ARTICLES
https://doi.org/10.1038/s41557-020-0425-4
nature chemistry



# Modular bismacycles for the selective C–H arylation of phenols and naphthols

Mark Jurrat[1,2], Lorenzo Maggi[1,2], William Lewis[2,3] and Liam T. Ball[1,2] ✉

**Given the important role played by 2-hydroxybiaryls in organic, medicinal and materials chemistry, concise methods for the synthesis of this common motif are extremely valuable. In seeking to extend the lexicon of synthetic chemists in this regard, we have developed an expedient and general strategy for the *ortho*-arylation of phenols and naphthols using readily available boronic acids. Our methodology relies on in situ generation of a uniquely reactive Bi(v) arylating agent from a bench-stable Bi(iii) precursor via telescoped B-to-Bi transmetallation and oxidation. By exploiting reactivity that is orthogonal to conventional metal-catalysed manifolds, diverse aryl and heteroaryl partners can be rapidly coupled to phenols and naphthols under mild conditions. Following arylation, high-yielding recovery of the Bi(iii) precursor allows for its efficient re-use in subsequent reactions. Mechanistic interrogation of each key step of the methodology informs its practical application and provides fundamental insight into the underexploited reactivity of organobismuth compounds.**

The 2-hydroxybiaryl motif forms the core of numerous biologically and synthetically important molecules (Fig. 1a). This includes more than 4,000 natural products, many of which possess antimalarial, anti(retro)viral or cytotoxic properties[1–4]. The frequency with which 2-hydroxybiaryls occur in functional molecules reflects the well-defined steric profile that results from the rigid biaryl axis (a feature that has been exploited routinely in 1,1′-bi-2-naphthol-derived asymmetric catalysts[5,6]) and the hydrogen-bonding abilities that are conferred by the phenolic hydroxyl group. Phenols constitute the most common type of hydroxyl in synthetic drugs,[7] and the combined rigidity and hydrogen-bonding properties of the 2-hydroxybiaryl moiety have been implicated in the bioactivity of both natural[8] and synthetic[9] therapeutics. Phenolic hydroxyls are better hydrogen-bond donors and poorer hydrogen-bond acceptors than aliphatic alcohols, and the donicity of this function can be modulated both by substitution of the phenolic ring itself[10], and also by through-space interactions with the flanking aromatic ring[11]. The ability of chemists to access diverse 2-hydroxybiaryls therefore enables precise modulation of the properties and ultimately the function of this important motif.

Given the broad significance of 2-hydroxybiaryls, methods for their preparation are highly valued and have been the subject of much research effort. The most widely used strategies involve metal-catalysed arylation of a hydroxyarene-derived substrate via either cross-coupling[12] or C–H functionalization[13–20]; however, although extremely powerful, the atom and step economies of these approaches are impacted by the need to prefunctionalize the substrate. Cross-coupling, for example, typically requires challenging *ortho*-selective halogenation or borylation of the hydroxyarene[13], whereas C–H functionalization demands installation and subsequent removal of Lewis-basic directing groups. Pioneering approaches that entirely avoid additional directing groups[21–23]—or that allow the in situ installation and removal of co-catalytic directing groups[21,24–26]—represent an almost ideal solution to the problems of step and atom efficiencies, but suffer from practical limitations such as moderate scope and poor selectivity. In addition to the potential issues surrounding the step count, the extant cross-coupling and C–H arylation strategies rely on activation of a carbon–halogen bond, resulting in chemoselectivity issues for polyhalogenated substrate combinations. Thus, there is still an unmet need for expedient, user-friendly *ortho*-arylation methods that can be applied directly to unmodified hydroxyarenes. Here we report the development of modular arylbismuth(v) reagents as a general solution to this challenge.

Pioneered by Barton and co-workers in the 1980s, Bi(v)-mediated oxidative arylation of phenols and naphthols does not require prefunctionalization of the substrate (Fig. 1b)[27–30]. This methodology benefits further from the low cost of bismuth and its salts, as well as the high stability and low toxicity of triarylbismuth reagents (for example, $LD_{50}(BiPh_3) = 180\,g\,kg^{-1}$ (ref. [31])). However, despite these appealing attributes, the synthetic potential of both Bi(v) and Bi(iii)[32] reagents for C–H arylation has been largely overlooked. This is due to several major challenges that limit its current practicality (Fig. 1b), including:

a. the poor availability of arylbismuth reagents, which necessitates their multistep synthesis;
b. the often unpredictable, substrate-controlled chemoselectivity between $C_{ortho}$- versus O-arylation;
c. the waste associated with transfer of just one of the three aryl groups available in $Ar_3BiX_2$; and
d. the lack of systematic studies of reaction scope or mechanism, which impedes extrapolation of the methodology to untested substrate combinations.

In this communication we present a convenient and general protocol for the Bi(v)-mediated arylation of phenols and naphthols that addresses each of the challenges outlined above. Arylation is achieved in a single telescoped operation that does not require exclusion of either air or moisture. All of the reagents employed are commercially available and the bismuth-containing co-product can be efficiently recovered and recycled. By exploiting reactivity that is orthogonal to conventional metal-catalysed manifolds, diverse aryl and heteroaryl partners can be rapidly coupled to phenols and naphthols under mild conditions. Supporting mechanistic studies

[1]GSK Carbon Neutral Laboratories for Sustainable Chemistry, University of Nottingham, Nottingham, UK. [2]School of Chemistry, University of Nottingham, University Park, Nottingham, UK. [3]School of Chemistry, The University of Sydney, Sydney, Australia. ✉e-mail: liam.ball@nottingham.ac.uk

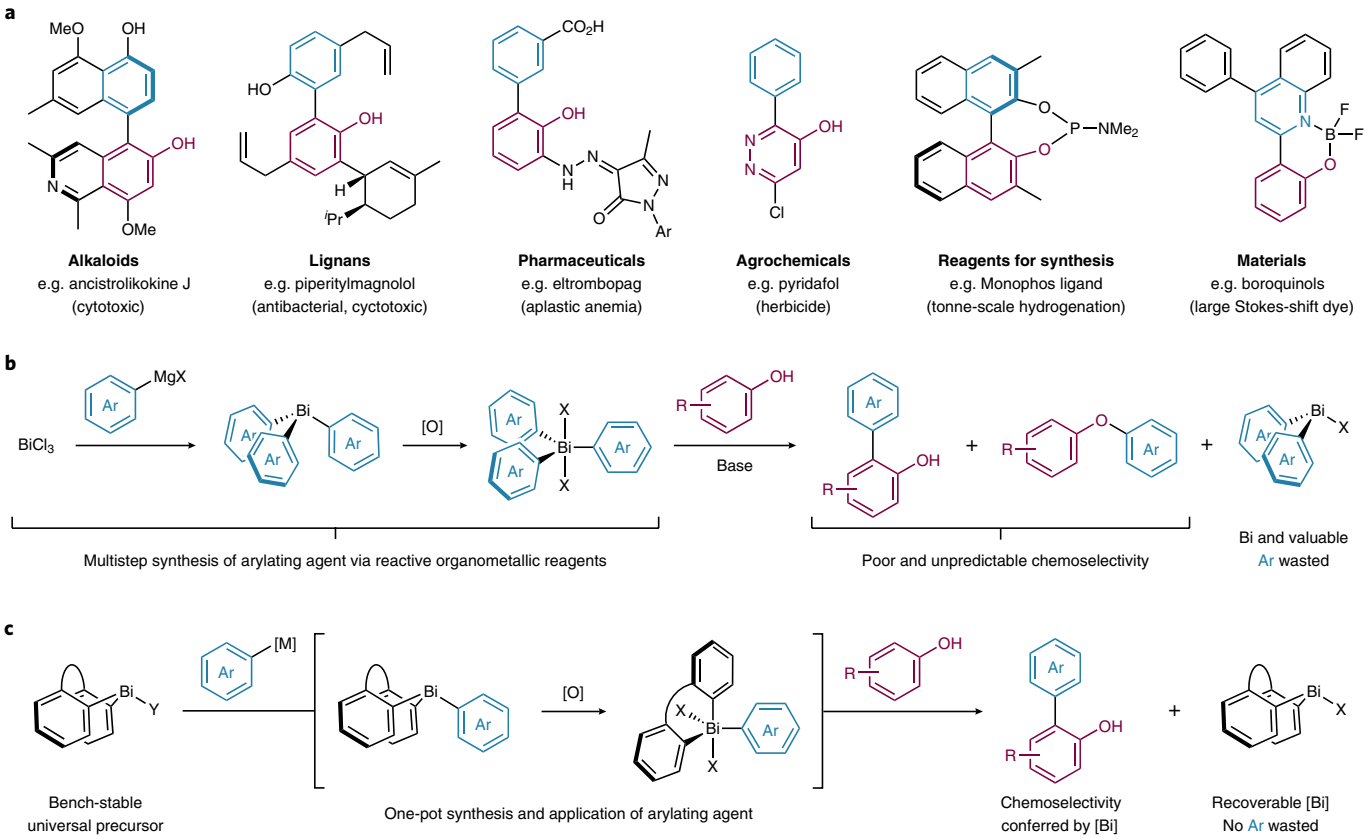



**Fig. 1 | Occurrence and Bi(v)-mediated synthesis of 2-hydroxybiaryls. a**, The 2-hydroxybiaryl motif is ubiquitous to societally important molecules, including biologically active natural and unnatural compounds, fine chemicals for synthesis and functional materials. Continued exploration of this privileged region of chemical space will benefit from efficient methods for synthesis of the key biaryl linkage. **b**, Barton's Bi(v) arylating agents offer unique reactivity, but the state of the art is marred by limited practicality, poor selectivity and unacceptable atom and step economies. **c**, The design strategy for this work. We propose that the challenges associated with Bi(v)-mediated arylation will be solved through the in situ formation and application of bismacyclic arylating agents, thereby providing a general and practical platform for the *ortho*-selective arylation of hydroxyarenes. Ar, aryl or heteroaryl; X and Y, (pseudo)halogen; [O], oxidant; R, aryl, alkyl or heteroatomic substituent; [M], metal.

render the methodology predictable and provide new fundamental insights into the reactivity of organobismuth compounds.

