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

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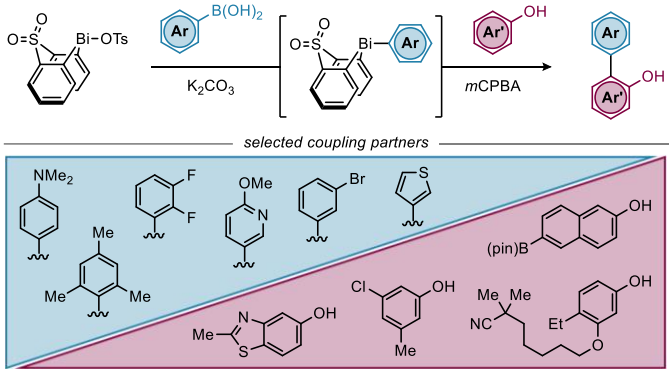


Abstract:

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 synthetic chemists' lexicon 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-catalyzed 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 under-exploited reactivity of organobismuth compounds.

The 2-hydroxybiaryl motif forms the core of numerous biologically and synthetically important molecules (Fig. 1a). This includes more than 4000 natural products, many of which possess antimalarial, anti(retro)viral or cytotoxic properties.[1,2,3,4] 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 BINOL-derived asymmetric catalysts[5,6] – and the hydrogen-bonding abilities conferred by the phenolic hydroxyl group. Indeed, 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 H-bond donors and poorer H-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 this broad significance, methods for the preparation of 2-hydroxybiaryls are highly valued and have been the subject of much research effort. The most widely used strategies involve metal-catalyzed arylation of a hydroxyarene-derived substrate *via* either cross-coupling[12] or C-H functionalization.[13,14,15,16,17,18,19,20] However, although extremely powerful, the atom and step economy of these approaches is impacted by the need to prefunctionalize the substrate. For example, cross-coupling 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[21,22,23] – or that allow the *in situ* installation and removal of co-catalytic directing groups[21,24,25,26] – represent an almost ideal solution to the problems of step- and atom-efficiency, but suffer from practical limitations such as moderate scope and poor selectivity. In addition to potential issues surrounding step count, the extant cross-coupling and C-H arylation strategies rely on activation of a carbon-halogen bond, which results 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.

