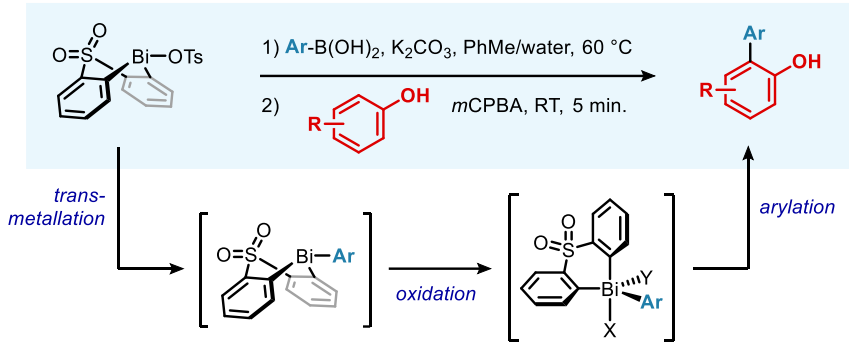
Bismuth(V)-mediated C-H Arylation of Phenols and Naphthols

Aaron Senior
Liam T. Ball*

School of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K.

liam.ball@nottingham.ac.uk

This paper is dedicated to Dr Mark Jurrat in celebration of the birth of his daughter, Merle Olivia.



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Abstract We recently reported a general and practical strategy for the Bi(V)-mediated C-H arylation of phenols and naphthols. Our telescoped protocol proceeds via transmetallation from readily available arylboronic acids to a stable Bi(III) precursor, oxidation to a reactive Bi(V) intermediate and subsequent *ortho*-selective phenol arylation. The process exhibits broad scope with respect to both components and tolerates functionality that is incompatible with conventional cross-coupling methods. Preliminary investigations provide insight into the mechanism of each key reaction step.

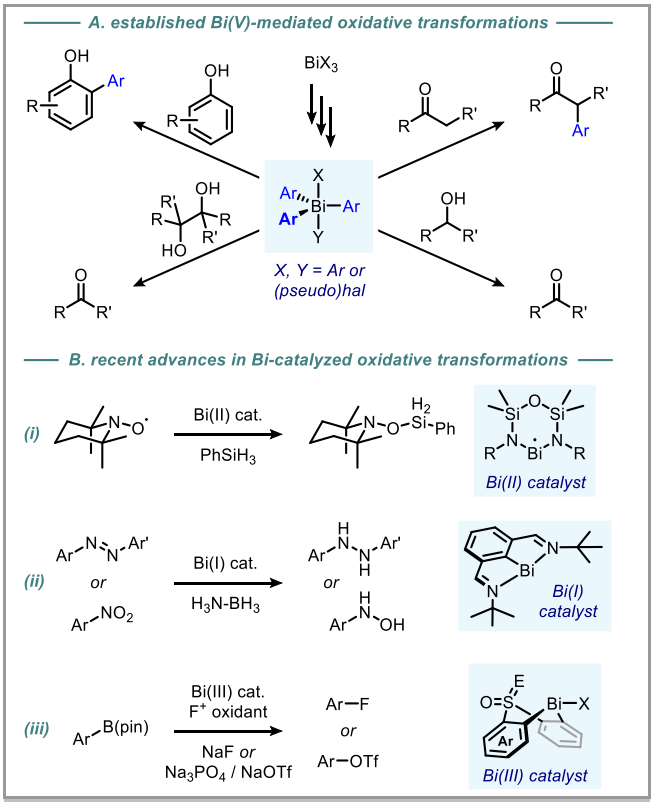
Key words bismuth, phenols, transmetallation, oxidation, C-H arylation

