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# Synthesis of Highly Functionalized Bismacycles via Post-Transmetallation Modification of Arylboronic Acids

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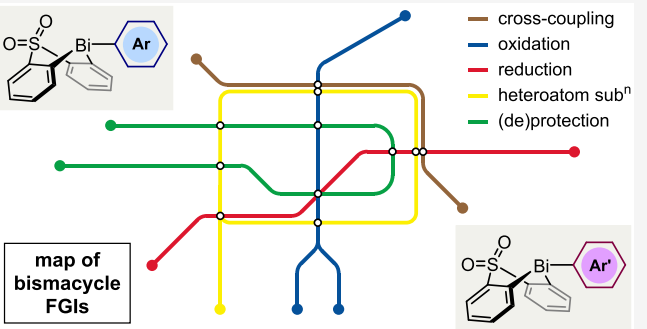
**ABSTRACT:** Bismacycles featuring a sulfone-bridged scaffold have recently been developed as versatile and convenient electrophilic arylating agents. Here, we report that the exocyclic aryl group, which is ultimately transferred to a nucleophilic coupling partner, can be functionalized through cross-coupling, heteroatom substitutions, oxidations and reductions, and protecting group manipulations. This "postsynthetic modification" approach provides concise and divergent access to complex aryl bismacycles. The utility of the functionalized bismacycles in electrophilic arylation of C−H and O−H bonds is demonstrated.





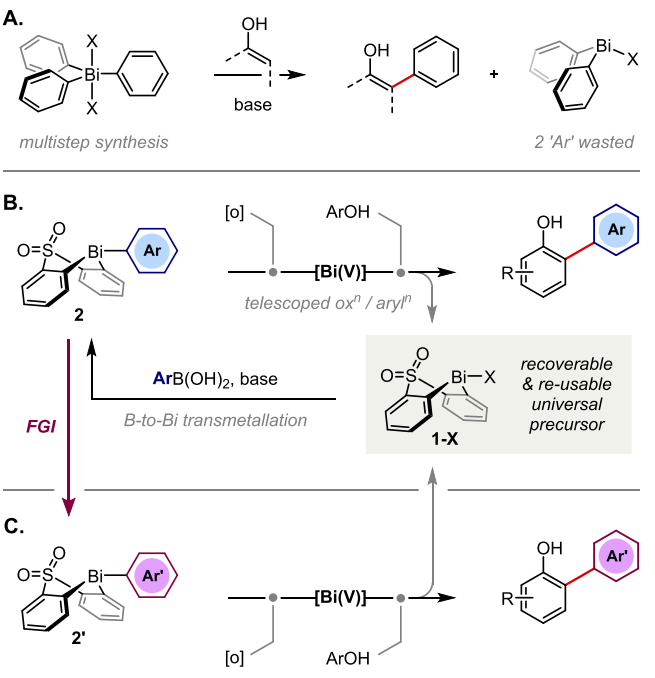

## INTRODUCTION

Couplings of C-, N-, and O-nucleophiles with aryl electrophiles are among the most valuable transformations in organic synthesis. Despite being comparatively underutilized, electrophilic arylation strategies based on hypervalent main group elements[1−7] represent powerful, and often complementary, alternatives to ubiquitous approaches such as transition metal catalysis or $S_NAr$.[8−10] For example, Barton,[11−18] Dodonov,[19,20] and many others[21−25] have demonstrated the utility of triarylbismuth(V) compounds as potent C−H arylating agents for phenol and enol nucleophiles (Scheme 1A). While the stability and low toxicity of triarylbismuth reagents in both the +3 and +5 oxidation states have undoubtedly contributed to their appeal, the field has traditionally suffered from significant practical issues that derive primarily from the homoleptic nature of simple arylbismuth species.

