo similar downfield shifts of approximately 0.27 upon encapsulation (since biphenyl **3** must remain in its *anti*-conformation while interacting with CB[7], see Fig. 3, spectra e and f). This is clearly not the case; hydrogens H(7) of biphenyl **1** are deshielded by only 0.18 ppm (see Fig. 3, spectra a and b, and Table 2). This effect is particularly visible in a competitive binding experiment between biphenyls **1** and **3** and CB[7] (see Fig. 5), with hydrogens H(7) of biphenyl **1** resonating at higher frequencies than biphenyl **3** in the absence of CB[7] (3.32 *vs.* 3.29 ppm, see spectrum a), and at lower frequencies when both guests are encapsulated inside the macrocycle (3.50 *vs.* 3.57 ppm; spectrum o). 4′-Methyl hydrogen H(4′) and especially hydrogens H(2) of biphenyls **1** and **3** can also been used as probes, and show very different chemical shifts upon interaction with CB[7]. H(4′) hydrogens are shifted upfield by 0.52 and 0.57 ppm, respectively, and H(2) nuclei are shifted downfield by 0.09 ppm in the case of biphenyl **1** and up to 0.23 ppm in biphenyl **3** (see Table 2).

The dismissal of the two borderline scenarios described above, reinforced by uniform CB[7]/guest binding affinities, strongly suggests that CB[7] encapsulation has little, if any effect on the *syn*/*anti* ratios of biphenyls **1–3**. The identical chemical shifts of hydrogens H(2), H(4′) and H(7) measured upon encapsulation of biphenyls **1** and **2** (+0.09, −0.52 and +0.18 ppm, respectively; see Table 2) indicate that the two guests are not only similarly affected by CB[7], but have indeed similar *syn*/*anti* ratios in both their free and bound forms (as long as the effects of the macrocycle and of the 4-substituents are cumulative, which is likely).

One can thus conclude that in this study, supramolecular buttressing only affects the position of the guests inside CB[7] (or more generally the geometry of our A·B assemblies; see introduction), but not the binding affinities of the two units. When the biphenyl derivatives adopt an *anti*-conformation, the two methyl groups of the dimethylsulfonium substituent are in direct contact with the "upper" carbonylated portal of CB[7], and tend to lift the encapsulated 4-tolyl unit further inside the cavity. Chemical shifts observed for H(4′) and H(3′) upon binding are −0.57 and −1.06 ppm for biphenyl *anti*-**3**, *vs.* −0.52 and −1.01 ppm with approximately 1 : 1 mixtures of *syn*- and *anti*-biphenyls **1** and **2**; during the "lifting process" of *anti*-conformers, H(2′) and H(6′) hydrogens are moving closer to the upper rim (the chemical shift upon CB[7] binding is −0.77 ppm in *anti*-biphenyl **3** *vs.* −0.81 ppm in mixtures of *syn*- and *anti*-biphenyls **1** and **2**). In their *syn*-conformations, biphenyls **1** and **2** lack proper contact between the dimethylsulfonium substituent and the upper CB[7] rim, and thus the encapsulated 4-tolyl moiety is located closer to the opposite "lower" portal compared to *anti*-conformers.

The lack of clear *anti* preference in CB[7]/biphenyl assemblies is very surprising, considering that Columbic interactions between the upper carbonylated portal of CB[7] and the region of low electron density surrounding the two methyl groups of the sulfonium substituent should favor this conformation (see Fig. 2b). Moreover, repulsion between the rim of CB[7] and the sulfur lone pair in a *syn* conformation should have further destabilized this arrangement. To assess the impact of the positively charged substituent on the binding affinity, we prepared biphenyl **4** (see Scheme 2), which bears a neutral isopropyl substituent instead of a dimethylsulfonium group at position 3, and a carboxylate group at the 4-position to enhance water solubility. Similar chemical shift patterns are observed upon interaction of biphenyls **3** and **4** with CB[7] (see Fig. 6; the lack of chemical shift of the 2-isopropyl hydrogen nucleus H(3) and the moderate downfield shifts of the two

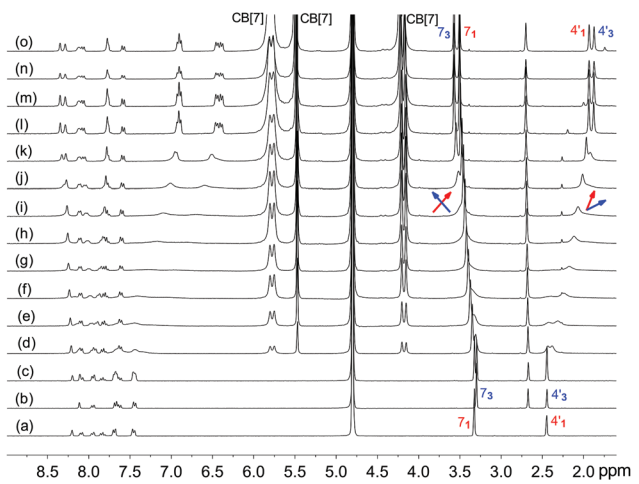
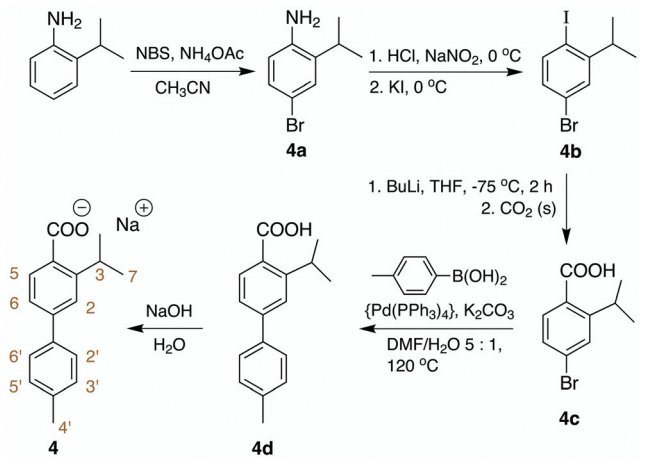


Fig. 5 ^{1}H NMR spectra of (a) free biphenyl **1**; (b) free biphenyl **3** and (c) biphenyls **1** and **3**. (d)–(o) Competitive ^{1}H NMR titration of biphenyls **1** and **3** (2.0 mM each) in the presence of increasing amounts of CB[7] (up to 6.0 mM; 0.50 mM increments) in deuterium oxide. Red arrows indicate the trend of hydrogens H (7) and H(4′) in biphenyl **1**, and blue arrows in biphenyl **3**.



Scheme 2 Preparation of carboxylate **4**, an isosteric, yet negatively charged analog of biphenyls **1–3**.