1. Introduction

Between 1980 and 1997, Professor Sir Derek Barton FRS published a 14-installment series of papers that explored the utility of organobismuth reagents in synthetic organic chemistry (Scheme 1A).[1] This pioneering contribution introduced a library of arylbismuth(V) compounds as reagents for the arylation of phenols and ketones,[1b,2] as catalysts for the oxidation of alcohols[1a] and the oxidative cleavage of diols,[3] and as stoichiometric transmetallating agents in palladium- and copper-catalysed cross-coupling.[1m,1n]

In addition to this diverse reactivity, bismuth benefits from low cost and negligible toxicity, and its compounds tend to be stable towards air, light and moisture.[4] However, despite its appealing attributes and rich synthetic potential, the ground-breaking work of Barton and important subsequent contributions from other laboratories[5] have been largely overlooked by the wider synthetic community.

Recently, we initiated a programme to re-explore organobismuth chemistry as an enabling tool for contemporary synthesis.[6] This same period has seen a wider resurgence of interest in organobismuth chemistry and the development of new bismuth redox manifolds and reactivity concepts (Scheme 1B).



Scheme 1 Synthetic applications of organobismuth redox chemistry.

For example, Schwamm *et al.* reported a bismuth(II)/(III) redox system for the catalytic coupling of TEMPO with phenyl silane (equation 1, Scheme 1B).[7] Here, oxidation of a stable Bi(II) radical by TEMPO affords a bismuth(III) TEMPOxide complex; subsequent O/H metathesis produces the silylated

TEMPOxide and a bismuth(III) hydride that dimerises via facile extrusion of dihydrogen. Bismuth(III) hydrides are also implicated as key intermediates in a novel bismuth(I)/(III) catalysis manifold reported by Cornella *et al.* (equation 2, Scheme 1B).[8] In this case, dehydrocoupling of ammonia-borane by a *N,C,N*-chelated bismuth(I) complex affords a bismuth(III) species that then mediates selective transfer hydrogenation of azo- and nitroarenes.

Cornella *et al*. subsequently reported a bismuth(III)/(V) manifold for the stoichiometric and catalytic synthesis of aryl fluorides[9] and sulfonates[10] from arylboron reagents (equation 3, Scheme 1B). In addition to being exciting conceptual advances for the field of organobismuth chemistry, these works represent important practical alternatives to transition metal catalysis in which the corresponding C-F or C-O bond-forming reductive eliminations are challenging.[11]