First, the synthesis of triarylbismuth(V) compounds typically requires multistep sequences in which the aryl moieties are introduced using Grignard reagents. The reliance on such a reactive class of organometallic reagents restricts functional group compatibility and ultimately limits the diversity of aryl groups that can be installed. In 1926, Adams reported a solution to this challenge in which triarylbismuth(V) reagents were functionalized through (1) electrophilic aromatic nitration or (2) oxidation of benzylic methyl substituents to carboxylic acids.[26] Postsynthetic functionalizations of triarylbismuth reagents in the +3 oxidation state are somewhat better explored,[27−29] with a particularly detailed study published by Gagnon in 2016.[30]

However, these strategies do not address the second issue associated with homoleptic bismuth reagents: atom economy. Not only is the metal rarely recoverable, but the transfer of

**Scheme 1. Bi(V)-Mediated Arylation**

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only one aryl moiety to the nucleophile also results in the remaining two aryl groups being wasted. In theory, this latter challenge could be addressed using heteroleptic triarylbismuth reagents bearing two low-value aryl groups that do not transfer, analogous to the "dummy aryl" concept that has been used to great effect in diaryliodonium chemistry.[31,32] However, selective transfer of a specific aryl group from a heteroleptic triarylbismuth(V) reagent has not been well explored and has been met with only limited success.[16,33−36] Furthermore, the synthesis of heteroleptic triarylbismuthanes is nontrivial, being both enabled and hindered by aryl scrambling.[37]

In 2020, we reported a solution to the dual challenges of accessibility and atom economy.[38,39] Using a general and stable bismuth(III) precursor based on Suzuki's sulfone-bridged bismacycle,[40] we developed a telescoped procedure consisting of B-to-Bi transmetallation, followed by oxidation and *ortho*-selective C−H arylation of a phenol (Scheme 1B). Crucially, the valuable aryl moiety is installed at bismuth in a modular fashion from 1.1 equiv of an arylboronic acid (**1-X** → **2**). The use of Grignard reagents is therefore avoided, which benefits the safety, convenience, and functional group compatibility of the process. Following oxidation to Bi(V), the subsequent electrophilic arylation proceeds with complete selectivity for transfer of the exocyclic aryl moiety (*Cf.* acyclic heteroleptic bismuthanes),[16,33−36] and the resulting bismacycle co-product can be recovered and reused in excellent yield. We have subsequently adapted our methodology to the *meta*-selective C−H arylation of phenols,[41] the *α*-arylation of cyclic and polyfluoroalkyl diones,[42] and the *O*-selective arylation of 2- and 4-pyridones.[43] Contemporaneously with our initial report, Cornella demonstrated the use of a structurally related sulfoximine-bridged bismacycle for catalytic $C_{Ar}$−F formation[44] and subsequently used substituted sulfone-bridged bismacycles in catalytic $C_{Ar}$-OTf formation[45] and sulfonyl fluoride synthesis.[46]

The utility of our bismuth-mediated arylation strategy hinges on the B-to-Bi transmetallation process (**1-X** → **2**, Scheme 1B), which we have so far demonstrated with over 65 distinct examples spanning a sterically and electronically diverse range of arylboronic acids.[38,41−43] However, while extremely enabling, the transmetallation comes with an implicit limitation: the requisite boronic acid must be accessible, either commercially or by de novo synthesis.

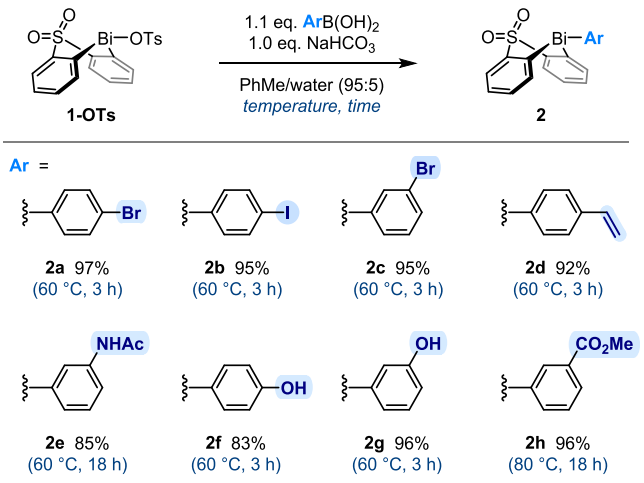
We anticipated that functional group interconversions (FGIs) at the exocyclic aryl group after its installation on bismuth (**2** → **2′**, Scheme 1C) would provide a convenient solution to this issue. Furthermore, as a general strategy, "post-transmetallation modification" would also enable (1) the rapid structural diversification of a common aryl bismacycle precursor for library synthesis, and (2) installation of aryl moieties for which direct B-to-Bi transmetallation is slow, such as from electron-poor and sterically hindered boronic acids.[42,43] Given that the B-to-Bi transmetallation is compatible with numerous synthetically versatile functional groups, including halides, alkenes, and carbonyls, there is a huge scope for the transformations that could potentially be achieved. However, the overall success of the strategy requires not only that the desired transformation proceeds efficiently, but also that the weak[47] Bi−C bonds remain intact during the reaction and any subsequent purifications.