## Results and discussion

**Strategic blueprint.** As outlined in Fig. 1c, our strategy was based on tethering two aryl rings of a homoleptic triarylbismuthane to form a bismacycle. The resulting diaryl scaffold would function as an inert spectator, enabling selective transfer of an exocyclic aryl group to and from the bismuth centre[33–35]. As a consequence, the efficiency with respect to the valuable aryl moiety would be improved, and the reactivity and selectivity of the arylating agent could be tuned by modification of the bismacyclic scaffold. We envisaged that in situ preparation of diverse bismacycle(v) arylating agents could be achieved from a universal bismacycle(iii) halide precursor via a modular, one-pot transmetallation/oxidation sequence. This telescoped process would avoid the need for multistep synthesis of each new bismacyclic reagent, which—in combination with a stable bismacycle(iii) precursor that is readily available on scale—would greatly enhance the practicality of the methodology.

**Synthesis of a universal Bi(iii) precursor.** We first had to identify an appropriate bismacyclic scaffold to deliver our proposed methodology. Initial assessments indicated that the sulfone-bridged bismacycle previously reported by Suzuki[34,36,37] (Fig. 2) was uniquely competent in model transmetallation, oxidation and C–H arylation reactions (Supplementary Section 2). A library of bismacycle halides and pseudohalides based on this scaffold (**1-X**) were prepared simply by changing the Brønsted acid employed in protodebismuthation of a common arylbismacycle(iii) intermediate (Supplementary Section 4). By telescoping the bismacycle construction and protodebismuthation steps (Fig. 2), bismacycle tosylate **1-OTs** was synthesized and isolated without chromatographic purification in excellent yield on a decagram scale (11 g of **1-OTs**, 93% yield over both steps). Unusually for a diarylbismuth (pseudo)halide, **1-OTs** is stable towards both hydrolysis (at neutral pH) and aryl ligand redistribution reactions. The compound can be handled and stored without exclusion of air, water or light, and shows no sign of decomposition following storage for two years under ambient laboratory conditions. Inspection of its solid-state structure reveals a short transannular contact between the bismuth centre and one oxygen of the sulfone (Bi···O = 2.556(5) Å), which is probably responsible for this uncharacteristic stability[34,38,39]. Bismacycle tosylate **1-OTs** is commercially available through Key Organics (catalogue number NS-00138).

**Development and scope of a one-pot arylation procedure.** Having identified bismacycle tosylate **1-OTs** as an easily accessible universal precursor, we turned our attention to development of the transmetallation process required to install an exocyclic aryl group at the Bi(iii) centre. Conventionally, transmetallation of an aryl group to Bi(iii) is achieved using reactive organometallic reagents (ArLi, ArMgX or ArZnX)[29], which require careful handling and

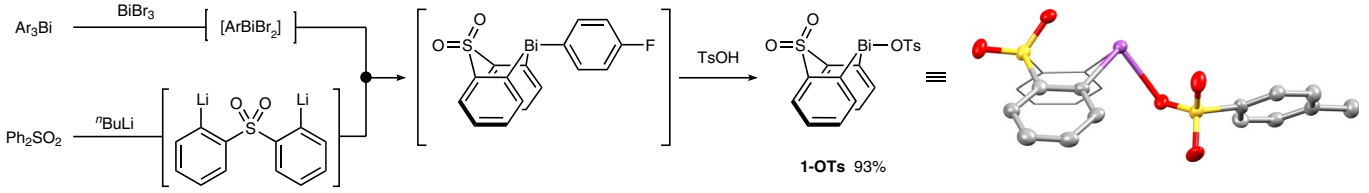



**Fig. 2 | Synthesis of a universal bismacycle(III) precursor.** Decagram quantities of bismacycle tosylate **1-OTs** can be prepared via a telescoped, chromatography-free route that starts from readily available starting materials. **1-OTs** is stable to ambient laboratory conditions, presumably due to intramolecular $O_{sulfone}$–Bi coordination (see X-ray diffraction structure; thermal ellipsoids are shown at 50% probability, hydrogen atoms are omitted for clarity), and is commercially available through Key Organics (catalogue number NS-00138). Ar, 4-$FC_6H_4$; Ts, tosyl.

have restricted functional group compatibility. Such methods were deemed antithetical to our objective of developing a practical and general one-pot procedure for the arylation of phenols and naphthols, which demands that transmetallation occurs from a convenient aryl donor under mild conditions. We therefore envisaged using a boron-based aryl donor, given the ease of handling and ready commercial availability of many arylboronic acids and esters. However, although B–to–Bi transmetallation is well precedented for Bi(V) (refs. [40–44]), this process is limited to just two examples for Bi(III): aryl transfer from tetraarylborates to $Bi(OAc)_3$ (ref. [45]) and from arylboronic acids to monoarylbismuth(III) oxides[46]. After investigation of different arylboron reagents and reaction variables (Supplementary Section 3), we identified robust conditions for transmetallation from boronic acids to **1-OTs** (Table 1). Notably, excellent conversions were achieved with just 1.1 equivalents of the arylboronic acid. The presence of added water and base, the choice of solvent and the identity of the (pseudo)halide associated with the bismacyclic precursor were found to be critical to the success of the transmetallation (Supplementary Section 3).

The scope of B–to–Bi transmetallation is extensive under our optimal conditions (Table 1), with electronically (**2a**–**2l**) and sterically (**2m**–**2p**) diverse aryl and heteroaryl (**2t**–**2aa**) boronic acids reacting in excellent spectroscopic yield. Although protodebismuthation renders isolation challenging for more electron-rich aryl moieties (for example, **2t** and **2w**), this is irrelevant in the proposed one-pot procedure where isolation of intermediates is neither necessary nor desirable. Notably, polyfluorophenyl moieties are transferred smoothly and afford stable, isolable arylbismacycles (**2q**–**2s**), despite the susceptibility of the corresponding boronic acids to protodeboronation[47,48]. The mildness of the transmetallation protocol is reflected in the diversity of compatible functionality, much of which is not tolerated by conventional organometallic routes to arylbismuthanes. Previous attempts to circumvent these incompatibilities have led to low yields of triarylbismuthanes containing, for example, aryliodides (21% yield via an aryldiazonium salt)[49] and aryl esters (26% yield over four steps)[50], both of which can be installed quantitatively in a single step by our method (**2h**, **2i**). Similarly, triarylbismuthanes that contain thienyl, furanyl, pyrrolyl or unprotected indolyl groups that are accessible in only moderate yields (28–53%) via conventional organometallic routes[51–55] can now also be prepared in excellent yield (**2t**–**2z**, >99% yield).

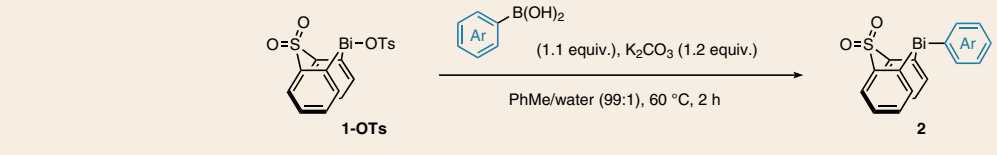
With conditions for transmetallation in hand, we next addressed the oxidation and arylation steps of our proposed methodology. We found that oxidation of aryl bismacycles **2** with *meta*-chloroperbenzoic acid (*m*CPBA) is rapid and that the in situ generated Bi(V) species are efficient arylating agents without the addition of base. Conveniently, commercial *m*CPBA can be used without prior purification, and the transmetallation (Table 1), oxidation and arylation procedures can be performed as a single telescoped operation (Fig. 3a). Arylation is typically complete within seconds at room temperature, occurs with exclusive transfer of the exocyclic aryl moiety and exhibits perfect $C_{ortho}$-versus-O chemoselectivity with respect to the substrate. The co-product of this one-pot procedure was identified spectroscopically as bismacycle *meta*-chlorobenzoate **1-O*m*CB** (Fig. 3a), the bismacyclic component of which can be recovered in excellent yield as the corresponding acetate (**1-OAc**) simply by column chromatography with acetic acid as the co-eluent. This material undergoes near-quantitative transmetallation under our standard conditions, allowing for effective recovery and recycling of the bismacyclic scaffold. Together this represents a facile process that proceeds from a readily available, universal precursor, is convenient to execute (no inert atmosphere/anhydrous conditions) and achieves economy with respect to both the aryl group being transferred (1.1 equiv. arylboronic acid relative to **1-OTs**) and the bismacycle itself (high-yielding recovery and recycling via **1-OAc**).