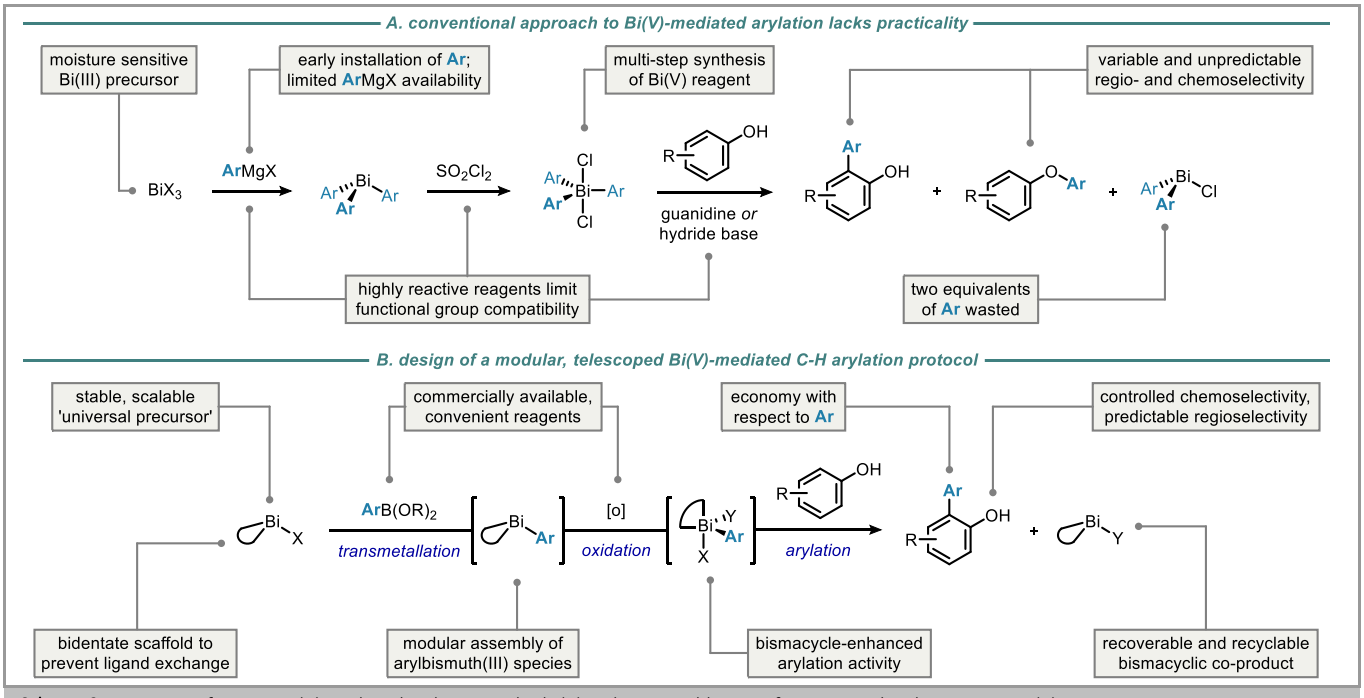
Contemporaneously, we sought to reimagine the most archetypal transformation of Barton's organobismuth legacy: the bismuth(V)-mediated oxidative C-H arylation of phenols and naphthols (Scheme 1A). This process provides facile access to 2-hydroxybiaryls, which are widely represented in natural products, pharmaceuticals and materials.[12] The synthesis of this important motif conventionally requires either (a) regioselective pre-activation of the phenol prior to cross-coupling, or (b) use of a metal-mediated C-H arylation procedure in combination with step-wise installation and removal of a directing group at the phenolic hydroxyl. While the Bi(V)-mediated C-H arylation methodology established by Barton saves on step-count, it suffers from several challenges that significantly limit it's practical synthetic utility (Scheme 2A). Furthermore, the chemoselectivity of the arylation is unpredictable, giving a mixture of *C*- and *O*-arylation products as a function of substrate, reaction *p*H, counterion, and solvent.[1b,1f]

2. Design of a Modular and Practical Arylating System

With these challenges in mind, we developed a strategic blueprint that would render Bi(V)-mediated C-H arylation of phenols a practical and economic tool for synthesis (Scheme 2B).[6] Central to delivering against this objective would be identification of a bismacyclic scaffold that provides a robust ligand sphere through which the reactivity of the metal centre could be tuned. To improve modularity, a stable, scalable bismuth(III) (*pseudo*)halide would act as a universal precursor to diverse arylbismuth(III) species *via* transmetallation from a convenient aryl donor. The subsequent arylation reaction must occur with C-*vs*-O chemoselectively and with complete selectivity for transfer of the valuable, unique aryl group. It must also be possible to recover and recycle the bismuth containing by-product. To improve its practicality and convenience still further, we recognised that the process should ideally be performed in a telescoped fashion, from precursor to product, without isolation of intermediates.

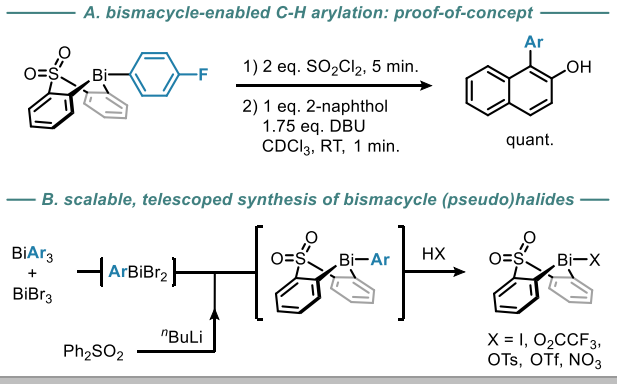
We initially sought to identify an appropriate bismacyclic framework that would support each of the key steps of our proposed one-pot process (Scheme 2B). Assessment of known bismacycles indicated that a sulfone bridged scaffold was highly competent in the arylation of 2-naphthol (Scheme 3A):[13] following oxidation of Bi(III) with sulfuryl chloride, arylation of 2-naphthol occurred quantitatively in under one minute at room temperature with perfect regio- and chemoselectivity, and with complete selectivity for transfer of the exocyclic aryl group.