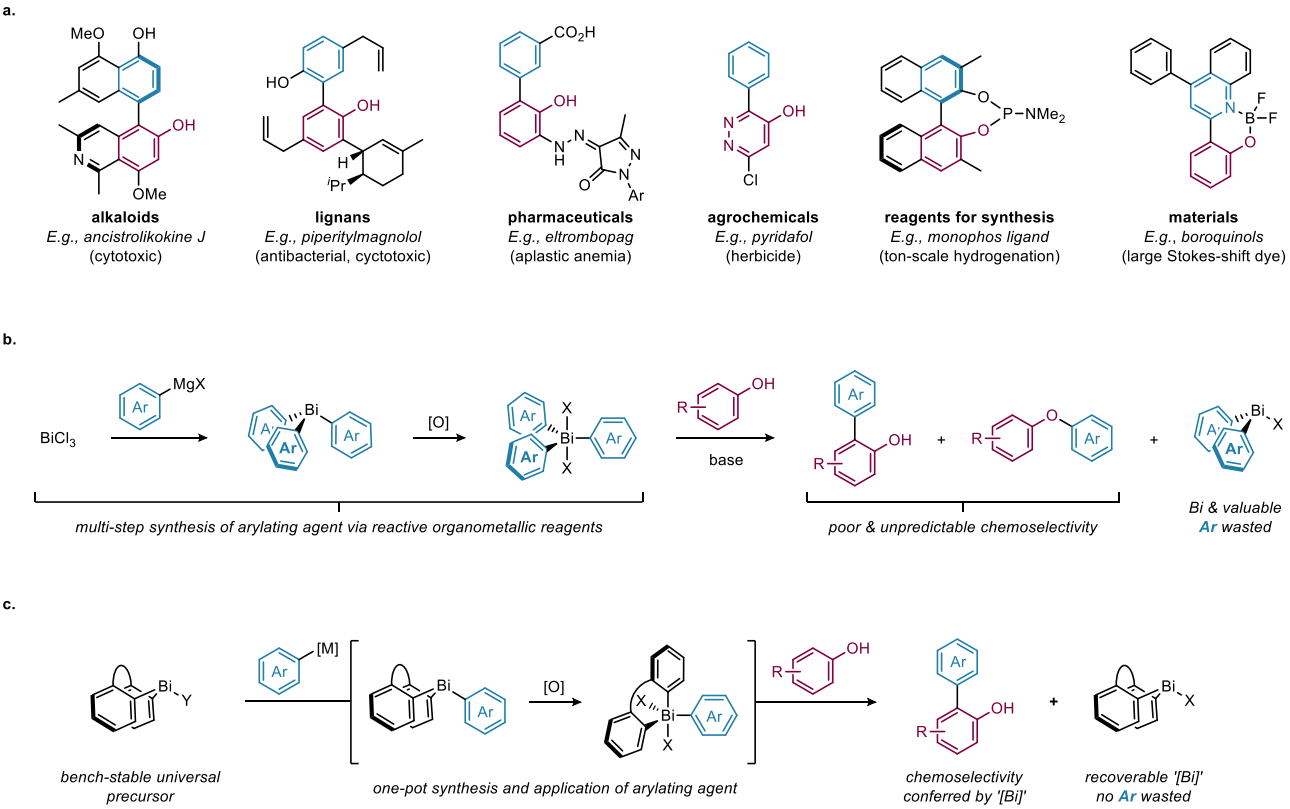


Fig. 1. Occurrence and Bi(V)-mediated synthesis of 2-hydroxybiaryls. a, The 2-hydroxybiaryl motif is ubiquitous to societally important molecules, including biologically-active natural and unnatural compounds, fine chemicals for synthesis and functional materials. Continued exploration of this privileged 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-economy. **c**, 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.

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).[27,28,29,30] This methodology benefits further from the low cost of Bi and its salts, and the high stability and low toxicity of triarylbismuth reagents (*e.g.*, $LD_{50}(BiPh_3)$ = 180 g/kg[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 multi-step synthesis,

(b) the often unpredictable, substrate-controlled chemoselectivity between C_{ortho}- *vs 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 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-

catalyzed manifolds, diverse aryl and heteroaryl partners can be rapidly coupled to phenols and naphthols under mild conditions. Supporting mechanistic studies render the methodology predictable and provide new fundamental insights into the reactivity of organobismuth compounds.

Results

Strategic blueprint. As outlined in Fig. 1c, our strategy was predicated 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 center.[33,34,35] 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 multi-step 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. To deliver our proposed methodology, we first had to identify an appropriate bismacyclic scaffold. 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 Information Section 2). A library of bismacycle halides and *pseudo*halides **1-X** based on this scaffold were prepared simply by changing the Brønsted acid employed in protodebismuthation of a common arylbismacycle(III) intermediate (Supplementary Information Section 4). By telescoping the bismacycle construction and protodebismuthation steps (Fig. 2), bismacycle tosylate **1-OTs** was synthesised 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, tosylate **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 2 years under ambient laboratory conditions. Inspection of its solid-state structure reveals a short transannular contact between the Bi center and one oxygen of the sulfone (Bi···O = 2.556(5) Å), which is likely responsible for this uncharacteristic stability.[34,38,39] Bismacycle tosylate **1-OTs** is commercially available through Key Organics (catalog number NS-00138).