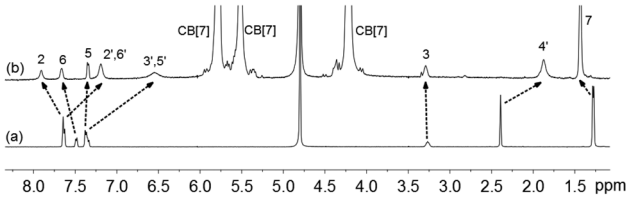


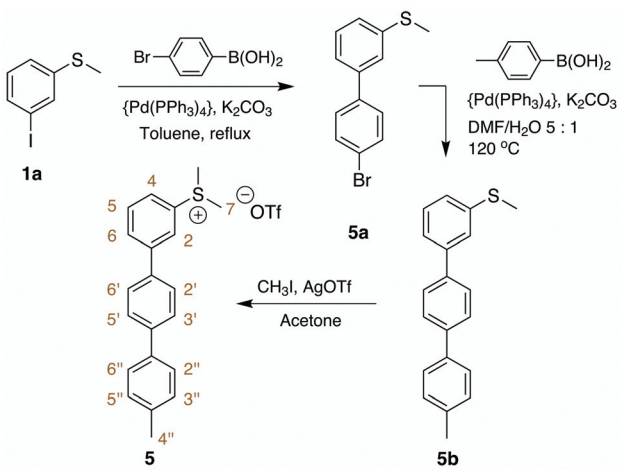
Fig. 6 ^{1}H NMR spectra of (a) biphenyl **4** and (b) its inclusion complex with CB[7]. See Scheme 2 for numbering.

neighboring methyl hydrogens H(7) clearly indicate *anti*-preference).

The affinity of biphenyl **4** towards CB[7] reached only 1.2×10^3 M^{-1}, approximately 1000 times weaker than biphenyl **1**, thereby indicating that Columbic forces do play a role in the interaction between biphenyls **1–3** and CB[7], even when the latter adopt a *syn* conformation. To reconcile this dilemma, we suggest that CB[7]-bound biphenyls **1** and **2** leave more water-accessible surface area in their *syn* conformation, and allow for a better solvation of the partially shielded upper carbonylated portal. Since the 4-tolyl group does not pierce through the lower CB[7] portal, Columbic interactions between the sulfonium unit of *syn*-biphenyls **1** and **2** and the upper CB[7] rim are likely mediated by water. We also note that the 1000-fold decrease in binding affinity, when the positive sulfonium anchor is replaced with an approximately isosteric isopropyl group, is reminiscent of the difference in CB[*n*] affinity between organic ammonium salts and their conjugate base (ratios between 16 and 3.2×10^4 are common).[6e,23]

Finally, we wanted to assess whether the dimethylsulfonium group could still interact with the carbonylated rim of CB[7], possibly *via* water mediation, if the separation between the two units became longer. To that aim, we designed terphenyl **5** (see Scheme 3), and envisioned two modes of interaction with CB[7]: (1) similarly to biphenyl **1**, the terminal 4″-methyl may behave as a pivot inside the cavity of the macrocycle, while leaving the lower carbonylated portal unshielded and fully available for interactions with the solvent; in this case, the sulfonium group would be fully detached from the upper CB[7] rim, regardless of its conformation. Water-mediated Columbic interactions would be consistent with terphenyl **5** binding to CB[7] with a stronger affinity than biphenyl **4** (*i.e.* greater than 1.2×10^3 M^{-1}). (2) The terphenyl axle may pierce through both CB[7] portals to allow direct contact between the sulfonium unit and the upper carbonylated rim of the macrocycle; in this case, an affinity ranging from 1.2×10^3 M^{-1} (biphenyl **4**) to 1.3×10^6 M^{-1} (biphenyl **1**) is expected. The ratio of the affinity of biphenyl **1** and terphenyl **5** would then correspond to the energy penalty imposed to the assembly for disrupting the solvation of the lower CB[7] portal.

^{1}H NMR spectroscopy validated the second scenario, since H(4″) hydrogens were barely shifted upfield upon addition of CB[7], contrary to hydrogens connected to the central phenyl unit at positions 2′, 6′, 3′ and 5′ which were shifted upfield by approximately 0.5 ppm. More peculiar is the weak or moderate upfield shift of *all* signals, including those from the dimethylsulfonium group H(7) (see Fig. 7, spectra a and b), which indicates that CB[7] shuttles along the terphenyl axle and sometimes even surrounds the positively charged group. The concomitant formation at higher CB[7] concentrations (>2.5 mM) of what is likely the loose ternary complex **5**·(CB[7])$_2$ was another surprise. Under these conditions, hydrogens H(7) and those at the opposite terminal phenyl ring were further shifted upfield, while hydrogens from the central aryl unit underwent downfield shifts (see Fig. 7, spectrum c). ITC experiments afforded a binding affinity of 8.9×10^4 M^{-1},[24] 15 times weaker than biphenyl **1**. This difference represents a 1.6 kcal mol^{-1} penalty for the disruption of the solvation shell surrounding the lower CB[7] portal, and is surprisingly entirely entropic in nature (binding enthalpies of biphenyls **1** and terphenyl **5** are −8.7 and −8.8 kcal mol^{-1}, while their binding entropies are −0.4 and −2.1 kcal mol^{-1}, respectively). A similar 13-fold difference was measured when comparing the affinities of pentyl- and hexylammonium towards CB[6] in a sodium chloride solution;[25] in this case, the aliphatic tail of the hexylammonium cation disrupted the interaction between sodium and the CB[6] portal.



Scheme 3 Preparation of terphenyl **5** by two consecutive Suzuki couplings.

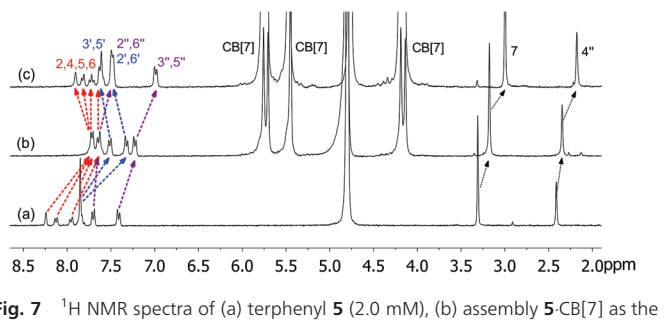


Fig. 7 ^{1}H NMR spectra of (a) terphenyl **5** (2.0 mM), (b) assembly **5**·CB[7] as the major component in the presence of 2.5 mM CB[7], and (c) a likely mixture of [2]pseudorotaxane **5**·CB[7] and [3]pseudorotaxane **5**·(CB[7])$_2$ in the presence of a higher concentration of CB[7] (7.0 mM). See Scheme 3 for numbering.