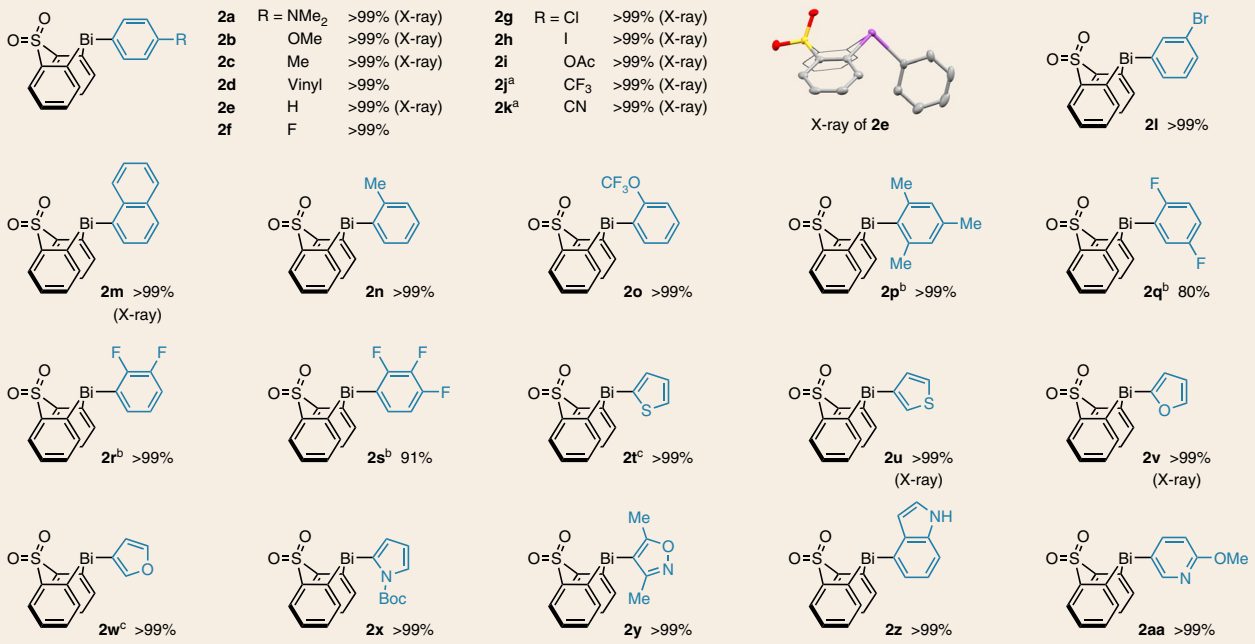
The resulting one-pot process exhibits excellent scope with respect to the aryl group being installed on the substrate (Fig. 3b), with electron-donating (**3**–**7**), -withdrawing (**9**–**15**), sterically demanding (**16** and **17**) and synthetically useful substituents (**6**, **7**, **10**, **12**, **13**) all being well tolerated. Although the propensity of polyfluorophenylboronic acids towards protodeboronation[48] renders them challenging partners in conventional cross-coupling[48,56,57], these moieties can be installed conveniently using our Bi(V)-mediated arylation methodology (**14** and **15**), allowing facile access to product motifs that are prized in materials chemistry research[58]. Notably, the bismacyclic framework improves reactivity relative to conventional Bi(V) reagents: following transmetallation and oxidation, arylation of 2-naphthol is complete in seconds at room temperature without the need for additional base. This high reactivity stands in contrast to Barton's triarylbismuth(V) reagents, which arylate 2-naphthol over several hours in the presence of guanidine or hydride bases. For example, whereas a mesityl group is transferred to 2-naphthol rapidly at room temperature by our method (**17**, 89%), only 61% yield is obtained after 27 h at 50 °C using trimesitylbismuth dichloride[59].

Installation of several heteroarenes, including those with basic nitrogen and an unprotected indole, can be achieved in good yield (**18**–**20**). However, very electron-rich heteroaryl groups are not well tolerated due to the sensitivity of the intermediate aryl bismacycle **2** to protodebismuthation and the inherent instability of the corresponding Bi(V) species (for example, 2-furyl gives 0% yield, Supplementary Table 2). Despite this limitation, the synthesis of **18**–**20** represents important first examples of heteroaryl Bi(V) species being used directly as arylating agents.

Electronically diverse naphthols are arylated in excellent yield with complete regio- and ($C_{ortho}$-versus-O) chemoselectivity (Fig. 3c, **21**–**25**). The methodology is equally applicable to heterocyclic naphthol analogues (**27**–**30**), a class of substrates that has not been explored previously in either Bi(V)-mediated arylation or C–H functionalization. Synthetically useful functionality such as bromides, iodides and boronic esters (**13**, **22**–**24**) are also compatible with the reaction, further illustrating its complementarity to both conventional cross-coupling and C–H functionalization strategies.

**Table 1 | Transmetallation to universal bismacyclic precursor 1-OTs from aryl- and heteroarylboronic acids**




Conversions were determined by $^1$H NMR spectroscopic analysis before characterization of isolated pure material. [a] The reaction time was 6 h. [b] The reaction time was 14 h. [c] Characterized without isolation. Ac, acetyl; Boc, *tert*-butoxycarbonyl.

Although 1-naphthol is a poor substrate for established Bi(v) reagents (48% with $BiPh_5$)[28] and metal-catalysed C–H functionalization (38–43% with 5 mol% rhodium at $T \geq 100\,°C$)[24–26], it is arylated efficiently using our protocol (**26**, 86%). The contrast between our results and those of Barton et al.[28] are especially striking and again highlight the enhanced reactivity conferred by Suzuki's sulfone-bridged bismacycle scaffold[34].

A similar reactivity enhancement is observed for phenols (Fig. 3d, **31**–**42**), which are arylated rapidly at room temperature by the bismacyclic system but require extended reaction times and elevated temperatures with Barton's Bi(v) reagents (for example, $Ph_3BiCl_2$: 48 h in refluxing THF with a guanidine base)[60]. In addition to benefitting reactivity, the use of a bismacycle also improves the chemoselectivity of phenol arylation: where Barton and co-workers observe competing $C_{ortho}$- and O-arylation, we observe exclusive $C_{ortho}$-arylation. Our methodology therefore provides not only an improvement on extant Bi(v)-mediated arylation methods, but also a useful complement to the copper-catalysed, oxygen-selective phenol arylation reported by Chan, Evans and Lam using boronic acids[61,62], or by Gagnon using Bi(III) reagents[63]. By contrast, the occurrence of 2,6-diarylation[60] is not appreciably influenced by the use of a bismacycle, but can be largely suppressed by using a higher relative stoichiometry of the phenol (Supplementary Fig. 8).

The scope of phenols extends from moderately electron-deficient to very electron-rich substrates under these modified conditions (**31**–**34**). The excess phenol remains unreacted and can be recovered in excellent yield (for example, in the synthesis of **45**, excess estrone is isolated in 97% yield). Very electron-deficient phenols such as 4-nitro- or 4-cyanophenol are not arylated under our standard conditions and can also be recovered unchanged from the reaction mixture.

Arylation of *meta*-substituted phenols has not been adequately explored in either the extant bismuth[60,64] or C–H functionalization[24–26] literature, but typically occurs with low regioselectivity. Competing 2,6-diarylation precludes the construction of meaningful structure–selectivity relationships from the few examples that do exist. Given that non-symmetrically (*meta*) substituted phenols also react to form regioisomeric mixtures under our conditions (**35**–**40**), we sought to understand the factors that govern this selectivity in greater detail.

For the arylation of 3-fluorophenol—where the 2- and 6- positions are electronically different[65,66] but sterically similar[67]—moderate selectivity (2.6:1, **35**:**35′**) is observed for the more electron-rich 6-position. Further investigation revealed that this regioselectivity was not appreciably impacted by variation of the reaction temperature (Supplementary Fig. 9) or the electronic properties of the aryl moiety being transferred (reaction constant ($\rho$) = 0.23; Fig. 3d, inset Hammett plot). Where the 2- and 6-positions are differentiated sterically rather than electronically, moderate regioselectivity is again observed (3.4:1; **36**:**36′**). The apparent preference for arylation of the more electron-rich, less sterically encumbered site is borne out in the arylation of other non-symmetrically substituted phenols (**37**–**40**) and gives an excellent linear correlation against a hybrid descriptor derived from Verloop's Sterimol B5 parameters[67], experimentally derived $\sigma_{para}$ (ref. [65]) and computed $\sigma_{ortho}$ (ref. [66]) values (Supplementary Fig. 11 and Supplementary Table 3), where $\sigma$ is the substituent constant.