Herein, we report the post-transmetallation modification of aryl bismacycles as a concise route to highly functionalized electrophilic arylating agents. The concept is illustrated using some of the most prevalent reaction types in drug discovery,[8−10] including cross-coupling, heteroatom functionalization, oxidations and reductions, and protecting group manipulations. In this way, we demonstrate a highly enabling extension to the growing toolbox of organobismuth chemistry.

## RESULTS AND DISCUSSION

In preparation for our studies, a library of aryl bismacycle substrates **2a−h** was synthesized via B-to-Bi transmetallation from the corresponding arylboronic acid (Scheme 2). The bismacycles were isolated as bench-stable solids in good yield following a simple aqueous workup.

**Scheme 2. Synthesis of Aryl Bismacycles via B-to-Bi Transmetallation**




Given their fundamental importance in contemporary synthesis, the first transformations to be considered were Pd-catalyzed cross-couplings. Suzuki−Miyaura cross-coupling of 4-bromophenyl bismacycle **2a** proceeded rapidly under Buchwald's conditions,[48] providing biaryl bismacycle **3** in good isolated yield (Scheme 3A). The same coupling can also be performed using $PPh_3$ as a ligand under more conventional conditions, whereas the reaction in micellar solution[49−51] proved unacceptably sluggish, presumably due to the poor solubility of **2a** in the aqueous reaction medium. Notably, products from cross-coupling of the Bi−C bonds were not observed under any of the conditions employed in this study. The apparent resistance of the aryl bismacycle to Bi-to-Pd transmetallation contrasts the extensive precedent for both Pd- and Cu-catalyzed couplings of homoleptic triarylbismuth reagents;[21,22,52] this stark difference illustrates that one cannot simply extend the reactivity patterns established for homoleptic bismuth species to bismacyclic compounds, highlighting the importance of the present study.

The Sonogashira coupling of 4-iodophenyl bismacycle **2b** proved similarly successful, affording alkyne **4** in 58% isolated yield (Scheme 3B). As anticipated, the equivalent Sonogashira coupling with 4-bromophenyl bismacycle **2a** did not proceed (not shown), consistent with the low reactivity of aryl bromides under these conditions.[53] Importantly, however, bismacycle **2a** was recovered unreacted, demonstrating its stability not only to a palladium catalyst but also to copper salts.

Moving beyond C−C bond formation, we were pleased to find that Buchwald−Hartwig amination of 3-bromophenyl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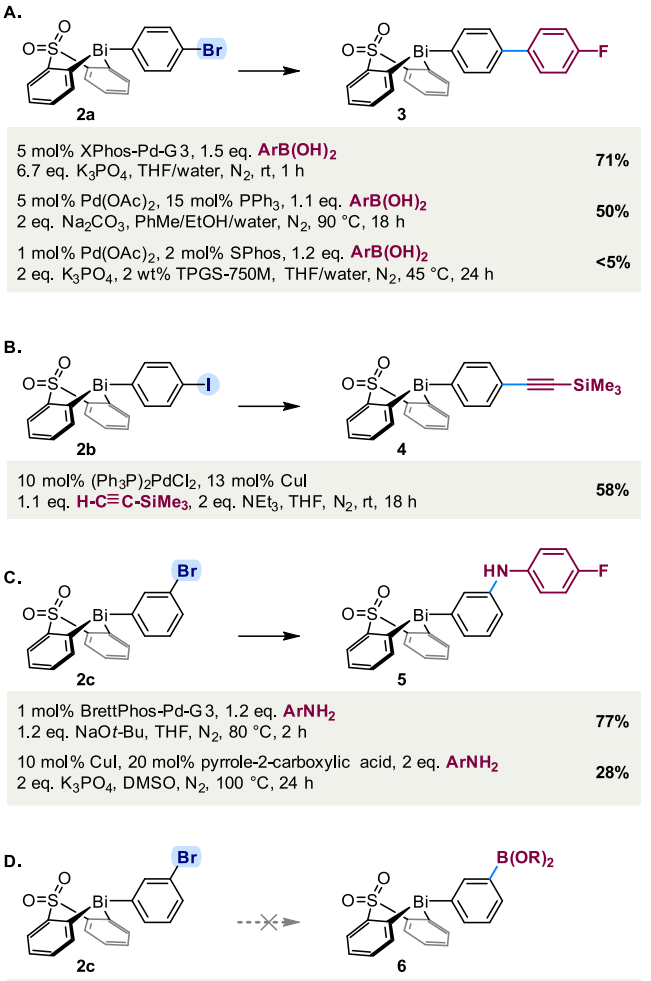
**Scheme 3. Pd-Catalyzed Cross-Couplings**[a]