Conclusions

We have shown that the buttressing of 3-dimethylsulfonium groups by vicinal 4-substituents mildly affects the geometry of CB[7]-bound biphenyls **1–3**, and in particular the extent of guest penetration inside the cavity of the macrocycle, thereby illustrating our concept of "supramolecular buttressing". When the biphenyl derivatives adopt an *anti*-conformation, the two methyl groups of the dimethylsulfonium substituent are in direct contact with the upper carbonylated portal of CB[7], and tend to lift the encapsulated 4-tolyl unit further inside the cavity. In their *syn*-conformations, biphenyls **1** and **2** lack proper support from the dimethylsulfonium substituent at the upper CB[7] rim, and therefore the trapped 4-tolyl unit is sitting closer to the opposite lower portal. However, the 4-tolyl group does not pierce through the lower portal to maximize Coulombic interactions between the sulfonium unit and the opposite rim of CB[7]; to the contrary, the lower portal remains fully solvated, and Coulombic interactions between the sulfonium unit and the upper CB[7] rim are likely mediated by water. The predominant role of solvation in the overall binding processes makes modelling particularly challenging. The polarizable continuum solvation model or the conductor-like screening model improve the accuracy of host–guest structure optimization, but are still not satisfactory. Whenever guests are not anchored to both CB[7] portals *via* dipole–dipole interactions, and their encapsulated moieties are not tightly nested inside the cavity of the macrocycle, we recommend using modeling with extra caution.

While supramolecular buttressing affects geometries, it does not influence binding affinities between CB[7] and the biphenyl guests. Regardless of the nature of the 4-substituent (H, F and CH_3), all binding constants range from 1.1 to 1.8 × 10^6 M^{-1}. Interactions between CB[7] and biphenyls **1–3** have thus no significant effect on *syn*/*anti* ratios, although CB[7] binding to *anti*-conformers had been expected to be much more favorable compared to *syn*-conformers. Here again, solvation dominates the recognition process and smoothes the influence of Coulombic interactions. The latter still play a role though; when the 3-dimethylsulfonium unit is replaced by the approximately isosteric isopropyl substituent, and a negative carboxylate group is attached to position 4 to enhance water solubility, the affinity of the guest decreases by 1000-fold. Also, when biphenyl scaffolds are replaced by a terphenyl unit, the longer axle pierces through both CB[7] portals to allow direct contact between the 3-dimethylsulfonium substituent and the upper CB[7] rim. Solvation of the lower rim is thus reminiscent of a thin membrane capping a container: interactions between sulfonium groups and the upper rim of CB[7], even when mediated by a thin water layer, can prevent perforation of the lower rim; to the contrary, the guest pierces the lower rim when the separation between the upper rim and the positive surface of the guest would have been too long otherwise.

Overall, supramolecular buttressing is a valid concept, although it operates in a milder manner than initially envisioned, at least with these CB[7]-containing assemblies. Solvation effects are not only key to the understanding of CB[*n*] recognition, but are also the main contributors to the subtlety of supramolecular buttressing.

Experimental section

Generalities

Starting materials were purchased from Sigma-Aldrich (St. Louis, MO), TCI America (Portland, OR) and Cambridge Isotope Laboratories (Andover, MA). ^{1}H NMR spectra were recorded at 300 MHz using a Bruker 300 spectrometer (Billerica, MA) and ^{1}H-decoupled ^{13}C NMR spectra were obtained at 75.5 MHz using the same Bruker 300 spectrometer at 25 °C. Chemical shifts δ refer to the residual HDO signal (δ 4.80 ppm) when the solvent is D_2O or to the residual CH_3CN signal (δ 1.96 ppm) when the solvent is acetonitrile-d^3. Products were also characterized by high-resolution mass spectrometry (HRMS) performed at the COSMIC facility of the Old Dominion University (Norfolk, VA) using a Bruker Daltonics 12 Tesla APEX-Qe FTICR mass spectrometer with an Apollo II Ion Funnel. CB[7] binding assays, including competitive binding experiments in the presence of two guests, were carried out using previously described methods.[26] ITC experiments were performed using an iTC_{200} calorimeter (Microcal Inc., GE Healthcare, Piscataway, NJ). Computational work was carried out using the Glenn cluster (IBM 1350) at the Ohio Supercomputer Center (Columbus, OH).

Intermediates and final products

3-Iodothioanisole (1a). To a solution of 3-(methylthio)-aniline (1.0 g, 7.2 mmol) in water (10 mL) at 0 °C was added conc. HCl (3.7 mL) followed by an aqueous solution of sodium nitrite (1.0 g, 15 mmol) in water (5.0 mL) over 30 min. The solution was kept at 0 °C for 1 h until the dropwise addition of a potassium iodide (2.4 g, 15 mmol) solution in water (10 mL). The reaction mixture was then kept at 25 °C for 6 h. The product was extracted with dichloromethane (3 × 50 mL), washed with water (0.10 L) and brine (0.10 L), dried with Na_2SO_4 and concentrated. The product was purified by chromatography (silica gel; eluent: petroleum ether–CH_2Cl_2, 19 : 1) to afford a light yellow liquid (1.2 g, 67%). ^{1}H NMR (CD_3CN): δ 7.63 (s, Ar-*H*, 1H), 7.53 (d, J = 9.0 Hz, Ar-*H*, 1H), 7.28 (d, J = 9.0 Hz, Ar-*H*, 1H), 7.08 (t, J = 6.0 Hz, Ar-*H*, 1H), 2.15 (s, S(CH_3), 3H) ppm. ^{13}C NMR: δ 141.6, 135.0, 134.9, 131.4, 126.4, 95.4 (Ar*C*), 16.1 (S(CH_3)) ppm. HRMS (ESI) m/z calcd for C_7H_7IS ($[M + H]^+$) 250.938590, found 250.938563.

Methyl(4′-methylbiphenyl-3-yl)sulfane (1b). A solution of potassium carbonate (0.82 g, 6.0 mmol) in H_2O (10 mL) was added to a solution of sulfide **1a** (0.75 g, 3.0 mmol), 4-tolylboronic acid (0.61 g, 4.5 mmol) and palladium(0) tetrakis-(triphenylphosphine) (0.32 g, 0.30 mmol) in *N*,*N*-dimethylformamide (50 mL) under inert atmosphere. The resulting mixture was heated at 120 °C for 12 h. After cooling to 25 °C, the reaction was filtered through a pad of celite. The filtrate was then poured into ice-cold water (30 mL), acidified with

1.0 M HCl (30 mL), and extracted with dichloromethane (3 × 30 mL). The organic fractions were washed with water (60 mL) and brine (60 mL), dried with anhydrous sodium sulfate, then concentrated *in vacuo*. The product was purified by chromatography (silica gel; eluent: hexane–dichloromethane, 49 : 1) to afford a colourless oil (0.42 g, 65%). ^{1}H NMR (CD_3CN): δ 7.54–7.52 (m, Ar-*H*, 3H), 7.38–7.37 (m, Ar-*H*, 2H), 7.28–7.26 (m, Ar-*H*, 3H), 2.53 (s, S(CH_3), 3H), 2.39 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 142.6 (Ar*C*), 140.3 (Ar*C*), 138.6 (Ar*C*), 138.5 (Ar*C*), 130.6 (Ar*C* × 2), 130.4 (Ar*C*), 127.9 (Ar*C* × 2), 125.8 (Ar*C*), 125.4 (Ar*C*), 124.5 (Ar*C*), 21.3 (Ar*C*), 15.8 (S(*C*H_3)) ppm. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}S$ ([M + H]$^+$) 215.088898, found 215.088971.