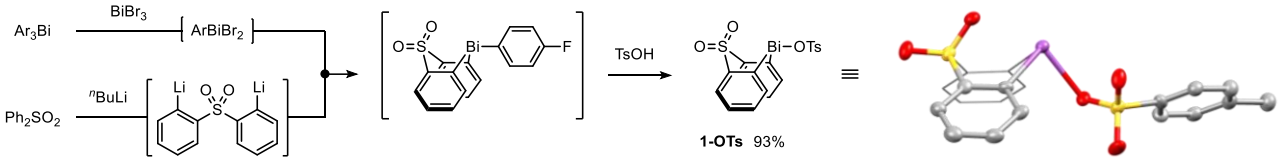
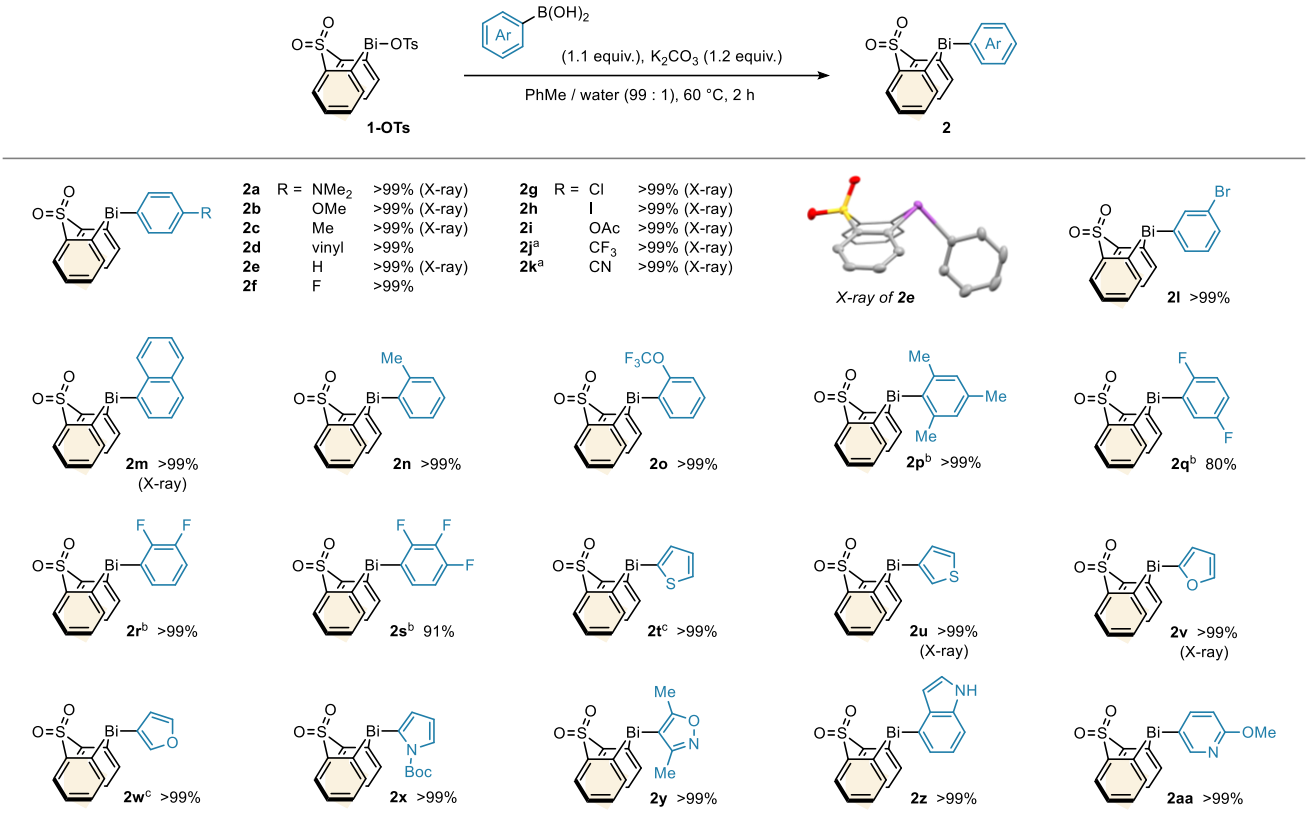


Fig. 2. Synthesis of a universal bismacycle(III) precursor. Decagram quantities of bismacycle tosylate **1-OTs** can be prepared *via* a telescoped, chromatography-free route that starts from readily available starting materials. **1-OTs** is stable to ambient laboratory conditions, presumably due to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

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) center. 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 which 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, while B-to-Bi transmetallation is well precedented for Bi(V),[40,41,42,43,44] this process is limited to just two examples for Bi(III): aryl transfer from tetraarylborates to $Bi(OAc)_3$,[45] and from arylboronic acids to monoarylbismuth(III) oxides.[46] After investigation of different arylboron reagents and reaction variables (Supplementary Information 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 Information Section 3).