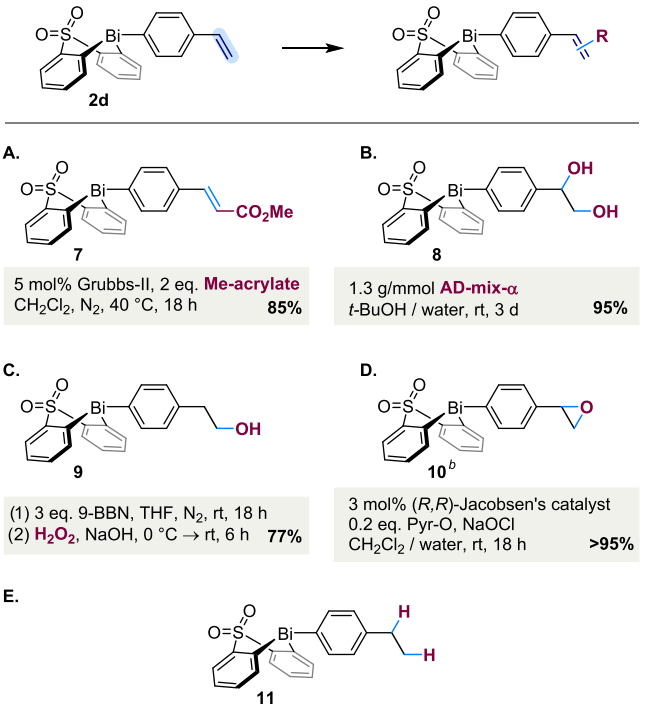

[a]n.d., not detected; 2-KEH, potassium 2-ethylhexanoate.

bismacycle **2c** afforded the corresponding diarylamine **5** in a good isolated yield (Scheme 3C). Alternatively, the same product can be accessed under Cu catalysis (Scheme 3C),[54] albeit in lower isolated yield. While application of the Pd-catalyzed protocol to regioisomeric 4-bromophenyl bismacycle **2a** also resulted in C−N cross-coupling, the (electron-rich) product proved unstable toward protodebismuthation during purification by chromatography on (basified) silica gel. This latter result highlights the potentially dichotomous stability of aryl bismacyclic species toward the functionalization conditions, here a strong base and a Pd catalyst, and subsequent manipulations, including purification.

Extending the scope of cross-couplings to Miyaura borylation proved unsuccessful under a range of conditions (Scheme 3D),[55−57] in each case furnishing a complex mixture. Attempts to prepare pinacol boronate **6** (Scheme 3D; $(OR)_2$ = pin) by sequential magnesium−halogen exchange/borylation also resulted in the complete consumption of bismacycle **2c** and formation of a complex mixture. Given that triarylbismuth species and arylboronates have been demonstrated to be compatible,[38,58] this observation is attributed to the conditions required to install the boryl moiety. Indeed, all attempts to use reactive organometallic reagents in conjunction with the sulfone-bridged bismacycle proved unsuccessful (see the SI), consistent with the known ability of organometallic reagents to form bismuth(III) "ate" complexes prior to substituent exchange/decomposition.[59−61]

To further explore the compatibility of our bismacycles with transition metal catalysis, we turned to functionalizations of styrenyl bismacycle **2d** (Scheme 4). Both cross-metathesis and

**Scheme 4. Alkene Functionalizations**[a]




[a]n.d., not detected; Pyr-O, pyridine *N*-oxide. [b]Yield determined by $^1$H NMR spectroscopic analysis prior to purification.