The sulfone-bridged bismacycle also provided facile access to a range of bismacycle (*pseudo*)halides (Scheme 3B) as plausible 'universal precursors'. This series of bismacycles exhibited comparable reactivity towards transmetallation (*vide infra*), irrespective of the identity of the (*pseudo*)halide. The



Scheme 2 Limitations of existing Bi(V)-mediated arylation methods (A) and strategic blueprint for a practical arylation strategy (B).

bismacycle tosylate, **Bi-OTs**, was thus selected for further investigation due to the convenience of its decagram-scale, chromatography-free synthesis from readily available starting materials, and its excellent stability to storage on the bench.

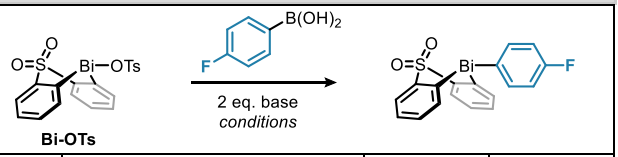


Scheme 3 A sulfonyl (-SO_2-) bridge confers high arylation activity (A) and ready accessibility (B) on the resulting bismacyclic scaffold. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Ts = toluenesulfonyl; Tf = trifluoromethanesulfonyl.

3. B-to-Bi Transmetallation: Scope and Mechanism

Transmetallation studies indicated that the unique, exocyclic aryl moiety could be transferred to **Bi-OTs** from an arylboronic acid (Table 1). This approach is especially appealing due to the diversity of commercial boronic acids, their convenient handling, and their compatibility with a broad range of useful functionality. Comprehensive optimisation of B-to-Bi transmetallation indicated that base was required, and that NaOH or $CsCO_3$ afforded comparable yields in the absence of added water (Table 1, entries 1-4). However, in the presence of water and with a modest increase in reaction temperature, excellent transmetallation yields could be achieved with K_2CO_3 as base in just 2 h (entries 5 and 6).

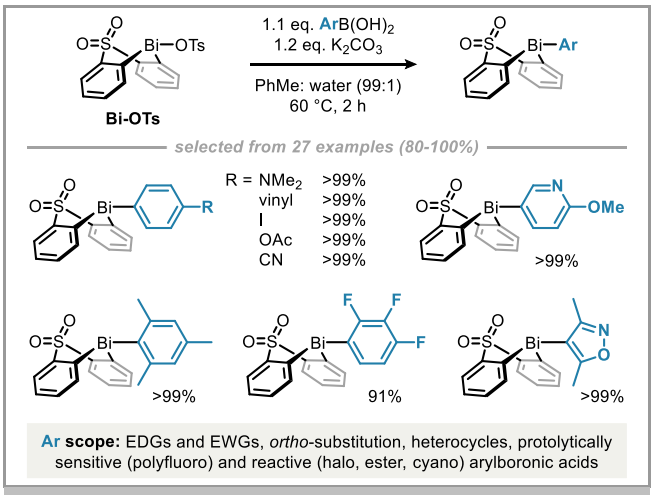
Table 1 Optimisation of B-to-Bi transmetallation (selected results).[a]



entry	conditions	base	% yield
1	$CDCl_3$, rt, 18 h	none	0
2	$CDCl_3$, rt, 18 h	K_2CO_3	22
3	$CDCl_3$, rt, 18 h	NaOH	50
4	$CDCl_3$, rt, 18 h	$CsCO_3$	54
5	PhMe:H_2O (99:1), 60 °C, 2 h	$CsCO_3$	88
6	PhMe:H_2O (99:1), 60 °C, 2 h	K_2CO_3	>99