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



Conversions were determined by ^{1}H NMR spectroscopic analysis prior to characterization of isolated pure material. [a] Reaction time was 6 h; [b] reaction time was 14 h; [c] characterized without isolation. Ac, acetyl; Boc, *tert*-butoxycarbonyl.

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 (*e.g.*, **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 4 steps),[50] both of which can be installed quantitatively in a single step by our method (**2h, 2i**).

Similarly, triarylbismuthanes containing thienyl, furanyl, pyrrolyl or unprotected indolyl groups that are accessible in only moderate yields (28-53%) *via* conventional organometallic routes[51,52,53,54,55] 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}-*vs*-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 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**).

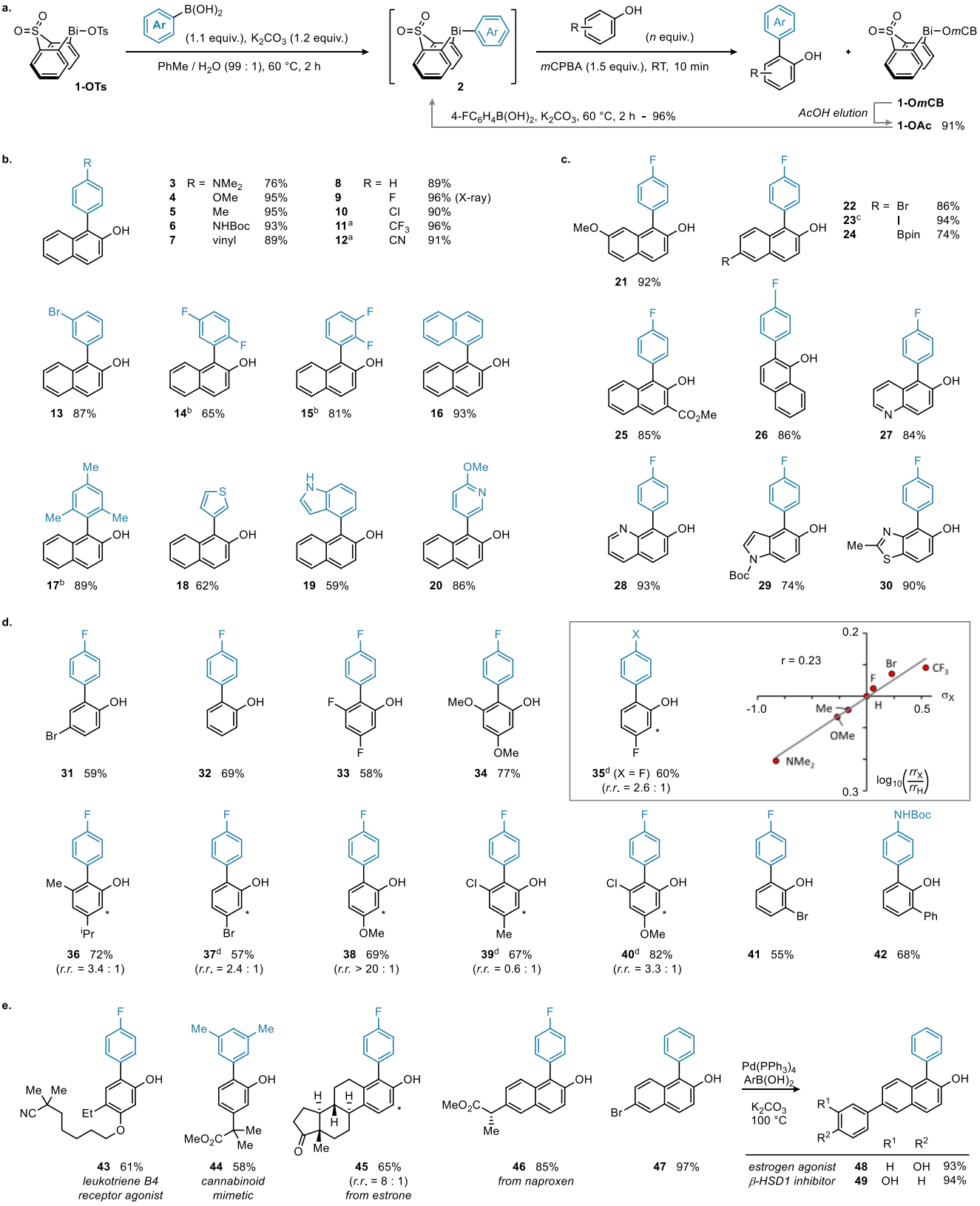


Fig. 3. One-pot, Bi(V)-mediated arylation of phenols and naphthols. a, Starting from bismacycle tosylate **1-OTs**, B-to-Bi transmetallation, oxidation and arylation can be performed as a single telescoped operation