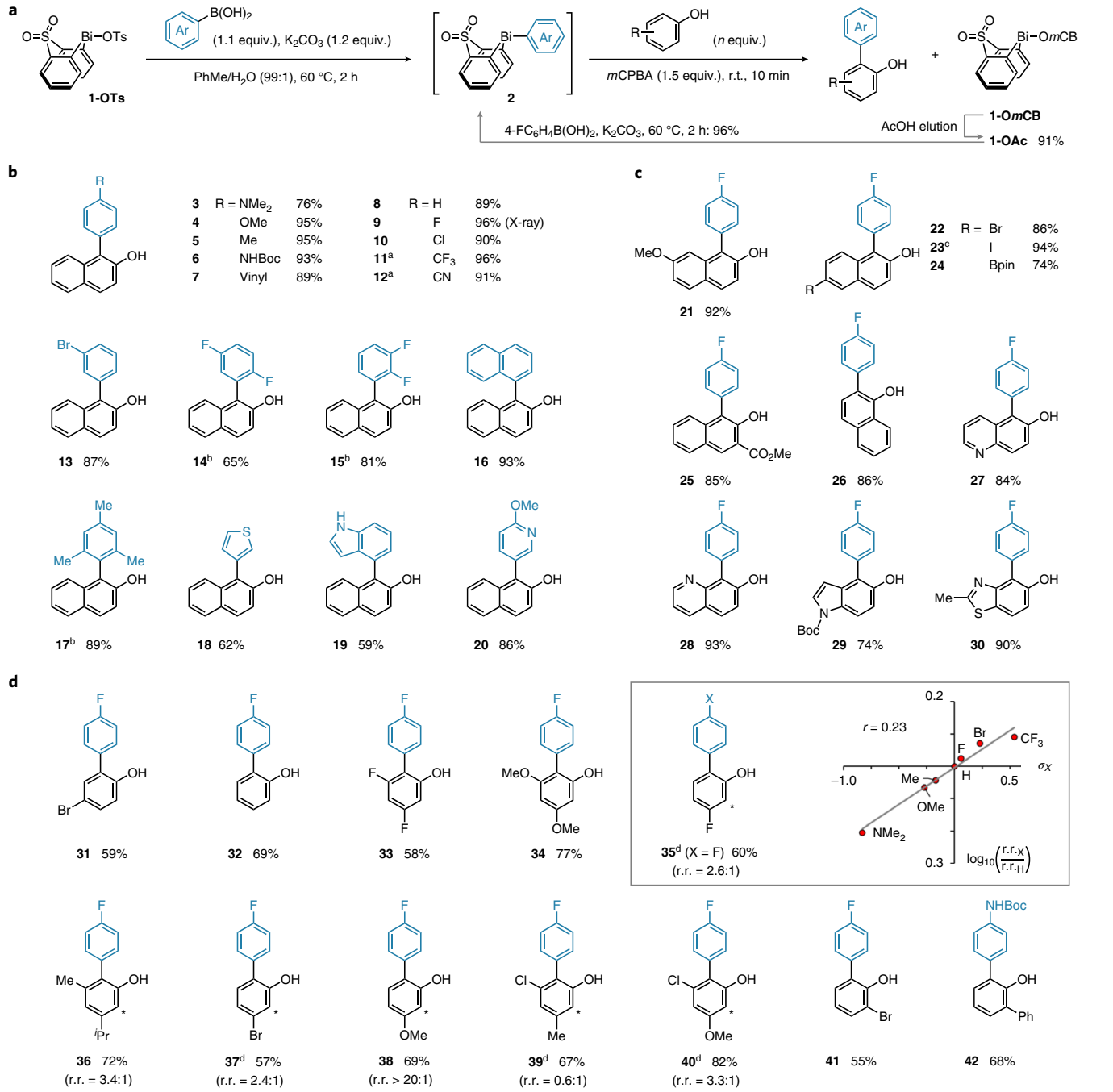



**Fig. 3 | One-pot, Bi(v)-mediated arylation of phenols and naphthols. a**, Starting from bismacycle tosylate **1-OTs**, B–to–Bi transmetallation, oxidation and arylation can be performed as a single telescoped operation without exclusion of air or moisture, and the bismacyclic scaffold can be recovered in a high yield as acetate **1-OAc**. **b**, The scope with respect to aryl- and heteroarylboronic acids ($n = 0.9$). **c**, The scope with respect to naphthol-like substrates ($n = 0.9$). **d**, The scope with respect to phenol substrates ($n = 3.0$) and a Hammett plot (inset) that quantifies the effect of the boronic acid on regioselectivity. The formation of **35–40** was accompanied by minor regioisomers (**35′–40′**) that arise from arylation at the positions denoted with an asterisk. Regisomeric ratios (r.r.) were determined by $^{19}$F NMR spectroscopic analysis before purification; where regioisomer separation was not possible, the composition was confirmed by comparison to authentic samples of single regioisomers prepared via alternative methods. [a]The transmetallation time was 6 h. [b]The transmetallation time was 14 h. [c]Arylation was performed in the presence of 1 equiv. *m*CBA. [d]Yields refer to mixtures of regioisomers. *m*CB, *meta*-chlorobenzoyl; Boc, *tert*-butoxycarbonyl; Bpin, pinacolatoboron.

The utility of our methodology is showcased in the concise synthesis of leukotriene $B_4$ receptor agonist **43** (ref. [68,69]) and cannabinoid mimetic **44** (ref. [70]), and in the late-stage arylation of estrone **45** and a naproxen derivative **46** (Fig. 4). The preference of Bi(v) for arylation of estrone at the 4-position is apparently unique in the literature, and provides a direct complement to metal-catalysed directed C–H arylations which favour functionalization of the 2-position[17,71–74]. Both 2- and 4-arylated estrones exhibit biological activity[75], so the ability to access both regioisomers in a single operation is of potential utility in discovery projects.

The complementarity of our bismuth-mediated arylation to conventional cross-coupling was exploited in the concise synthesis of

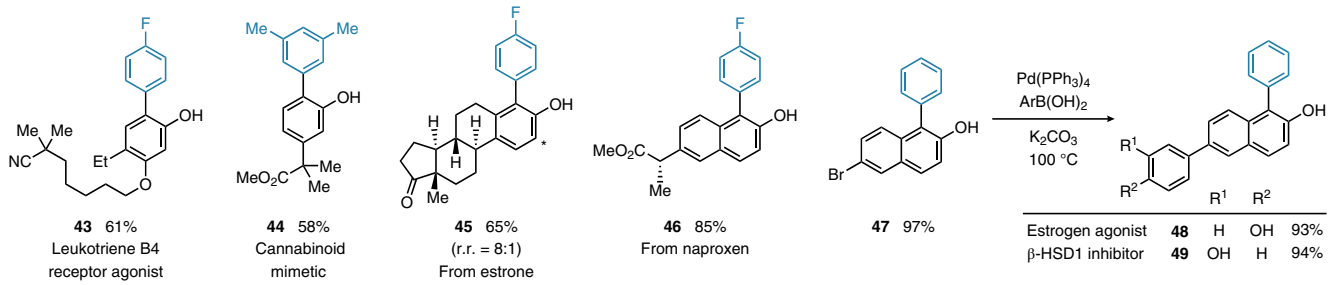



**Fig. 4 | Bi(v)-mediated arylation enables concise synthesis and diversification of biologically active compounds without substrate prefunctionalization.** As demonstrated by the preparation of **48** and **49** via intermediate **47**, the orthogonality that exists between Bi(v)-mediated arylation and conventional cross-coupling can be exploited in the design of new, modular synthetic strategies. Bi(v)-mediated arylation was performed as per Fig. 3a, with the following substrate stoichiometries: $n = 3.0$ (**43** and **44**), 5.0 (**45**) or 0.9 (**46** and **47**). Formation of **45** was accompanied by a minor regioisomer (**45′**) that arises from arylation at the position denoted with an asterisk. The regisomeric ratio (r.r.) was determined by $^{19}$F NMR spectroscopic analysis before purification. Detailed conditions for the synthesis of **48** and **49** from **47** are provided in the Supplementary Section 6.

estrogen receptor agonist **48** (ref. [76]) and β-HSD1 inhibitor **49** (ref. [77]) (Fig. 4). Although **48** and **49** were previously prepared in seven steps (which included four separate cross-coupling and three non-productive halogenation/deprotection operations), our methodology delivers both compounds in >90% yield in just three total steps via common intermediate **47**.

Having investigated their scope, we sought to better understand the transmetallation, oxidation and arylation processes. We envisaged that an appreciation of the fundamental processes would not only provide new fundamental insight, but would also help to explain observations and ultimately guide application and future development of our methodology.