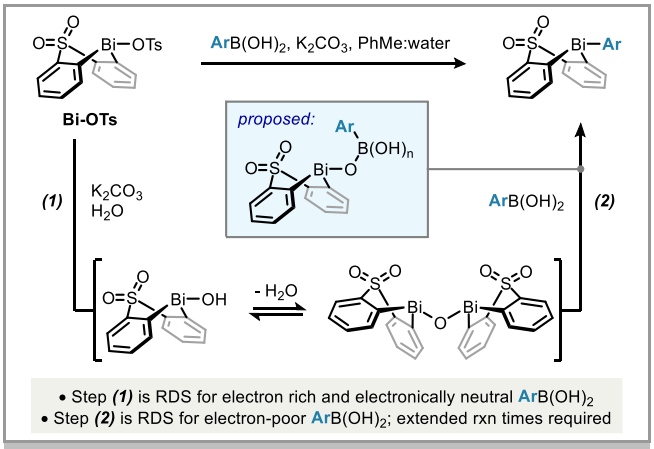
[a] Yields determined by ^{19}F NMR spectroscopic analysis *vs* internal standard.

As illustrated in Scheme 4, these conditions enable sterically and electronically diverse (hetero)arylbismuth species to be synthesised in outstanding yields, often without recourse to chromatographic purification. Notably, cyano- and iodo-substituted aryl groups, which are challenging to install through traditional approaches based on aryl Grignard reagents, were perfectly compatible. Furthermore, polyfluorophenylboronic acids transmetallate smoothly, despite their propensity towards protodeboronation[14] and the instability of the analogous aryllithium and Grignard reagents. By using mild conditions tolerant of a variety of aryl groups, this convenient methodology neatly compliments Gagnon's post-synthesis modification strategies.[15] Furthermore, the resulting arylbismuth reagents are robust, and we are yet to observe any degradation of the bismuth products after storing under ambient conditions for over a year.



Scheme 4 B-to-Bi transmetallation provides facile access to diverse arylbismacycles from readily available arylboronic acids.

Preliminary mechanistic studies suggest that B-to-Bi transmetallation proceeds *via* initial hydrolysis of **Bi-OTs** to an equilibrating mixture of the corresponding bismuth hydroxide and μ-oxo bridged dimer (Scheme 5). Involvement of these hydrolysed intermediates, which proved kinetically competent in base-free transmetallation, is consistent with the observations that transmetallation in the absence of added water is typically sluggish and fails to reach completion. We tentatively propose that the aryl transfer process may involve a fleeting pre-transmetallation B-O-Bi intermediate, analogous to the bismuth-oxy-boron complexes reported by Dostál *et al.*,[16] and the palladium-oxo pathway for transmetallation in Suzuki-Miyaura cross-coupling.[17]