Sharpless dihydroxylation proceeded smoothly (Scheme 4A,4B). The value of the "post-transmetallation modification" concept is illustrated by the fact that the boronic acid needed to prepare diol **8** directly via B-to-Bi transmetallation is only accessible in low yield (8%, from 4-styrenyl boronic acid),[62] whereas performing dihydroxylation after transmetallation affords the same product in >90% over the two steps. Similarly, primary alcohol **9** was accessed via a hydroboration−oxidation sequence (Scheme 4C), the latter step of which is incompatible with the parent boronic acid.

While Jacobsen−Katsuki epoxidation[63] did proceed quantitatively, as determined by $^1$H NMR spectroscopy (Scheme 4D), epoxide **10** proved extremely sensitive to isolation and therefore could not be obtained pure. Notably, the opposite chemoselectivity is observed with *m*CPBA, which we have previously demonstrated oxidizes the bismuth center to Bi(V) in preference to epoxidizing a pendant styrene[38] or mediating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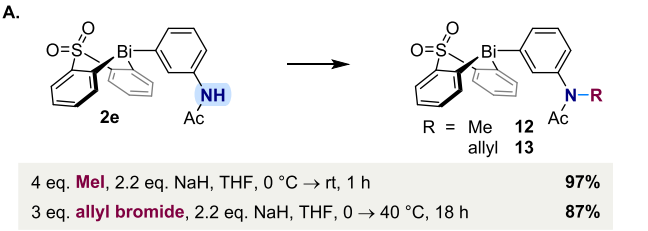
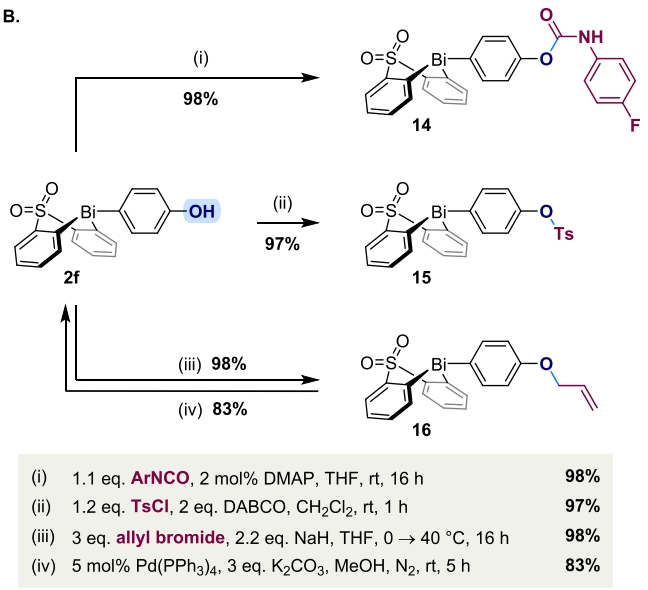
Baeyer−Villiger rearrangement on a pendant formyl substituent.[41]

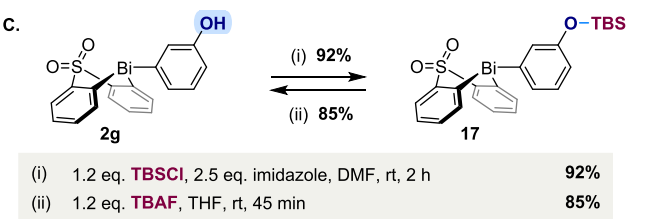
Although styrenyl bismacycle **2d** tolerates both oxidants (Scheme 4B) and reductants (Scheme 4C), not all redox processes were compatible. For example, only the unreacted starting material was recovered following attempted hydrogenation of **2d** with $H_2$ and either Pd/C or Wilkinson's catalyst (Scheme 4E), while complete decomposition was observed when using HBPin/$Pd(OAc)_2$[64] or hydrazine/$NiCl_2$.[65] Furthermore, all attempted functionalizations based on photoredox catalysis proved unsuccessful (see the SI), despite the stability of the bismacycle to irradiation with visible light.