without exclusion of air or moisture, and the bismacyclic scaffold can be recovered in a high yield as acetate **1-OAc**. **b,** Scope with respect to aryl and heteroarylboronic acids (n = 0.9). **c,** Scope with respect to naphthol-like substrates (n = 0.9). **d,** Scope with respect to phenol substrates (n = 3.0), and Hammett plot (inset) quantifying the effect of the boronic acid on regioselectivity. Formation of **35**-**40** was accompanied by minor regioisomers (**35'-40'**) arising from arylation at the position denoted with an asterisk. Regisomeric ratios (*r.r.*) were determined by ^{19}F NMR spectroscopic analysis prior to purification; where regioisomer separation was not possible, the composition was confirmed by comparison to authentic samples of single regioisomers prepared *via* alternative methods. **e**, Application to the synthesis and diversification of biologically active compounds; substrate stoichiometries: n = 3.0 (**43** and **44**), 5.0 (**45**) or 0.9 (**46** and **47**). [a] Transmetallation time was 6 h; [b] 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.

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**), electron-withdrawing (**9-15**), sterically demanding (**16** and **17**) and synthetically useful substituents (**6, 7, 10, 12, 13**) all being well tolerated. While 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 hours 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 (*e.g.*, 2-furyl gives 0%, 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}-*vs*-*O*) chemoselectivity (Fig. 3c, **21-25**). The methodology is equally applicable to heterocyclic naphthol analogs (**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.

While 1-naphthol is a poor substrate for both established Bi(V) reagents (48% with $BiPh_5$)[28] and metal catalyzed C-H functionalization (38-43% with 5 mol% Rh at $T \geq 100$ °C),[24,25,26] it is arylated efficiently using our protocol (**26**, 86%). The contrast between our results and those of Barton[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 which require extended reaction times and elevated temperatures with Barton's Bi(V) reagents (*e.g.*, 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 observes 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-catalyzed *O*-selective phenol arylation reported by Chan, Evans and Lam using boronic acids,[61,62] or by Gagnon

using Bi(III) reagents.[63] In contrast, the occurrence of 2,6-diarylation[60] is not significantly influenced by the use of a bismacycle, but can be largely suppressed by using a higher relative stoichiometry of the phenol (Supplementary Fig. 8).

Under these modified conditions, the scope of phenols extends from moderately electron-deficient to very electron-rich substrates (**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[24,25,26] literature, but typically occurs with low regioselectivity. Competing 2,6-diarylation precludes 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 governing this selectivity in greater detail.

For 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 is not significantly impacted by variation of the reaction temperature (Supplementary Fig. 9) or the electronic properties of the aryl moiety being transferred (ρ = 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 σ_{para}[65] and computed σ_{ortho}[66] values (Supplementary Fig. 11 and Supplementary Table 3).

The utility of our methodology is showcased in the concise synthesis of leukotriene B_4 receptor agonist **43**[68,69] and cannabinoid mimetic **44**,[70] and in the late-stage arylation of estrone **45** and a naproxen derivative **46** (Fig. 3e). 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-catalyzed directed C-H arylations which favor functionalization of the 2-position.[17,71,72,73,74] 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 estrogen receptor agonist **48**[76] and β-HSD1 inhibitor **49**[77] (Fig. 3e). Notably, whereas **48** and **49** were previously prepared in 7 steps – which included 4 separate cross-coupling and 3 non-productive halogenation / deprotection operations – our methodology delivers both compounds in >90% yield each, with 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: transmetallation. Transmetallation from electronically-neutral or -rich boronic acids to bismacycle tosylate **1-OTs** reaches completion in under 2 hours without observable intermediates (Table 1). In contrast, cyano- and trifluoromethyl-substituted phenylboronic acids require *ca* 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. 4a). 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