Dimethyl(4′-methylbiphenyl-3-yl)sulfonium tetrafluoroborate (1). Trimethyloxonium tetrafluoroborate (76 mg, 0.51 mmol) was added to a solution of biphenyl **1b** (0.10 g, 0.47 mmol) in nitromethane (3.0 mL) under nitrogen atmosphere. The reaction mixture was heated to 80 °C for 12 h. After cooling to 25 °C, methanol (10 mL) was added, and the solvent was evaporated under vacuum. Addition of diethyl ether (15 mL) resulted in the formation of the title compound as a white solid (0.14 g, 95%); m.p. 113–114 °C. ^{1}H NMR (CD_3CN): δ 8.16 (s, Ar-*H*, 1H), 8.03 (d, *J* = 7.7 Hz, Ar-*H*, 1H), 7.89 (d, *J* = 7.9 Hz, Ar-*H*, 1H), 7.78 (t, *J* = 8.0, Ar-*H*, 1H), 7.65 (d, *J* = 8.1 Hz, Ar-*H*, 2H), 7.36 (d, *J* = 7.9 Hz, Ar-*H*, 2H), 3.23 (s, S(CH_3)$_2$, 6H), 2.42 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 144.6 (Ar*C*), 140.1 (Ar*C*), 136.4 (Ar*C*), 133.6 (Ar*C*), 132.4 (Ar*C*), 130.9 (Ar*C* × 2), 129.1 (Ar*C*), 128.8 (Ar*C*), 128.2 (Ar*C* × 2), 127.0 (Ar*C*), 29.3 (S(*C*H_3)$_2$), 21.3 (Ar*C*H_3). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}S$ ([M]$^+$) 229.104548, found 229.104452.

***O*-(5-Bromo-2-fluorophenyl)dimethylthiocarbamate (2a).** Potassium carbonate (3.6 g, 26 mmol) was added to a solution of 5-bromo-2-fluorophenol (5.0 g, 26 mmol) in water (30 mL), and the resulting solution was kept at 25 °C for 15 min, then cooled to 10 °C. A solution of *N*,*N*-dimethylthiocarbamoylchloride (4.2 g, 34 mmol) in tetrahydrofuran (10 mL) was added subsequently. The reaction mixture was stirred at 25 °C for 6 h and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with water (0.15 L) and brine (0.15 L) and concentrated *in vacuo*. The product was purified by chromatography (silica gel; eluent: hexane–dichloromethane, 9 : 1) to afford a white solid (3.6 g, 50%); m.p. 100–102 °C. ^{1}H NMR (CD_3CN): δ 7.48–7.41 (m, Ar-*H*, 1H), 7.37–7.34 (m, Ar-*H*, 1H), 7.16 (t, *J* = 9.7 Hz, Ar-H, 1H), 3.38 (s, NCH_3, 3H), 3.31 (s, NCH_3, 3H) ppm. ^{13}C NMR: δ 186.9 (s, ArO*C*S), 155.1 (d, *J* = 248 Hz, Ar*C*F), 143.1 (d, *J* = 13.1 Hz, Ar*C*O), 131.2 (d, *J* = 7.8 Hz), 129.3 (Ar*C*), 119.1 (d, *J* = 20.5 Hz), 116.4 (d, *J* = 3.4 Hz), 41.7 (N(*C*H_3)$_2$) ppm. HRMS (ESI) *m*/*z* calcd for $C_9H_9BrFNOS$ ([M + Na]$^+$) 299.946446, found 299.946435.

***S*-(5-Bromo-2-fluorophenyl)dimethylthiocarbamate (2b).** Dimethylthiocarbamate **2a** (3.6 g, 13 mmol) was dissolved in diphenyl ether (0.10 L) and heated to 260 °C for 10 h. After cooling, the reaction mixture was loaded onto a silica gel column and eluted with hexane. After the elution of diphenyl ether, the product was isolated (eluent: hexane–ethyl acetate 1 : 1) as a light brown solid (3.2 g, 89%); m.p. 80–81 °C. ^{1}H NMR (CD_3CN): δ 7.71–7.62 (m, Ar-*H*, 2H), 7.18 (t, *J* = 8.7 Hz, Ar-*H*, 1H), 3.10 (s, NCH_3, 3H), 3.00 (s, NCH_3, 3H) ppm. ^{13}C NMR: δ 163.2 (d, *J* = 248 Hz, Ar*C*F), 164.3 (ArS*C*O), 140.9 (Ar*C*), 135.8 (d, *J* = 8.3 Hz, Ar*C*), 120.2 (d, *J* = 20.3 Hz, Ar*C*), 118.7 (Ar*C*), 116.8 (d, *J* = 3.7 Hz, Ar*C*), 37.4 (N(*C*H_3)$_2$) ppm. HRMS (ESI) *m*/*z* calcd for $C_9H_9BrFNOS$ ([M + Na]$^+$) 299.946446, found 299.946317.

5-Bromo-2-fluorobenzenethiol (2c). To a solution of thiocarbamate **2b** (3.2 g, 12 mmol) in ethylene glycol (60 mL) was added potassium hydroxide (0.97 g, 17 mmol) in water (17 mL) and the mixture was heated to 150 °C for 6 h. The reaction was cooled to 0 °C, diluted with water and acidified with 1.0 M HCl (0.10 L) before extraction with ethyl acetate (3 × 0.10 L). The combined organic layers were washed with water (0.15 L), brine (0.15 L) and dried with Na_2SO_4. Evaporation of the solvent afforded the title compound as a colorless oil (1.6 g, 67%). ^{1}H NMR (CD_3CN): δ 7.58 (d, *J* = 8.7 Hz, Ar-*H*, 1H), 7.37–7.33 (m, Ar-*H*, 1H), 7.08 (t, *J* = 9.1 Hz, Ar-*H*, 1H), 4.14 (s, S*H*, 1H) ppm. ^{13}C NMR: δ 159.2 (d, *J* = 242 Hz, Ar*C*F), 133.6 (Ar*C*), 130.8 (d, *J* = 7.8 Hz, Ar*C*), 123.0 (d, *J* = 21.4 Hz), 118.1 (Ar*C*), 117.5 (d, *J* = 3.9 Hz, Ar*C*) ppm. HRMS (ESI) *m*/*z* calcd for C_6H_3BrFS ([M]$^{2+}$) 409.824025, found 409.824090.