**Mechanistic observations pertaining to transmetallation.** Transmetallation from electron-neutral or -rich boronic acids to bismacycle tosylate **1-OTs** reaches completion in less than 2 h without observable intermediates (Table 1). In contrast, cyano- and trifluoromethyl-substituted phenylboronic acids require ~6 h to reach completion; in these cases, an ill-defined mixture of species accumulates prior to formation of aryl bismacycle **2j** or **2k**. The mixture of intermediates could be recreated by subjecting bismacycle tosylate **1-OTs** to the transmetallation conditions in the absence of boronic acid (Fig. 5a). This allowed isolation of μ-oxo-bridged dimer $\mathbf{1_2O}$, which was found to equilibrate with the corresponding monomeric bismuth hydroxide **1-OH** in the presence of trace water. Analogous behaviour has been reported for related bismuth(III) hydroxides and oxides[78,79]. Reaction of isolated dimer $\mathbf{1_2O}$ with 4-fluorophenylboronic acid in the absence of base afforded aryl bismacycle **2f** quantitatively in under 1 min at room temperature. The higher rate of transmetallation to $\mathbf{1_2O}$ (<1 min, r.t.) versus **1-OTs** (~1 h with base, 60 °C) indicates that **1-OH**/$\mathbf{1_2O}$ are kinetically competent intermediates. The accumulation of these Bi–oxo species for electron-deficient boronic acids suggests a substrate-dependent change in rate-determining step for the overall transmetallation process. The potential involvement of a Bi–O–B pre-transmetallation intermediate (Fig. 5a, inset) is analogous to the Pd–oxo transmetallation pathway in Suzuki–Miyaura cross-coupling[80–82], and has been implicated in Si–to–Bi[52] and B–to–Bi[46] transmetallation.

**Mechanistic observations pertaining to oxidation and arylation.** Oxidation of aryl bismacycle **2f** with commercial *m*CPBA of ~75% purity furnishes an equilibrating mixture of stable Bi(v) species, the composition of which could not be elucidated directly. However, treatment of the mixture with base allowed for the isolation of bis(μ-oxo)-bridged dimer **50** (Fig. 5b). Characterization by single-crystal diffraction reveals a distorted trigonal bipyramidal geometry at bismuth in the solid state (Fig. 5c), as has been observed previously in a related bis(μ-oxo)-bridged Bi(v) dimer[83]. Each bismuth centre supports a diphenylsulfone scaffold that spans an equatorial and apical position, and distinct equatorial and apical Bi–$O_{oxo}$ bonds (2.03 Å versus 2.20 Å, respectively). Titration of this dimer with *meta*-chlorobenzoic acid (*m*CBA) allowed sequential spectroscopic identification of Bi(v) hydroxy benzoate **51** and Bi(v) dibenzoate **52** (Fig. 5d). Bi(v) hydroxy benzoate **51** can also be obtained directly as a single species by oxidation of aryl bismacycle **2f** with one equivalent of purified *m*CPBA. For *m*CBA:Bi ratios of between ~1.3 and 2, Bi(v) hydroxy benzoate **51** and Bi(v) dibenzoate **52** equilibrate at a rate commensurate with the NMR timescale. This results in a single broadened feature in the $^{19}$F NMR spectrum, consistent with that observed when aryl bismacycle **2f** is oxidized with commercial (impure) *m*CPBA.

Bismuth(v) species **50**–**52** exhibit very distinct reactivity towards phenol (Fig. 5b). Bis(μ-oxo)-bridged dimer **50** does not arylate phenol, but instead undergoes unproductive reduction to **2f** in under 1 min. By contrast, Bi(v) hydroxy benzoate **51** reacts with 1 equivalent of phenol to afford the expected $C_{ortho}$-arylation products quantitatively within seconds. Finally, in the presence of excess *m*CBA, Bi(v) dibenzoate **52** shows no reactivity towards phenol over 48 h. On the basis of these studies, Bi(v) hydroxy benzoate **51** is identified as the kinetically competent arylating reagent.

The dichotomous behaviour of bismacycles **50**–**52** highlights the major reactivity consequences of seemingly minor changes to the Bi(v) ligand sphere. Although the fundamental origins of these differences are not yet known, we propose that the unique reactivity of Bi(v) hydroxy benzoate **51** reflects the ability of the basic hydroxide moiety to facilitate formation of key Bi(v) phenoxy benzoate intermediate **54** (Fig. 5e) without added base. Similar phenoxide intermediates have been widely proposed in the group transfer chemistry of bismuth and other main-group elements[84] and are well documented in copper-mediated phenol *ortho*-oxygenation[85,86]. Furthermore, Bi(v) phenoxides have been isolated and characterized for electron-poor phenols and have been shown to undergo ligand coupling upon heating[87].

The divergent chemoselectivity exhibited by bismacycles **50** and **51** has parallels in other systems that are based on bismuth(v)[60], iodine(III)[88,89] and lead(IV)[90,91], each of which engage phenols in either oxidation or aryl transfer processes as a function of the ligands at the metal centre[13]. Although the basicity of the ligands associated with Bi(v) clearly differentiates **50** and **51**, the dimeric nature of the former may also contribute to the observed chemoselectivity differences. By contrast, the lack of reactivity observed in the presence of excess *m*CBA presumably reflects the absence of an appropriate base, either at the metal centre of Bi(v) dibenzoate **52**

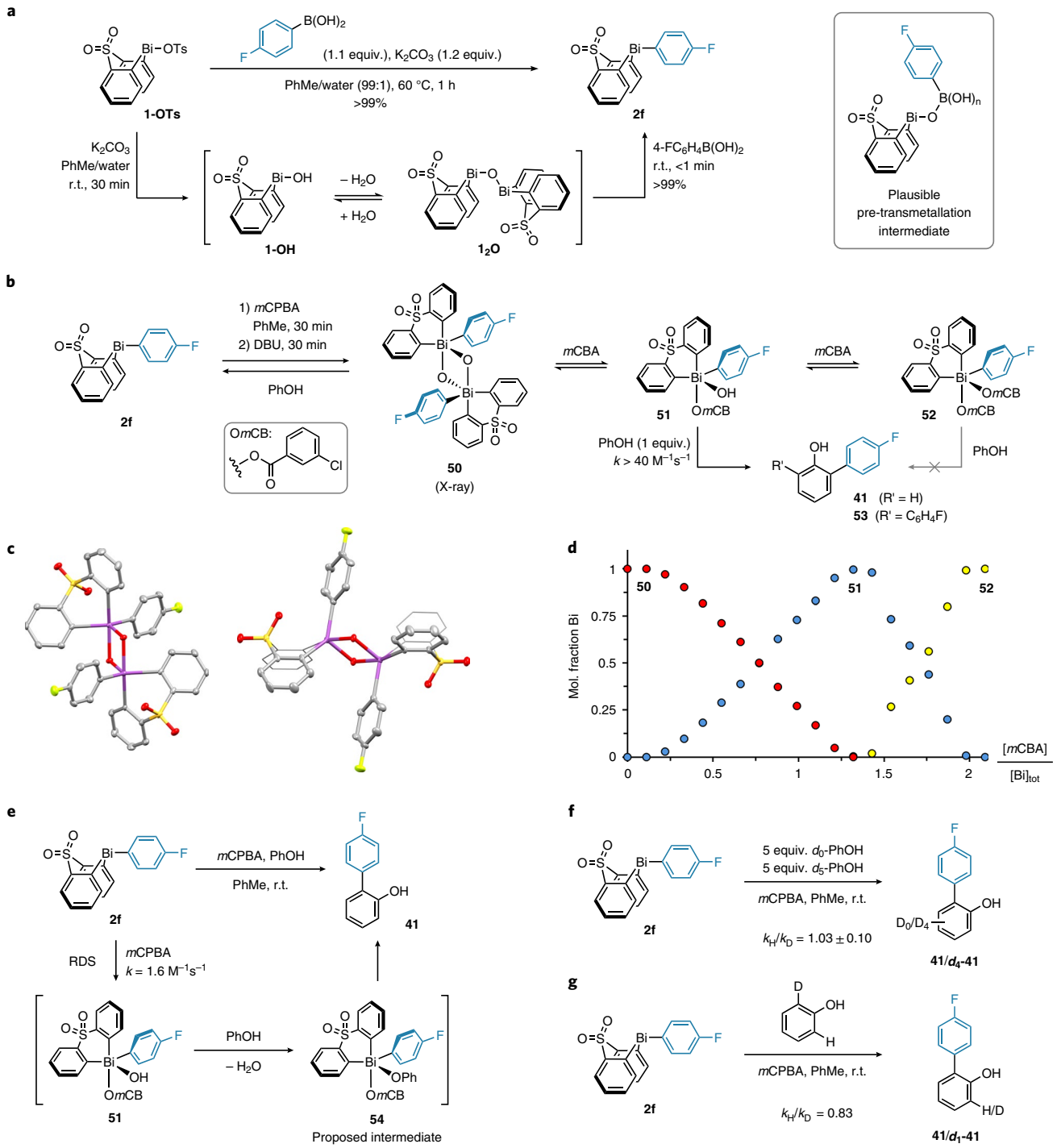



**Fig. 5 | Preliminary mechanistic investigations. a**, Bi(III)–oxo species generated by basic hydrolysis of **1-OTs** are kinetically competent intermediates en route to aryl bismacycles **2**. The rate-determining step (RDS) for very electron-deficient arylboronic acids changes from hydrolysis to B-to-Bi transmetallation. By analogy to the Suzuki–Miyaura cross-coupling, an oxo-bridged Bi–O–B species is proposed as a plausible, fleeting pre-transmetallation intermediate. **b**, Bi(V) species **51** and **52** can be accessed via oxidation of **2f** with commercial *m*CPBA, or titration of isolable bis-μ-oxo dimer **50** with *m*CBA. Only hydroxy benzoate **51** engages in productive arylation of phenol. DBU, 1,8-diazabicyclo(5.4.0)undec-7-ene. **c**, Different orientations of the single crystal X-ray diffraction structure of **50** are shown (thermal ellipsoids shown at 50% probability; all hydrogen atoms and a molecule of acetonitrile are omitted for clarity). **d**, Titration of bis-μ-oxo dimer **50** with *m*CBA affords Bi(V) species **51** and **52**, confirming their formation by direct oxidation of **2f**. **e**, Oxidation of **2f** with *m*CPBA is slower than the subsequent arylation of phenol by the resulting Bi(V) species, precluding direct kinetic interrogation of the arylation process. **f**, No appreciable KIE is observed in the intermolecular competition between $d_0$- and $d_5$-PhOH in Bi(V)-mediated arylation. **g**, An α-SKIE (α-secondary kinetic isotope effect) of 0.83 is observed for the Bi(V)-mediated arylation of 2-$d_1$-phenol. The apical/equatorial distribution of substituents in **50**–**52** and **47** in solution is unknown. All yields were determined by $^{19}$F NMR spectroscopy against an internal standard.

or in solution. The different reactivity of Bi(V) hydroxy benzoates and dibenzoates is reproduced in simple triaryl bismuth systems (Supplementary Figs. 14 and 15).