behavior has been reported for related bismuth(III) hydroxides and oxides.[78,79] Reaction of isolated dimer **1_2O** with 4-fluorophenylboronic acid in the absence of base afforded aryl bismacycle **2f** quantitatively in under one minute at room temperature. The higher rate of transmetallation to **1_2O** (<1 min, RT) *vs* **1-OTs** (*ca* 1 h with base, 60 °C) indicates that **1-OH** / **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. 4a, inset) is analogous to the Pd-oxo transmetallation pathway in Suzuki-Miyaura cross-coupling,[80,81,82] and has been implicated in Si-to-Bi[52] and B-to-Bi[46] transmetallation.

Mechanistic observations: oxidation and arylation. Oxidation of aryl bismacycle **2f** with commercial *m*CPBA of *ca* 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 isolation of bis(μ-oxo)-bridged dimer **50** (Fig. 4b). Characterization by single crystal diffraction reveals a distorted trigonal bipyramidal geometry at Bi in the solid state (Fig. 4c), as has been observed previously in a related bis(μ-oxo)-bridged Bi(V) dimer.[83] Each Bi center supports a diphenylsulfone scaffold that spans an equatorial and an apical position, and distinct equatorial and apical Bi-O_{oxo} bonds (2.03 Å *vs* 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. 4d). 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 *ca* 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.