5-Bromo-2-fluorothioanisole (2d). A mixture of thiol **2c** (1.5 g, 7.2 mmol), methyl iodide (5.1 g, 36 mmol) and dry potassium carbonate (3.0 g, 22 mmol) in acetone (60 mL) was heated to 40 °C for 15 h, before being concentrated. The residue was then dissolved in ethyl acetate (0.10 L) and washed with water (0.10 L) and brine (75 mL), and dried with Na_2SO_4. The evaporation of the solvent afforded the product as a light yellow liquid (1.4 g, 88%). ^{1}H NMR (CD_3CN): δ 7.42 (dd, *J* = 9.1, 2.3 Hz, Ar-*H*, 1H), 7.35–7.30 (m, Ar-*H*, 1H), 7.02 (t, *J* = 9.7 Hz, Ar-*H*), 2.49 (s, S(CH_3), 3H) ppm. ^{13}C NMR: δ 159.7 (d, *J* = 243 Hz, Ar*C*F), 130.5 (d, *J* = 3.3 Hz, Ar*C*), 130.1 (d, *J* = 7.5 Hz, Ar*C*), 129.8 (d, *J* = 18.8 Hz, Ar*C*), 117.9 (d, *J* = 3.3 Hz, Ar*C*), 117.7 (d, *J* = 23.3 Hz, Ar*C*), 14.9 (S(*C*H_3)) ppm.

(4-Fluoro-4′-methylbiphenyl-3-yl)(methyl)sulfane (2e). Prepared similarly to biphenyl **1b**, with 5-bromo-2-fluorothioanisole **2d** (0.50 g, 2.3 mmol) instead of 3-iodothioanisole. The product was purified by chromatography (silica gel; eluent: hexane–dichloromethane, 19 : 1) to afford a colorless oil (0.27 g, 51%). ^{1}H NMR (CD_3CN): δ 7.56–7.52 (m, Ar-*H*, 3H), 7.46–7.41 (m, Ar-*H*, 1H), 7.32 (s, Ar-*H*, 1H), 7.29 (s, Ar-*H*, 1H), 7.17 (t, *J* = 8.8 Hz, 1H), 2.56 (s, S(CH_3), 3H), 2.40 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 160.3 (d, *J* = 242 Hz, Ar*C*F), 139.0 (d, *J* = 3.4 Hz, Ar*C*), 138.6 (Ar*C*), 137.8 (Ar*C*), 130.6 (Ar*C* × 2), 127.9 (Ar*C* × 2), 127 (d, *J* = 17.8 Hz, Ar*C*), 127 (d, *J* = 2.8 Hz, Ar*C*), 126.1 (d, *J* = 8.3 Hz, Ar*C*), 116.3 (d, *J* = 22.0 Hz, Ar*C*), 21.2 (Ar*C*H_3), 15.2 (d, *J* = 2.3 Hz, S(*C*H_3)$_2$) ppm. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{12}FS$ ([M]$^+$) 232.071705, found 232.071651.

(4-Fluoro-4′-methylbiphenyl-3-yl)dimethylsulfonium tetrafluoroborate (2). Obtained similarly to sulfonium **1**, using biphenyl **2e** (0.10 g, 0.43 mmol) instead of biphenyl **1b**. White solid (0.12 g, 86%); m.p. 144–145 °C. ^{1}H NMR (CD_3CN): δ 8.11–8.04 (m, Ar-*H*, 2H), 7.62 (d, *J* = 8.0 Hz, Ar-*H*, 2H), 7.56 (t, *J* = 9.1 Hz, Ar-*H*, 1H), 7.36 (d, *J* = 7.9 Hz, Ar-*H*, 2H), 3.28 (s, S(CH_3)$_2$, 3H), 2.42 (s, Ar-CH_3, 3H). ^{13}C NMR: δ 161.7 (d, *J* = 255 Hz, Ar*C*F),

140.9 (d, J = 3.2 Hz, Ar*C*), 140.0 (Ar*C*), 136.4 (d, J = 8.7 Hz, Ar*C*), 135.7 (Ar*C*), 131.0 (2 × Ar*C*), 130.0 (Ar*C*), 128.1 (2 × Ar*C*), 119.2 (d, J = 21 Hz, Ar*C*), 113.5 (d, J = 14.7 Hz, Ar*C*), 28.6 (d, J = 2.1 Hz, S(CH$_3$)$_2$), 21.2 (ArCH$_3$) ppm. HRMS (ESI) m/z calcd for $C_{15}H_{16}S$ ([M]$^+$) 247.095126, found 247.094982.

5-Bromo-2-methylaniline (3a).[27] Tin chloride dihydrate (21 g, 93 mmol) was added portion wise to a solution of 4-bromo-2-nitrotoluene (5.0 g, 23 mmol) in ethyl acetate (0.10 L) at 0 °C. The reaction mixture was heated to reflux for 4 h and neutralized with 1.0 M NaOH (0.10 L) after cooling to 0 °C. The reaction mixture was filtered and the precipitate washed with ethyl acetate (0.20 L). The combined organic layers were washed with water (2 × 0.10 L) and brine (0.10 L), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by chromatography (silica gel; eluent: hexane–ethyl acetate, 9 : 1) to afford a dark brown liquid (4.2 g, 97%). ^{1}H NMR (CD_3CN): δ 6.89 (d, J = 7.9 Hz, Ar-*H*, 1H), 6.82 (s, Ar-*H*, 1H), 6.72 (d, J = 7.9 Hz, Ar-*H*, 1H), 4.20 (br, NH_2, 2H), 2.07 (Ar-CH_3, 3H) ppm. ^{13}C NMR: 148.6, 132.7, 122.0, 120.7, 120.4, 117.4 (Ar*C*), 17.2 (ArCH$_3$) ppm. HRMS (ESI) m/z calcd for C_7H_8BrN ([M + H]$^+$) 185.991288, found 185.991305.