Competitive kinetic isotope effect (KIE) studies provide valuable insight into the key product-forming processes that follow Bi(III) → Bi(V) oxidation (Fig. 5f,g). The absence of an observable KIE

in intermolecular competition between $d_0$- and $d_5$-PhOH (Fig. 5f) is consistent with selectivity-determining formation of a Bi(v) phenoxide of type **54** (Fig. 5e). That this step involves attack by the phenolic oxygen on Bi(v) is supported by preliminary studies of competitions between different phenols ($\rho^+ = -1.4$; Supplementary Fig. 20). An α-SKIE (secondary kinetic isotope effect) of 0.83 from intramolecular competition (Fig. 5g) suggests that the subsequent C–C bond-forming step involves selectivity-determining dearomatization of the phenol before rapid rearomatization, as per a conventional electrophilic aromatic substitution[92]. Notably, very similar α-SKIEs have been measured for copper-catalysed electrophilic *ortho*-oxygenation of phenols, which proceeds via intramolecular group-transfer[85,93,94].

Together, these preliminary experiments provide unique insight into the nature of the elementary steps involved in reductive ligand coupling at a Bi(v) centre and add credence to Barton and co-workers's proposed (but unsubstantiated) mechanistic hypotheses[60,64,84,95]. Taken with our experimental observations (Fig. 3d), they also form the basis of a practical user's guide that allows the selectivity of the arylation process to be predicted. Specifically: (1) selectivity between mixtures of phenols is determined at the point of attack on Bi(v), and results in preferential arylation of the more electron-rich phenol; and (2) regioselectivity between non-equivalent $C_{ortho}$ positions is determined at the point of C–C bond-formation, favours the less sterically hindered, more electron-rich $C_{ortho}$ position, and is only moderately sensitive to the electronic character of the aryl group being installed.

## Conclusions

We have developed a step- and atom-economic method for the bismuth-mediated *ortho*-arylation of phenols and naphthols that exhibits broad substrate scope and tolerates synthetically useful functionality. The reaction proceeds under mild conditions without the need to exclude air or moisture, and employs commercially available starting materials. Crucial enabling advances include the introduction of B–to–Bi(III) transmetallation as a convenient new route to functionalized arylbismuthanes, and identification of an ancillary scaffold that simultaneously confers stability, selectivity and enhanced arylating ability on the resulting bismuth reagents. Supporting kinetic and structural investigations provide the first experimental insight into the mechanism of bismuth-mediated arylation and render the synthetic methodology predictable.

We envisage that the new reactivity and fundamental understanding communicated herein will not only find immediate application in synthesis, but will also underpin the development of new bismuth-mediated arylation strategies in the future.

## Methods

**General procedure for oxidative arylation of naphthols and phenols.** A suspension of bismacycle tosylate **1-OTs** (1.0 equiv.; initial concentration = 0.05 M), $K_2CO_3$ (1.2 equiv.) and arylboronic acid (1.1 equiv.) in toluene/water (99:1, v/v) was stirred at 60 °C for 2 h. After cooling to room temperature, substrates (naphthols, 0.90 equiv.; phenols, 3.0 equiv.) and *m*CPBA (titrated; 1.5 equiv.) were added. The reaction was stirred for 10 min at room temperature and then methanol (2 ml) was added. The mixture was diluted with diethyl ether and washed with a saturated aqueous solution of $KHCO_3$. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated in vacuo before purification by flash column chromatography on silica gel. Following isolation of the desired arylation product, bismacycle acetate **1-OAc** can be recovered by flushing the column with diethyl ether to remove organic impurities before elution with 2% acetic acid in methanol.

## Online content

Any Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-020-0425-4.

Received: 20 March 2019; Accepted: 21 January 2020;
Published online: 27 February 2020

## References

1. Ibrahim, S. R. M. & Mohamed, G. A. Naphthylisoquinoline alkaloids potential drug leads. *Fitoterapia* **106**, 194–225 (2015).
2. Teponno, R. B., Kusari, S. & Spiteller, M. Recent advances in research on lignans and neolignans. *Nat. Prod. Rep.* **33**, 1044–1092 (2016).
3. Quideau, S., Deffieux, D., Douat-Casassus, C. & Pouysegu, L. Plant polyphenols: chemical properties, biological activities, and synthesis. *Angew. Chem. Int. Ed.* **50**, 586–621 (2011).
4. Stockert, A. L. & Hill, M. in *Bioactive Components, Diet and Medical Treatment in Cancer Prevention* (eds Waly, M. & Rahman, M.) Ch. 2, 25–50 (Springer, 2018).
5. Parmar, D., Sugiono, E., Raja, S. & Rueping, M. Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: history and classification by mode of activation; Brønsted acidity, hydrogen bonding, ion pairing, and metal phosphates. *Chem. Rev.* **114**, 9047–9153 (2014).
6. Reid, J. P. & Goodman, J. M. Selecting chiral BINOL-derived phosphoric acid catalysts: general model to identify steric features essential for enantioselectivity. *Chem. Eur. J.* **23**, 14248–14260 (2017).
7. Cramer, J., Sager, C. P. & Ernst, B. Hydroxyl groups in synthetic and natural-product-derived therapeutics: a perspective on a common functional group. *J. Med. Chem.* **62**, 8915–8930 (2019).
8. Zhang, H. et al. Molecular determinants of Magnolol targeting both RXRα and PPARγ. *PLOS ONE* **6**, e28253 (2011).
9. Marchais-Oberwinkler, S. et al. New drug-like hydroxyphenylnaphthol steroidomimetics as potent and selective 17β-hydroxysteroid dehydrogenase type 1 inhibitors for the treatment of estrogen-dependent diseases. *J. Med. Chem.* **54**, 534–547 (2010).
10. Gross, K. C. & Seybold, P. G. Substituent effects on the physical properties and p$K_a$ of phenol. *Int. J. Quantum Chem.* **85**, 569–579 (2001).
11. Bosmans, V. et al. Probing through-space polar–$\pi$ interactions in 2,6-diarylphenols. *J. Org. Chem.* **84**, 3632–3637 (2019).
12. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E. & Lemaire, M. Aryl–aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **102**, 1359–1470 (2002).
13. Huang, Z. & Lumb, J.-P. Phenol-directed C–H functionalization. *ACS Catal.* **9**, 521–555 (2019).
14. Alberico, D., Scott, M. E. & Lautens, M. Aryl–aryl bond formation by transition-metal-catalyzed direct arylation. *Chem. Rev.* **107**, 174–238 (2007).
15. Zhao, X., Yeung, C. S. & Dong, V. M. Palladium-catalyzed *ortho*-arylation of *O*-phenylcarbamates with simple arenes and sodium persulfate. *J. Am. Chem. Soc.* **132**, 5837–5844 (2010).
16. Bedford, R. B., Webster, R. L. & Mitchell, C. J. Palladium-catalysed *ortho*-arylation of carbamate-protected phenols. *Org. Biomol. Chem.* **7**, 4853–4857 (2009).
17. Bedford, R. B. et al. Palladium-catalyzed *ortho*-arylation of carbamate-protected estrogens. *J. Org. Chem.* **81**, 3473–3478 (2016).
18. Xiao, B. et al. Pd(II)-catalyzed C–H activation/aryl–aryl coupling of phenol esters. *J. Am. Chem. Soc.* **132**, 468–469 (2010).
19. Ackermann, L., Diers, E. & Manvar, A. Ruthenium-catalyzed C–H bond arylations of arenes bearing removable directing groups via six-membered ruthenacycles. *Org. Lett.* **14**, 1154–1157 (2012).
20. Gu, S., Chen, C. & Chen, W. *Ortho*-functionalization of 2-phenoxypyrimidines via palladium-catalyzed C–H bond activation. *J. Org. Chem.* **74**, 7203–7206 (2009).
21. Bedford, R. B. et al. Simple rhodium–chlorophosphine pre-catalysts for the *ortho*-arylation of phenols. *Chem. Commun.* 990–992 (2008).
22. Bajracharya, G. B. & Daugulis, O. Direct transition-metal-free intramolecular arylation of phenols. *Org. Lett.* **10**, 4625–4628 (2008).
23. Truong, T. & Daugulis, O. Divergent reaction pathways for phenol arylation by arynes: synthesis of helicenes and 2-arylphenols. *Chem. Sci.* **4**, 531–535 (2013).
24. Bedford, R. B. & Limmert, M. E. Catalytic intermolecular *ortho*-arylation of phenols. *J. Org. Chem.* **68**, 8669–8682 (2003).
25. Oi, S., Watanabe, S., Fukita, S. & Inoue, Y. Rhodium-HMPT-catalyzed direct *ortho*-arylation of phenols with aryl bromides. *Tetrahedron Lett.* **44**, 8665–8668 (2003).
26. Bedford, R. B., Haddow, M. F., Webster, R. L. & Mitchell, C. J. The catalytic *ortho*-arylation of tyrosine. *Org. Biomol. Chem.* **7**, 3119–3127 (2009).
27. Barton, D. H. R., Lester, D. J., Motherwell, W. B. & Papoula, M. T. B. Observations on the cleavage of the bismuth–carbon bond in $Bi^V$ compounds: a new arylation reaction. *J. Chem. Soc. Chem. Commun.* 246–247 (1980).
28. Barton, D. H. R. et al. Comparative arylation reactions with pentaphenylbismuth and with triphenylbismuth carbonate. *J. Chem. Soc. Chem. Commun.* 827–829 (1980).
29. Gagnon, A., Dansereau, J. & Le Roch, A. Organobismuth reagents: synthesis, properties and applications in organic synthesis. *Synthesis* **49**, 1707–1745 (2017).