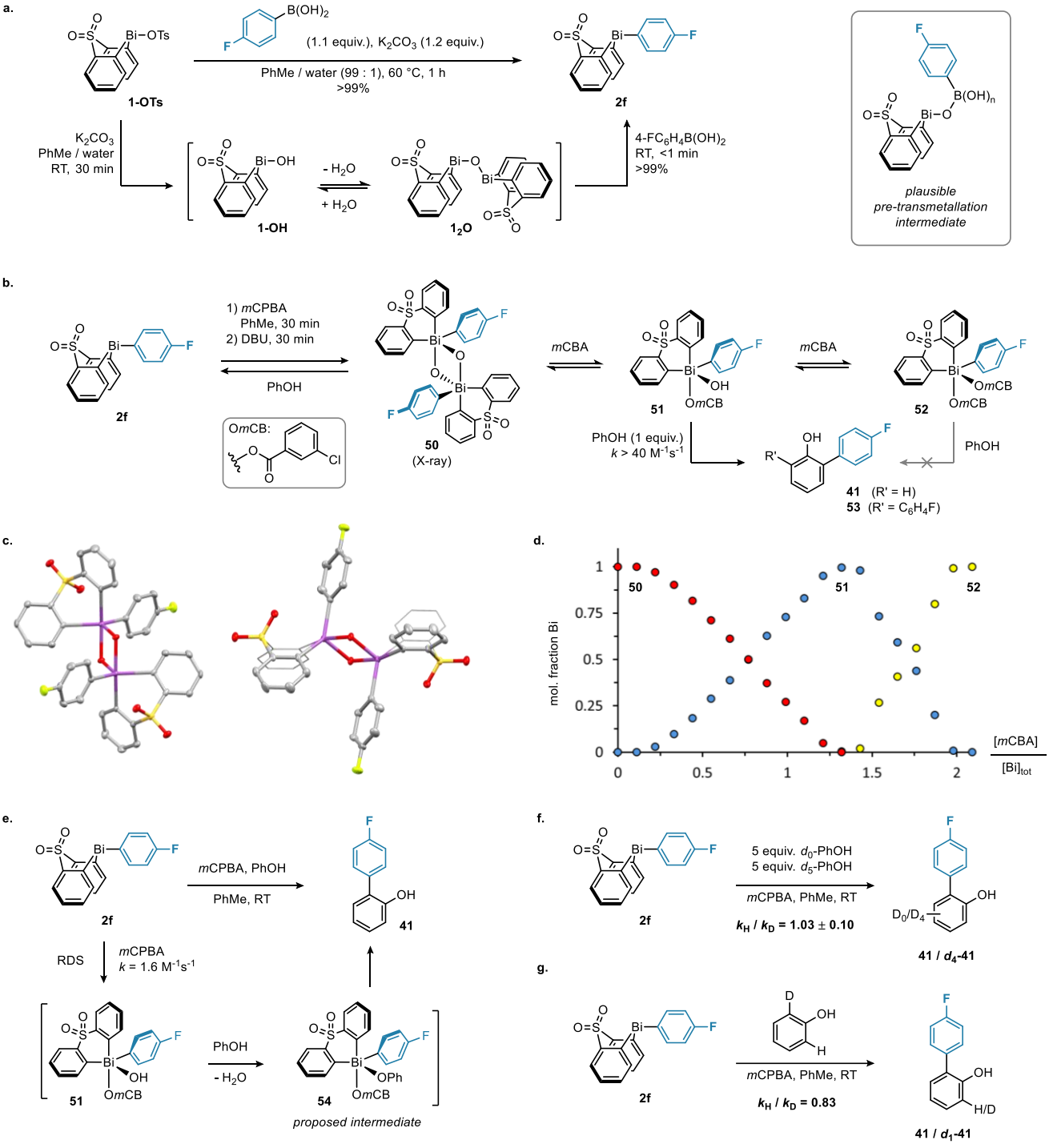


Fig. 4. Preliminary mechanistic investigations. All yields were determined by ^{19}F NMR spectroscopy against an internal standard. **a,** Bi(III)-oxo species generated *via* basic hydrolysis of **1-OTs** are kinetically competent intermediates *en route* to aryl bismacycles **2**. For very electron-deficient arylboronic acids, the rate-determining step 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. **c,** Different orientations of the single crystal X-ray diffraction structure of **50** (thermal ellipsoids shown at 50% probability; all H 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 *via* 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-phenol and d_5-phenol 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.

Bismuth(V) species **50**-**52** exhibit very distinct reactivity towards phenol (Fig. 4b). Bis(μ-oxo)-bridged dimer **50** does not arylate phenol, but instead undergoes unproductive reduction to **2f** in under 1 minute. In 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 hours. On the basis of these studies, Bi(V) hydroxy benzoate **51** is identified as the kinetically competent arylating reagent.

The dichotomous behavior of bismacycles **50**-**52** highlights the significant 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. 4e) 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 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 center.[13] While 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. In 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 center of Bi(V) dibenzoate **52**, or in solution. The different reactivity of Bi(V) hydroxy benzoates and dibenzoates is reproduced in simple triaryl bismuth systems (Supplementary Fig. 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. 4f and 5g). The absence of an observable KIE in intermolecular competition between d_0-phenol and d_5-phenol (Fig. 4f) is consistent with selectivity-determining formation of a Bi(V) phenoxide of type **54** (Fig. 4e). That this step involves attack by the phenolic oxygen on Bi(V) is supported by preliminary studies of competitions between different phenols (ρ^+ = -1.4; Supplementary Fig. 20). An α-SKIE (secondary kinetic isotope effect) of 0.83 from intramolecular competition (Fig. 4g) suggests that the subsequent C-C bond forming step involves selectivity-determining dearomatization of the phenol prior to rapid rearomatization, as per a conventional electrophilic aromatic substitution.[92] Notably, very similar α-SKIEs have been measured for Cu-catalyzed electrophilic *ortho*-oxygenation of phenols, which proceeds via intramolecular group-transfer.[85,93,94]

Together, these preliminary experiments provide the greatest insight yet into the nature of the elementary steps involved in reductive ligand coupling at a Bi(V) center and add credence to Barton's proposed – but unsubstantiated – mechanistic hypotheses.[64,60,84,95] 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, favors 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 Bi-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 Bi reagents. Supporting kinetic and structural investigations provide the first experimental insight into the mechanism of Bi-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 Bi-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.; $[]_0$ = 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, substrate (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, 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* prior to 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 prior to elution with 2% acetic acid in methanol.

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 *via* 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 files, or from the corresponding author upon request.

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Author contributions

M.J. and L.T.B. conceived this work. M.J. and L.M. performed the experiments and analyzed 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

The authors declare no competing interests.

Additional information

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