***S*-5-Bromo-2-methylphenyl *O*-ethyl carbonodithioate (3b).**[27] Concentrated HCl (8.0 mL) was added to a cooled suspension of aniline **3a** (8.5 g, 46 mmol) in water (25 mL) followed by a solution of sodium nitrite (3.2 g, 46 mmol) in water (10 mL) over a 30 min period. The solution was kept at 0 °C for 2 h, and a solution of potassium ethyl xanthate (15 g, 91 mmol) in water (15 mL) was added dropwise. The reaction mixture was then heated to 55 °C for 1 h. The product was extracted with diethyl ether (3 × 0.10 L), washed with water (2 × 0.10 L) and brine (0.10 L), dried with Na_2SO_4 and concentrated. The product was purified by chromatography (silica gel; eluent: hexane); further purification by recrystallization in hexane afforded pure white needles (2.1 g, 16%); m.p. 62–63 °C. ^{1}H NMR (CD_3CN): δ 7.68 (s, Ar-*H*, 1H), 7.57 (d, J = 8.2 Hz, Ar-*H*, 1H), 7.31 (d, J = 8.2 Hz, Ar-*H*, 1H), 4.60 (q, J = 7.1 Hz, OCH_2, 2H), 2.36 (s, Ar-CH_3, 3H), 1.30 (t, J = 7.08 Hz, CH_3, 3H) ppm. ^{13}C NMR: δ 213.0 (*C*S), 143.3, 139.5, 135.1, 134.0, 132.9, 120.3 (Ar*C*), 72.4 (ArCH$_3$), 20.82 (OCH$_2$), 14.3 (ArCH$_3$) ppm. HRMS (ESI) m/z calcd for $C_{10}H_{12}BrOS_2$ ([M + H]$^+$) 290.950745, found 290.950881.

5-Bromo-2-methylbenzenethiol (3c).[27] Xanthate **3b** (3.0 g, 10 mmol) was heated to reflux with potassium hydroxide (1.7 g, 31 mmol) in ethanol (30 mL) for 5 h. The solution was neutralized with HCl (10% in water), extracted with diethyl ether (3 × 75 mL), dried with Na_2SO_4 and evaporated to afford a light yellow liquid (1.9 g, 89%). ^{1}H NMR (CD_3CN): δ 7.82 (s, Ar-*H*, 1H), 7.24 (d, J = 8.1 Hz, Ar-*H*, 1H), 7.11 (d, J = 8.1 Hz, Ar-*H*, 1H), 3.98 (s, Ar-S*H*, 1H), 2.25 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 136.1, 135.6, 133.1, 132.5, 129.7, 120.3 (Ar*C*), 20.82 (ArCH$_3$) ppm. HRMS (ESI) m/z calcd for C_7H_6BrS ([M]$^{2+}$) 401.874168, found 401.874474.

5-Bromo-2-methylthioanisole (3d). A mixture of thiol **3c** (1.7 g, 8.6 mmol), methyl iodide (7.3 g, 51 mmol) and dry potassium carbonate (3.6 g, 26 mmol) in acetone (60 mL) were heated to 40 °C for 15 h. The reaction mixture was concentrated. The product was then dissolved in ethyl acetate (0.10 L), washed with water (2 × 75 mL) and brine (75 mL), and dried with Na_2SO_4. Evaporation of the solvent afforded the title compound as a light yellow liquid (1.8 g, 97%). ^{1}H NMR (CD_3CN): δ 7.31 (s, Ar-*H*, 1H), 7.22 (d, J = 8.1 Hz, Ar-*H*, 1H), 7.09 (d, J = 8.0 Hz, Ar-*H*, 1H), 2.49 (s, S(CH_3), 3H), 2.25 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 142.0, 135.5, 132.5, 128.4, 127.4, 121.1 (Ar*C*), 20.0 (ArCH$_3$), 15.5 (S(CH$_3$)) ppm.

(4,4′-Dimethylbiphenyl-3-yl)methylsulfane (3e). Prepared similarly to biphenyl **1b**, with 5-bromo-2-methylthioanisole **3d** (0.50 g, 2.0 mmol) instead of 3-iodothioanisole. The product was purified by chromatography (silica gel; eluent: hexane–dichloromethane 99 : 1) to afford a colorless oil, which solidifies upon standing (0.32 g, 61%); m.p. 30–31 °C. ^{1}H NMR (CD_3CN): δ 7.56 (d, J = 7.9 Hz, Ar-*H*, 2H), 7.42 (s, Ar-*H*, 1H), 7.34–7.23 (m, 4H, Ar-*H*), 2.55 (s, S(CH_3), 3H), 2.39 (s, Ar-CH_3, 3H), 2.34 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 140.8, 139.7, 139.2, 138.6, 135.6, 132.0 (Ar*C*), 131.0 (Ar*C* × 2), 128.2 (Ar*C* × 2), 124.4 (Ar*C*), 124.1 (Ar*C*), 21.7 (ArCH$_3$), 20.2 (ArCH$_3$), 15.8 (S(CH$_3$)) ppm. HRMS (ESI) m/z calcd for $C_{15}H_{16}S$ ([M + H]$^+$) 229.104548, found 229.104679.

(4,4′-Dimethylbiphenyl-3-yl)dimethylsulfonium tetrafluoroborate (3). Obtained similarly to sulfonium **1**, using biphenyl **3e** (0.10 g, 0.44 mmol) instead of biphenyl **1b**. White solid (0.12 g, 83%); m.p. 140–141 °C. ^{1}H NMR (CD_3CN): δ 8.01 (s, Ar-*H*, 1H), 7.91 (d, J = 8.0 Hz, Ar-*H*, 1H), 7.65 (d, J = 8.0 Hz, Ar-*H*, 2H), 7.56 (d, J = 8.1 Hz, Ar-*H*, 1H), 7.36 (d, J = 7.8 Hz, Ar-*H*, 2H), 3.20 (s, S(CH_3)$_2$, 6H), 2.65 (s, Ar-CH_3, 3H), 2.42 (s, Ar-CH_3, 3H) ppm. ^{13}C NMR: δ 143.0, 140.1, 139.8, 136.5, 133.7, 133.5 (Ar*C*), 130.9 (Ar*C* × 2), 128.1 (Ar*C* × 2), 126.7, 126.1 (Ar*C*), 29.0 (S(CH$_3$)$_2$), 21.3 (ArCH$_3$), 19.6 (ArCH$_3$) ppm. HRMS (ESI) m/z calcd for $C_{16}H_{19}S$ ([M]$^+$) 243.120198, found 243.120065.