30. Gagnon, A, Benoit, E. & Le Roch, A. *Sci. Synth., Knowl. Updates* **4**, 2–112 (2018).
31. Suzuki, H. et al. *Organobismuth Chemistry* 1st edn (Elsevier, 2001).
32. Balsane, K. E., Gund, S. H. & Nagarkar, J. M. Atom economic palladium catalyzed novel approach for arylation of benzothiazole and benzoxazole with triarylbismuth reagents via C-H activation. *Catal. Commun.* **89**, 29–33 (2017).
33. Fedorov, A. Y. & Finet, J.-P. Synthesis and reactivity of pentavalent biphenyl-2,2′-ylenebismuth derivatives. *J. Chem. Soc., Perkin Trans. 1*, 3775–3778 (2000).
34. Suzuki, H., Murafuji, T. & Azuma, N. Synthesis and reactions of some new heterocyclic bismuth-(iii) and -(v) compounds. 5,10-Dihydrodibenzo[*b*,*e*] bismine and related systems. *J. Chem. Soc. Perkin Trans. 1*, 1593–1600 (1992).
35. Sakurai, N. & Mukaiyama, T. A new preparative method of aryl sulfonate esters by using cyclic organobismuth reagents. *Heterocycles* **74**, 771–790 (2007).
36. Murafuji, T. et al. Bismuth heterocycles based on a diphenyl sulfone scaffold: synthesis and substituent effect on the antifungal activity against *Saccharomyces cerevisiae*. *Eur. J. Med. Chem.* **46**, 519–525 (2011).
37. Murafuji, T., Nagasue, M., Tashiro, Y., Sugihara, Y. & Azuma, N. Structural characteristics of aryloxybismuthanes stabilized by hypervalent bond formation. Synthesis, incorporation of 4-methoxyphenol through hydrogen bonding, and crystal supramolecularity. *Organometallics* **19**, 1003–1007 (2000).
38. Ohkata, K., Takemoto, S., Ohnishi, M. & Akiba, K. Synthesis and chemical behaviors of 12-substituted dibenz[*c*,*f*][1,5]azastibocine and dibenz[*c*,*f*][1,5] azabismocine derivatives: evidences of 10-Pn-4 type hypervalent interaction. *Tetrahedron Lett.* **30**, 4841–4844 (1989).
39. Ikegami, T. & Suzuki, H. A stabilized triarylbismuthane imide: synthesis and first X-ray structure analysis. *Organometallics* **17**, 1013–1017 (1998).
40. Matano, Y., Begum, S. A., Miyamatsu, T. & Suzuki, H. A new and efficient method for the preparation of bismuthonium and telluronium salts using aryl- and alkenylboronic acids. First observation of the chirality at bismuth in an asymmetrical bismuthonium salt. *Organometallics* **17**, 4332–4334 (1998).
41. Yoshihiro, M., Takashi, M. & Hitomi, S. Synthesis and reaction of unsymmetrical tetraarylbismuthonium salts. First isolation of bismuthonium salts bearing all different aryl groups. *Chem. Lett.* **27**, 127–128 (1998).
42. Matano, Y., Begum, S. A., Miyamatsu, T. & Suzuki, H. Synthesis and stereochemical behavior of unsymmetrical tetraarylbismuthonium salts. *Organometallics* **18**, 5668–5681 (1999).
43. Matano, Y., Begum, S. A. & Suzuki, H. A new synthesis of triarylbismuthanes via directed ligand coupling of oxazoline-substituted tetraarylbismuthonium salts: synthesis of polystyrenes bearing the diarylbismuthino group. *Synthesis* 1081–1085 (2001).
44. Matano, Y. & Imahori, H. A new, efficient method for direct α-alkenylation of β-dicarbonyl compounds and phenols using alkenyltriarylbismuthonium salts. *J. Org. Chem.* **69**, 5505–5508 (2004).
45. Stavila, V., Thurston, J. H., Prieto-Centurión, D. & Whitmire, K. H. A new methodology for synthesis of aryl bismuth compounds: arylation of bismuth(III) carboxylates by sodium tetraarylborate salts. *Organometallics* **26**, 6864–6866 (2007).
46. Dostál, L. et al. From stiba- and bismaheteroboroxines to N,C,N-chelated diorganoantimony(III) and bismuth(III) cations—an unexpected case of aryl group migration. *Inorg. Chem.* **54**, 6010–6019 (2015).
47. Cox, P. A., Leach, A. G., Campbell, A. D. & Lloyd-Jones, G. C. Protodeboronation of heteroaromatic, vinyl, and cyclopropyl boronic acids: pH–rate profiles, autocatalysis, and disproportionation. *J. Am. Chem. Soc.* **138**, 9145–9157 (2016).
48. Cox, P. A. et al. Base-catalyzed aryl-$B(OH)_2$ protodeboronation revisited: from concerted proton transfer to liberation of a transient aryl anion. *J. Am. Chem. Soc.* **139**, 13156–13165 (2017).
49. Kozminskaya, T. K., Nadj, M. M. & Kocheshkov, K. A. The synthesis of organo-bismuth compounds of the type $R_3Bi$ by the method of double diazonium salts. *Zh. Obshch. Khim.* **16**, 891–896 (1946).
50. Matano, Y. et al. Water-soluble non-ionic triarylbismuthanes. First synthesis and properties. *J. Chem. Soc., Perkin Trans. 1*, 2511–2518 (1998).
51. Hébert, M. et al. Synthesis of highly functionalized triarylbismuthines by functional group manipulation and use in palladium- and copper-catalyzed arylation reactions. *J. Org. Chem.* **81**, 5401–5416 (2016).
52. Preda, A. M. et al. Heteroaryl bismuthines: a novel synthetic concept and metal$\cdots\pi$ heteroarene interactions. *Dalton Trans.* **46**, 8269–8278 (2017).
53. Petiot, P. & Gagnon, A. Palladium-catalyzed cross-coupling reaction of functionalized aryl- and heteroarylbismuthanes with 2-halo(or 2-triflyl)azines and -diazines. *Eur. J. Org. Chem.* **24**, 5282–5289 (2013).
54. Merck and Co. *O*-Heteroaryl, *O*-alkylheteroaryl, *O*-alkenylheteroaryl and *O*-alkynylheteroarylmacrolides having immunosuppressive activity. US patent US5252732 (1993).
55. Urgin, K. et al. Advanced preparation of functionalized triarylbismuths and triheteroaryl-bismuths: new scope and alternatives. *Tetrahedron Lett.* **53**, 1894–1896 (2012).
56. Kinzel, T., Zhang, Y. & Buchwald, S. L. A new palladium precatalyst allows for the fast Suzuki–Miyaura coupling reactions of unstable polyfluorophenyl and 2-heteroaryl boronic acids. *J. Am. Chem. Soc.* **132**, 14073–14075 (2010).
57. Chen, L., Sanchez, D. R., Zhang, B. & Carrow, B. P. "Cationic" Suzuki–Miyaura coupling with acutely base-sensitive boronic acids. *J. Am. Chem. Soc.* **139**, 12418–12421 (2017).
58. Babudri, F., Farinola, G. M., Naso, F. & Ragni, R. Fluorinated organic materials for electronic and optoelectronic applications: the role of the fluorine atom. *Chem. Commun.* 1003–1022 (2007).
59. Fedorov, A., Combes, S. & Finet, J.-P. Influence of the steric hindrance of the aryl group of pentavalent triarylbismuth derivatives in ligand coupling reactions. *Tetrahedron* **55**, 1341–1352 (1999).
60. Barton, D. H. R. et al. The chemistry of pentavalent organobismuth reagents: Part X. Studies on the phenylation and oxidation of phenols. *Tetrahedron* **43**, 323–332 (1987).
61. Evano, G., Blanchard, N. & Toumi, M. Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis. *Chem. Rev.* **108**, 3054–3131 (2008).
62. Qiao, J. X. & Lam, P. Y. S. Copper-promoted carbon-heteroatom bond cross-coupling with boronic acids and derivatives. *Synthesis* **6**, 829–856 (2011).
63. Crifar, C., Petiot, P., Ahmad, T. & Gagnon, A. Synthesis of highly functionalized diaryl ethers by copper-mediated *O*-arylation of phenols using trivalent arylbismuth reagents. *Chem. Eur. J.* **20**, 2755–2760 (2014).
64. Barton, D. H. R. et al. Pentavalent organobismuth reagents. Part 2. The phenylation of phenols. *J. Chem. Soc. Perkin Trans. 1*, 2657–2665 (1985).
65. Hansch, C., Leo, A. & Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **97**, 165–195 (1991).
66. Takahata, Y. & Chong, D. P. Estimation of Hammett sigma constants of substituted benzenes through accurate density-functional calculation of core-electron binding energy shifts. *Int. J. Quantum Chem.* **103**, 509–515 (2005).
67. Selassie, C. & Verma, R. P. *Burger's Medicinal Chemistry, Drug Discovery, and Development* 6th edn, Vol. 1 (John Wiley & Sons, 2003).
68. Sofia, M. J. et al. *o*-Phenylphenols: potent and orally active leukotriene B4 receptor antagonists. *J. Med. Chem.* **36**, 3978–3981 (1993).
69. Sawyer, J. S. et al. Synthetic and structure/activity studies on acid-substituted 2-arylphenols: discovery of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenoxy]benzoic acid, a high-affinity leukotriene B4 receptor antagonist. *J. Med. Chem.* **38**, 4411–4432 (1995).
70. Worm, K., Zhou, Q. J., Stabley, G. J., DeHaven, R. N. & Dolle, R. E. Biaryl cannabinoid mimetics—synthesis and structure–activity relationship. *Bioorg. Med. Chem. Lett.* **17**, 3652–3656 (2007).
71. Zhang, L. et al. Highly regio- and chemoselective oxidative C–H/C–H cross-couplings of anilines and phenols enabled by a co-oxidant-free Rh(I)/$Zn(NTf_2)_2$/air catalytic system. *ACS Catal.* **9**, 5358–5364 (2019).
72. Hu, Z. & Liu, G. Rhodium(III)-catalyzed cascade redox-neutral C–H functionalization and aromatization: synthesis of unsymmetrical *ortho*-biphenols. *Adv. Synth. Catal.* **359**, 1643–1648 (2017).
73. Xiao, B. et al. Synthesis of dibenzofurans via palladium-catalyzed phenol-directed C–H activation/C–O cyclization. *J. Am. Chem. Soc.* **133**, 9250–9253 (2011).
74. Ciana, C.-L., Phipps, R. J., Brandt, J. R., Meyer, F.-M. & Gaunt, M. J. A highly *para*-selective copper(II)-catalyzed direct arylation of aniline and phenol derivatives. *Angew. Chem. Int. Ed.* **50**, 458–462 (2011).
75. Ivanova, A. et al. Synthesis, functionalization and biological activity of arylated derivatives of (+)-estrone. *Bioorg. Med. Chem.* **25**, 949–962 (2017).
76. Mewshaw, R. E. et al. ERβ Ligands. 3. Exploiting two binding orientations of the 2-phenylnaphthalene scaffold to achieve ERβ selectivity. *J. Med. Chem.* **48**, 3953–3979 (2005).
77. Marchais-Oberwinkler, S. et al. Substituted 6-phenyl-2-naphthols. Potent and selective nonsteroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1): design, synthesis, biological evaluation, and pharmacokinetics. *J. Med. Chem.* **51**, 4685–4698 (2008).
78. Yin, S.-F., Maruyama, J., Yamashita, T. & Shimada, S. Efficient fixation of carbon dioxide by hypervalent organobismuth oxide, hydroxide, and alkoxide. *Angew. Chem. Int. Ed.* **47**, 6590–6593 (2008).
79. Qiu, R. et al. Synthesis and structure of binuclear O/S-bridged organobismuth complexes and their cooperative catalytic effect on $CO_2$ fixation. *ChemPlusChem* **77**, 404–410 (2012).
80. Carrow, B. P. & Hartwig, J. F. Distinguishing between pathways for transmetalation in Suzuki–Miyaura reactions. *J. Am. Chem. Soc.* **133**, 2116–2119 (2011).
81. Lennox, A. J. J. & Lloyd-Jones, G. C. Transmetallation in Suzuk–Miyaura coupling: the fork in the trail. *Angew. Chem. Int. Ed.* **52**, 7362–7370 (2013).
82. Thomas, A. A. & Denmark, S. E. Pre-transmetalation intermediates in the Suzuki–Miyaura reaction revealed: the missing link. *Science* **352**, 329–332 (2016).