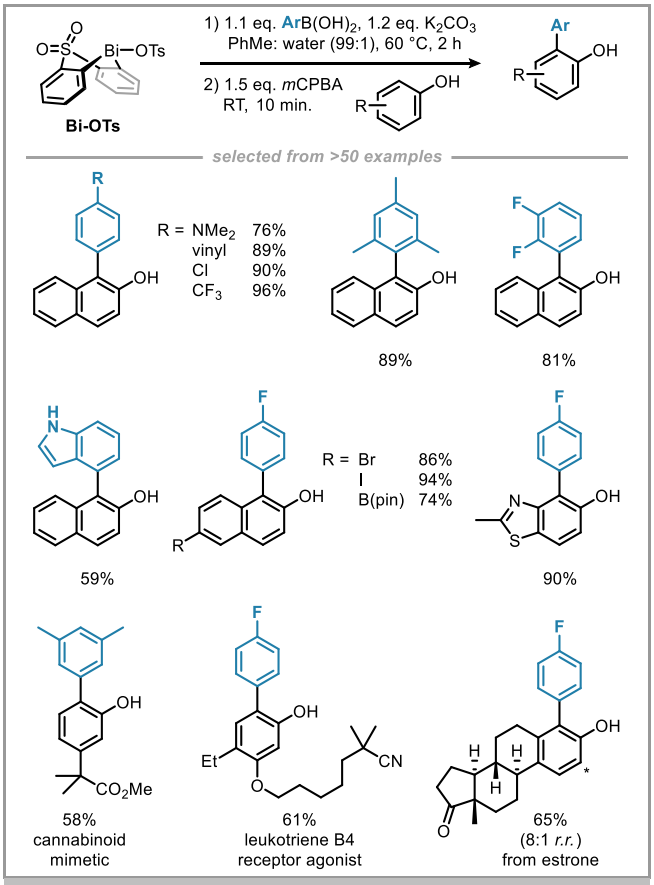


Scheme 5 Preliminary mechanistic studies suggest that B-to-Bi transmetallation proceeds via initial hydrolysis of **Bi-OTs**.

4. Oxidative C-H Arylation: Exemplification and Mechanism

Our attention then turned to the arylation reaction. For our strategic blueprint to be realised, the reaction must be

performed as a telescoped one-pot strategy. As such, both the oxidant and the resulting Bi(V) species must be compatible with residual water and base from the transmetallation step. Thus, although sulfuryl chloride is an established oxidant for Bi(III) (*cf.* Scheme 3A), its sensitivity to water and functional group intolerance means it did not meet our criteria. A comprehensive assessment of oxidants identified *m*CPBA (*meta*-chloroperbenzoic acid) as an appropriate alternative that mediates rapid, quantitative oxidation, and is stable to reaction conditions. Moreover, *m*CPBA is a convenient, commercially-available, fridge stable solid that is ubiquitous in synthetic laboratories. Pleasingly, performing this oxidation in the presence of the phenol or naphthol substrate results in efficient C-H arylation without the need for added base (Scheme 6).



Scheme 6 The telescoped transmetallation-oxidation-arylation process exhibits broad scope and a functional group compatibility that complements conventional cross-coupling methodologies. pin = pinacolato.

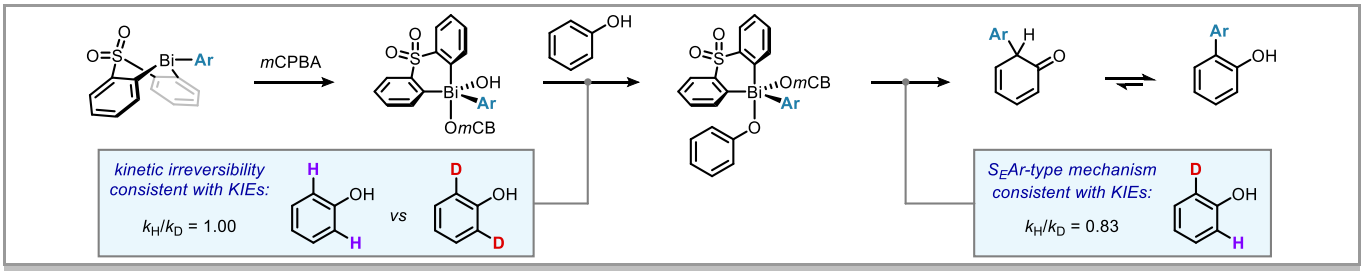
The telescoped transmetallation-oxidation-arylation process exhibits excellent functional group tolerance (Scheme 6). Electron-rich, electron-poor, and sterically demanding aryl and heteroaryl groups are all transferred in good to excellent yields. While naphthols and related π-extended substrates react with perfect regioselectivity, non-symmetrical phenols typically afford a mixture of regioisomers dominated by arylation at the more electron-rich, more sterically accessible *ortho* position.