4-Bromo-2-isopropylaniline (4a). *N*-Bromosuccinimide (7.2 g, 41 mmol) was added to a mixture of 2-isopropylaniline (5.0 g, 37 mmol) and ammonium acetate (0.29 g, 3.7 mmol) in acetonitrile (0.15 L), and the resulting solution was kept at 25 °C for 1 h. The reaction mixture was concentrated, diluted with water (0.15 L) and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were combined and washed with brine (0.10 L), dried with Na_2SO_4 and concentrated *in vacuo*. The product was purified by chromatography (silica gel; eluent: hexane–ethyl acetate, 9 : 1) to afford a colorless liquid (4.2 g, 53%). ^{1}H NMR (CD_3CN): δ 7.21 (s, Ar-*H*, 1H), 7.09 (d, J = 8.6 Hz, Ar-*H*, 1H), 6.61 (d, J = 8.5 Hz, Ar-*H*, 1H), 4.10 (br, Ar-NH_2, 2H), 2.90 (hept., J = 6.8 Hz, Ar-C*H*, 1H), 1.21 (d, J = 6.8 Hz, CH-(CH$_3$)$_2$, 6H) ppm. ^{13}C NMR: δ 145.0, 135.6, 129.9, 128.9, 117.9, 110.0 (Ar*C*), 28.3 (*C*H(CH$_3$)$_2$), 22.5 ((*C*H$_3$)$_2$) ppm. HRMS (ESI) m/z calcd for $C_9H_{12}BrN$ ([M + H]$^+$) 214.022588, found 214.022652.

4-Bromo-1-iodo-2-isopropylbenzene (4b). To a suspension of aniline **4a** (4.0 g, 19 mmol) in water (20 mL) was added conc. HCl (9.3 mL) dropwise, before cooling the mixture to 0 °C. An ice-cold solution of sodium nitrite (2.6 g, 37 mmol; 20 mL) was added dropwise and the reaction mixture was allowed to stand for 1 h at 0 °C until the addition of a solution of potassium iodide (6.2 g, 37 mmol) in water (25 mL). The reaction mixture

was then kept at 25 °C for 6 h. The product was extracted with ethyl acetate (2 × 0.10 L), and the combined organic layers were washed with brine (0.10 L), dried with Na_2SO_4 and evaporated. The product was purified by chromatography (silica gel; eluent: hexane–dichloromethane, 19 : 1) to afford a light brown liquid (2.8 g, 46%). ^{1}H NMR (CD_3CN): δ 7.72 (d, J = 8.4 Hz, Ar-*H*, 1H), 7.45 (s, Ar-*H*, 1H), 7.07 (d, J = 8.4 Hz, Ar-*H*, 1H), 3.14 (hept., J = 6.8 Hz, C*H*(CH_3)$_2$, 1H), 1.21 (d, J = 6.5 Hz, CH(C*H*$_3$)$_2$, 6H) ppm. ^{13}C NMR: δ 153.8, 141.9, 131.8, 130.2, 123.7, 99.6 (Ar*C*), 39.1 (*C*H(CH_3)$_2$), 23.1 ((CH_3)$_2$) ppm.

4-Bromo-2-isopropylbenzoic acid (4c). A solution of butyllithium (2.0 M) in hexane (3.7 mL, 9.3 mmol) was added to a solution of bromoarene **4b** (2.8 g, 8.4 mmol) in dry tetrahydrofuran (50 mL), and the reaction mixture was kept at −75 °C for 2 h before being poured onto an excess of freshly crushed dry ice. The resulting slurry was subsequently acidified with a solution of hydrogen chloride in diethyl ether (10 mL). After evaporation of the solvent, the precipitate was diluted with water (50 mL) and the product extracted with ethyl acetate (3 × 75 mL). The residue crystallized as white needles in hexane (1.2 g, 58%); m.p. 105–106 °C. ^{1}H NMR (CD_3CN): δ 9.65 (br, Ar-COO*H*, 1H), 7.66 (m, Ar-*H*, 2H), 7.45 (d, J = 8.3 Hz, Ar-*H*, 1H), 3.78 (hept., J = 6.8 Hz, C*H*(CH_3)$_2$, 1H), 1.25 (d, J = 6.8 Hz, CH(C*H*$_3$)$_2$, 6H) ppm. ^{13}C NMR: δ 169.2 (Ar*C*OOH), 153.2, 132.7, 130.6, 130.0, 129.8, 127.2 (Ar*C*), 30.4 (*C*H(CH_3)$_2$), 24.0 ((CH_3)$_2$) ppm. HRMS (ESI) m/z calcd for $C_{10}H_{10}BrO_2$ ([M − H]$^-$) 240.985869, found 240.986963.

3-Isopropyl-4′-methylbiphenyl-4-carboxylic acid (4d). Prepared similarly to biphenyl **1b**, with 4-bromo-2-isopropylbenzoic acid **4c** (0.40 g, 1.6 mmol) instead of 3-iodothioanisole. The title compound crystallized as white prisms in acetonitrile (0.26 g, 62%); m.p. 168–169 °C. ^{1}H NMR (CD_3CN): δ 9.45 (br, ArCOO*H*, 1H), 7.83 (d, J = 8.1 Hz, Ar-*H*, 1H), 7.70 (s, Ar-*H*, 1H), 7.61 (d, J = 8.0 Hz, Ar-*H*, 2H), 7.51 (d, J = 8.0 Hz, Ar-*H*, 1H), 7.31 (d, J = 7.8 Hz, Ar-*H*, 2H), 3.87 (hept., J = 6.8 Hz, C*H*(CH_3)$_2$, 1H), 2.41 (s, Ar-C*H*$_3$, 3H), 1.30 (d, J = 6.8 Hz, CH(C*H*$_3$)$_2$, 6H) ppm. ^{13}C NMR: δ 169.6 (Ar*C*OOH), 151.5, 145.3, 139.2, 138.2 131.7 (Ar*C*), 130.7 (Ar*C* × 2), 129.3 (Ar*C*), 128.1 (Ar*C* × 2), 125.7, 125.0 (Ar*C*), 30.7 (*C*H(CH_3)$_2$), 24.2 ((CH_3)$_2$), 21.2 (Ar*C*H$_3$) ppm. HRMS (ESI) m/z calcd for $C_{17}H_{17}O_2$ ([M − H]$^-$) 253.12230, found 253.123337.

Sodium 3-isopropyl-4′-methylbiphenyl-4-carboxylate (4). NaOH (97% pellets; 8.5 mg, 0.21 mmol) was added to a suspension of carboxylic acid **4d** (50 mg, 0.19 mmol) in water (5.0 mL), and the solution was kept at 25 °C for 1 h, before being concentrated. The residue was dried under high vacuum; white solid (54 mg, 99%); m.p. >300 °C. ^{1}H NMR (D_2O): δ 7.61–7.58 (m, Ar-*H*, 3H), 7.47–7.44 (m, Ar-*H*, 1H), 7.34–7.32 (m, Ar-*H*, 3H), 3.26 (hept., J = 6.7 Hz, C*H*(CH_3)$_2$, 1H), 2.36 (s, Ar-C*H*$_3$, 3H), 1.26 (d, J = 6.8 Hz, 6H) ppm. ^{13}C NMR: δ 179.5 (Ar-*C*OONa), 145.3, 140.5, 138.7, 138.1, 137.6 (Ar*C*), 129.8 (Ar*C* × 2), 126.9 (Ar*C* × 2), 126.4, 124.0, 123.8 (Ar*C*), 30.5 (*C*H(CH_3)$_2$), 23.4 ((CH_3)$_2$), 20.2 (Ar*C*H$_3$) ppm. HRMS (ESI) m/z calcd for $C_{17}H_{17}O_2$ ([M + 2Na]$^+$) 299.101846, found 299.101804.