83. Matano, Y. & Nomura, H. Dimeric triarylbismuthane oxide: a novel efficient oxidant for the conversion of alcohols to carbonyl compounds. *J. Am. Chem. Soc.* **123**, 6443–6444 (2001).
84. *Tetrahedron Organic Chemistry Series* (ed. Finet, J.-P.) Vol. 18, Ch. 2 (Elsevier, 1998).
85. Askari, M. S., Esguerra, K. V. N., Lumb, J.-P. & Ottenwaelder, X. A biomimetic mechanism for the copper-catalyzed aerobic oxygenation of 4-*tert*-butylphenol. *Inorg. Chem.* **54**, 8665–8672 (2015).
86. Itoh, S. & Fukuzumi, S. Monooxygenase activity of type 3 copper proteins. *Acc. Chem. Res.* **40**, 592–600 (2007).
87. Hoppe, S. & Whitmire, K. H. Synthesis and structure of pentavalent bismuth(v) alkoxides and ligand redistribution equilibria in solution. *Organometallics* **17**, 1347–1354 (1998).
88. Ozanne-Beaudenon, A. & Quideau, S. Regioselective hypervalent-iodine(III)-mediated dearomatizing phenylation of phenols through direct ligand coupling. *Angew. Chem. Int. Ed.* **44**, 7065–7069 (2005).
89. Pouységu, L., Deffieux, D. & Quideau, S. Hypervalent iodine-mediated phenol dearomatization in natural product synthesis. *Tetrahedron* **66**, 2235–2261 (2010).
90. Barton, D. H. R., Donnelly, D. M. X., Guiry, P. J. & Finet, J.-P. *ortho*-Arylation of 3,5-di-*tert*-butylphenol with aryllead(IV) derivatives: a facile synthesis of sterically hindered phenols. *J. Chem. Soc. Perkin Trans. 1*, 2921–2926 (1994).
91. Mihailović, M. L., Čeković, Z. & Mathes, B. M. in *Encyclopedia of Reagents for Organic Synthesis* (John Wiley & Sons, 2005); https://doi.org/10.1002/047084289X.rl006.pub2
92. Taylor, R. *Electrophilic Aromatic Substitution* (John Wiley & Sons, 1990).
93. Mirica, L. M. et al. Tyrosinase reactivity in a model complex: an alternative hydroxylation mechanism. *Science* **308**, 1890–1892 (2005).
94. Fujieda, N. et al. Activation mechanism of melB tyrosinase from *Aspergillus oryzae* by acidic treatment. *J. Biol. Inorg. Chem.* **18**, 19–26 (2013).
95. Combes, S. & Finet, J.-P. On the exclusion of radical species in the ligand coupling reactions with pentavalent triarylbismuth derivatives. *Tetrahedron* **55**, 3377–3386 (1999).

## Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers 1904059 (**1-OTs**), 1904060 (**2a**), 1904061 (**2b**), 1904062 (**2c**), 1904063 (**2e**), 1904064 (**2g**), 1904065 (**2h**), 1904066 (**2i**), 1904069 (**2j**), 1904067 (**2k**), 1904068 (**2m**), 1904070 (**2u**), 1904071 (**2v**), 1904072 (**9**) and 1904073 (**50**). Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif. The authors declare that all other data supporting the findings of this study are available within the paper and its Supplementary information.

## Acknowledgements

This work was supported by The University of Nottingham.

## Author contributions

M.J. and L.T.B. conceived this work. M.J. and L.M. performed the experiments and analysed the data. W.L. acquired and solved X-ray diffraction data. L.T.B. wrote the manuscript with input from M.J. and L.M.

## Competing interests

Bismacycle 1-OTs has been made commercially available via Key Organics. The sales revenue that is returned to the University of Nottingham covers the costs of commercialization; the authors do not receive profit from any of the sales that are made.

## Additional information

**Supplementary information** is available for this paper at https://doi.org/10.1038/s41557-020-0425-4.

**Correspondence and requests for materials** should be addressed to L.T.B.

**Reprints and permissions information** is available at www.nature.com/reprints.