Notably, polyfluorophenyl groups – which are typically incompatible with traditional Suzuki-Miyaura cross-coupling conditions – are transferred in good yields.[14] Furthermore, both halogens and boronate esters are tolerated, illustrating the orthogonality that exists between our oxidative C-H arylation strategy and conventional cross-coupling approaches.

The utility of our methodology was further demonstrated through the synthesis of biologically relevant molecules, including a leukotriene B4 receptor agonist and a cannabinoid mimetic, and the derivatisation of estrone.

To improve the overall atom economy of our methodology, we sought to develop an efficient protocol for reuse of the bismacycle. Conveniently, the bismacycle can be recovered in a near quantitative yield as the corresponding acetate via simple elution from silica gel with acetic acid and methanol. This recovered material performs analogously to **Bi-OTs** in the B-to-Bi transmetallation, thereby allowing straightforward reuse of the bismacyclic scaffold without any additional reactivation procedures.

Preliminary mechanistic studies suggest that oxidation of the arylbismacycle with commercial *m*CPBA affords an equilibrating mixture of Bi(V) species, of which only the bismacycle hydroxybenzoate is reactive in C-H arylation (Scheme 7). Following oxidation, arylation is rapid and appears to proceed in 2 steps: (1) irreversible formation of a bismuth(V) phenoxide,[18] via a process which resembles nucleophilic attack at the Bi(V) centre and which determines selectivity between different phenols, followed by (2) product-forming ligand coupling, which resembles electrophilic aromatic substitution in which regioselectivity is determined at the point of dearomatizing C-C bond formation. Notably, the proposed S_EAr-type pathway is consistent with Barton's earlier – but unsubstantiated – postulations, the regioselectivity trends we observed in the arylation of *meta*-substituted phenols, and an α–secondary kinetic isotope effect of 0.83 (Scheme 7).



Scheme 7 Preliminary mechanistic studies suggest that C-H arylation proceeds via rate-limiting formation of a Bi(V) phenoxide intermediate prior to rapid, regioselectivity-determining ligand coupling that resembles electrophilic aromatic substitution. *m*CB = *meta*-chlorobenzoyl.

5. Conclusions

We have developed a concise and convenient protocol for the bismuth-mediated, *ortho*-selective C-H arylation of phenols and naphthols. The methodology tolerates a wide range of synthetically useful functionality, employs commercially available starting materials, proceeds under mild conditions, and does not require the exclusion of air or moisture. A stable, sulfone-bridged bismacycle scaffold confers both improved selectivity and enhanced reactivity during C-H arylation, and allows for facile recovery and recycling of the reagent. Preliminary mechanistic studies provide detailed insight into each key step of the process. We anticipate that this new reactivity and understanding will underpin future advances in the field of organobismuth chemistry.

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Biosketches

	**Liam Ball** obtained his undergraduate degree from the University of Bristol, UK. Following doctoral studies with Dr Chris Russell and Prof. Guy Lloyd-Jones FRS FRSE at the University of Bristol (2009-2013), he moved to the University of Edinburgh, UK, as a postdoctoral researcher with Prof. Guy Lloyd-Jones FRS FRSE (2014-2015). In 2015, Liam was appointed Assistant Professor of Organic Chemistry at the University of Nottingham, where his research centres on exploiting mechanistic insight in the design and development of new synthetic methods.
	**Aaron Senior** completed his undergraduate degree at the University of Nottingham, where he stayed to undertake a Masters project under the supervision of Dr Andrew Nortcliffe (2013-2017). He subsequently enrolled in the EPSRC Centre of Doctoral Training in Sustainable Chemistry, completing a training year before joining Dr Liam Ball's lab in 2018 where he is currently investigating new synthetic methodologies centering around organobismuth chemistry.