(4′-Bromobiphenyl-3-yl)(methyl)sulfane (5a). An aqueous solution of sodium carbonate (2.0 M; 5.0 mL) and 4-bromophenylboronic acid (0.80 g, 4.0 mmol) in methanol (5 mL) were added to a mixture of 3-iodothioanisole (**1a**; 1.0 g, 4.0 mmol) and palladium(0) tetrakis(triphenylphosphine) (0.21 g, 0.20 mmol) in degassed toluene (20 mL). The reaction mixture was heated to 80 °C for 24 h under an inert atmosphere. After evaporating the solvent, the precipitate was treated with a 2.0 M sodium carbonate solution (25 mL) and with concentrated ammonia (5.0 mL), then it was extracted with ethyl acetate (2 × 0.20 L). The combined organic layers were passed through a pad of celite, and the filtrate was washed with water (0.10 L), dried with Na_2SO_4 and evaporated. The product was purified by chromatography (silica gel; eluent: hexane–dichloromethane (19 : 1) to afford a light yellow liquid (0.66 g, 59%). ^{1}H NMR (CD_3CN): δ 7.66–7.57 (m, Ar-*H*, 4H), 7.51 (s, Ar-*H*, 1H), 7.41–7.40 (m, Ar-*H*, 2H), 7.30 (m, Ar-*H*, 1H), 2.55 (s, S(C*H*$_3$), 3H) ppm. ^{13}C NMR: δ 141.7, 141.0, 140.9 (Ar*C*), 133.2 (Ar*C* × 2), 130.9 (Ar*C*), 130.3 (Ar*C* × 2), 126.7, 125.7, 124.8, 122.8 (Ar*C*), 16.0 (S(*C*H$_3$)) ppm. HRMS (ESI) m/z calcd for $C_{13}H_{11}BrS$ ([M]$^+$) 277.975935, found 277.976001.

Methyl(4″-methyltriphenyl-3-yl)sulfane (5b). Prepared similarly to biphenyl **1b**, with biphenyl **5a** (0.50 g, 1.8 mmol) instead of 3-iodothioanisole (**1a**). The product was purified by chromatography (silica gel; eluent: hexane–ethyl acetate, 9 : 1 to afford a white solid (0.35 g, 67%); m.p. 112–113 °C. ^{1}H NMR (CD_3CN): δ 7.74 (s, Ar-*H*, 4H), 7.61 (t, J = 6.0 Hz, Ar-*H*, 3H), 7.45 (dt, J = 15.0, 9.0 Hz, Ar-*H*, 2H), 7.33–7.28 (m, Ar-*H*, 3 H), 2.57 (s, S(C*H*$_3$), 3H), 2.41 (s, Ar-C*H*$_3$, 3H) ppm. ^{13}C NMR: δ 142.2, 141.2, 140.5, 140.2, 138.6, 138.4 (Ar*C*), 130.7 (Ar*C* × 2), 130.5 (Ar*C*), 128.5 (Ar*C* × 2), 128.2 (Ar*C* × 2), 127.78 (Ar*C* × 2), 126.2, 125.4, 124.6, 21.2 (Ar*C*H$_3$), 15.7 (S(*C*H$_3$)) ppm. HRMS (ESI) m/z calcd for $C_{20}H_{18}S$ ([M + H]$^+$) 291.120198, found 291.120379.

Dimethyl(4″-methyltriphenyl-3-yl)sulfonium trifluoromethanesulfonate (5). Iodomethane (24 mg, 0.17 mmol) and silver triflate (23 mg, 90 μmol) were added to a solution of sulfide **5b** (25 mg, 80 μmol) in acetone and the reaction mixture was kept at 25 °C for 12 h. The precipitate was filtered, and evaporation of the filtrate afforded the title compound as a white solid (32 mg, 82%); m.p. 137–138 °C. ^{1}H NMR (CD_3CN): δ 8.21 (s, Ar-*H*, 1H), 8.12 (d, J = 9.0 Hz, Ar-*H*, 1H), 7.91–7.79 (m, Ar-*H*, 6H), 7.64 (d, J = 8.1 Hz, Ar-*H*, 2H), 7.34 (d, J = 7.8 Hz, 2H), 3.21 (s, S(C*H*$_3$)$_2$, 6H), 2.42 (s, Ar-C*H*$_3$, 3H) ppm. ^{13}C NMR: δ 144.3, 142.3, 139.0, 138.0, 137.9, 133.8, 132.4 (Ar*C*), 130.7 (Ar*C* × 2), 129.5, 128.9 (Ar*C*), 128.8 (Ar*C* × 2), 128.5 (Ar*C* × 2), 127.9 (Ar*C* × 2), 126.9 (Ar*C*), 29.4 (S(*C*H$_3$)$_2$), 21.2 (Ar*C*H$_3$) ppm. HRMS (ESI) m/z calcd for $C_{21}H_{21}OS$ ([M]$^+$) 305.135848, found 305.135464.

Computational work

Calculations were carried out with the TURBOMOLE suite of programs (version 6.3.1),[28] and with the Gaussian 09 package.[29] For TURBOMOLE jobs, input files were first generated with the graphical interface TmoleX (version 3.3)[30] with default parameters, and corrected manually or with TURBOMOLE 6.3.1 to satisfy calculation needs; the m4 grid[31] was used throughout this study. Gaussian 09 jobs were generated

using GaussView 5.0,[32] and corrected manually; the ultrafine grid was employed. In all cases, convergence criteria were 10^{-7} Hartree and 10^{-4} atomic units as the maximum norm of the Cartesian gradient. Def2-TZVPP basis sets[14] were used for the evaluation of free guests, and def2-SVP basis sets for CB[7]-containing assemblies. All DFT-D and MP2 calculations were carried out with TURBOMOLE within the resolution of the identity approximation. IEFPCM corrections to the electronic energies were obtained using Gaussian 09 by calculating the energy difference between single point calculations carried out with and without the solvent on B3LYP-D-optimized structures. The B97-D functional as implemented in Gaussian 09 was used for these single point calculations. COSMO was applied with default parameters using TURBOMOLE.

Acknowledgements

This work was supported by the American Chemical Society Petroleum Research Fund (PRF No. 51053-ND4), the Department of Chemistry and Biochemistry, the College of Arts and Sciences and the Vice President for Research at Ohio University. We are extremely grateful to the Ohio Supercomputer Center (OSC) in Columbus for its generous allocation of computing time.

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