Attention was next turned to electrophilic substitutions at heteroatoms, which are among the most widely used transformations in pharmaceutical discovery chemistry.[8] In this regard, 3-acetamidophenyl bismacycle **2e** underwent both *N*-methylation and *N*-allylation in excellent isolated yield (Scheme 5A), demonstrating the stability of the bismacyclic scaffold to a strong base.

**Scheme 5. Electrophilic Substitutions**




Carbamoylation, tosylation, and allylation of 4-hydroxyphenyl bismacycle **2f** also proceeded in quantitative yields (Scheme 5B). In the latter case, initial attempts at *O*-allylation using $K_2CO_3$ in acetone led to cleavage of the exocyclic Bi−$C_{Ar}$ bond via protodebismuthation, presumably due to the sensitivity of the very electron-rich phenoxy bismuth intermediate to the protic reaction environment ($\sigma_p(O^-)$ = −0.81).[66] However, the use of NaH as a base under aprotic conditions allowed for high-yielding allylation. Subsequent deprotection of allyl ether **16** proceeded smoothly under palladium catalysis to regenerate hydroxyphenyl bismacycle **2f**. Reproducibly high yields were achieved only when the deallylation was quenched as soon as full conversion had been reached (ca. 5 h); a prolonged reaction time (overnight) led to significant decomposition, again underscoring the sensitivity of electron-rich bismacycles to protodebismuthation.

Continuing the theme of protection/deprotection, *O*-silylation of 3-hydroxyphenyl bismacycle **2g** proceeded in excellent yield using *tert*-butyldimethylsilyl chloride (Scheme 5C). Subsequent desilylation of **17** with TBAF regenerated free phenol **2g**. Unlike the manipulations of regioisomeric **2f** (vide supra), protodebismuthation side-reactions were not observed for **2g**, consistent with the electron-withdrawing character of the *meta* hydroxy substituent ($\sigma_m$(OH) = 0.12, vs $\sigma_p$(OH) = −0.37).[66]

Finally, we explored manipulations of ester **2h** (Scheme 6), which represent work-horse transformations in all aspects of synthesis. Following hydrolysis with NaOH, carboxylic acid **18** was isolated by precipitation upon careful acidification. Ester **2h** could be reformed by treatment of acid **18** with TMS-diazomethane; alternatively, amide coupling mediated by HATU afforded amides **19** and **20** in good yields. Reduction of ester **2h** with DIBAL-H gave access to primary benzylic alcohol **21**, which could then be converted selectively to aldehyde **22** by TEMPO-catalyzed oxidation with iodobenzene diacetate. The observed inertness of the bismacycle toward oxidation by I(III) is consistent with our earlier findings[38] and stands in contrast to the reactivity reported previously for homoleptic triarylbismuth reagents.[67,68] To demonstrate the compatibility of the bismacyclic scaffold with nucleophilic reductants, aldehyde **22** was subsequently reduced back to the primary alcohol **21** using sodium borohydride in nearly quantitative yield.

To showcase the broader utility of post-transmetallation functionalization in synthesis, we applied TBS-protected hydroxyphenyl bismacycle **17** to the electrophilic arylations developed previously in our laboratory (Scheme 7).[38,41−43] Thus, the products from *O*-selective arylation of pyridones (**23**), *ortho*-selective arylation of naphthols (**25**), *meta*-selective arylation of phenols (**28**), and $\alpha$-selective arylation of cyclic 1,3-diketones (**29**) were obtained in good yields. Due to the silyl protecting group in **17**, the arylations, and selected subsequent manipulations (**25** → **26**, **29** → **30**), all proceeded without the chemoselectivity issues that would accompany the direct use of parent hydroxyphenyl bismacycle **2g**.

## CONCLUSIONS

In this publication, we have explored the compatibility of aryl bismacycles with some of the most widely used functional group interconversions in discovery chemistry. The ability to modify and add functionality to the bismacycles provides access to complex electrophilic arylating agents and overcomes



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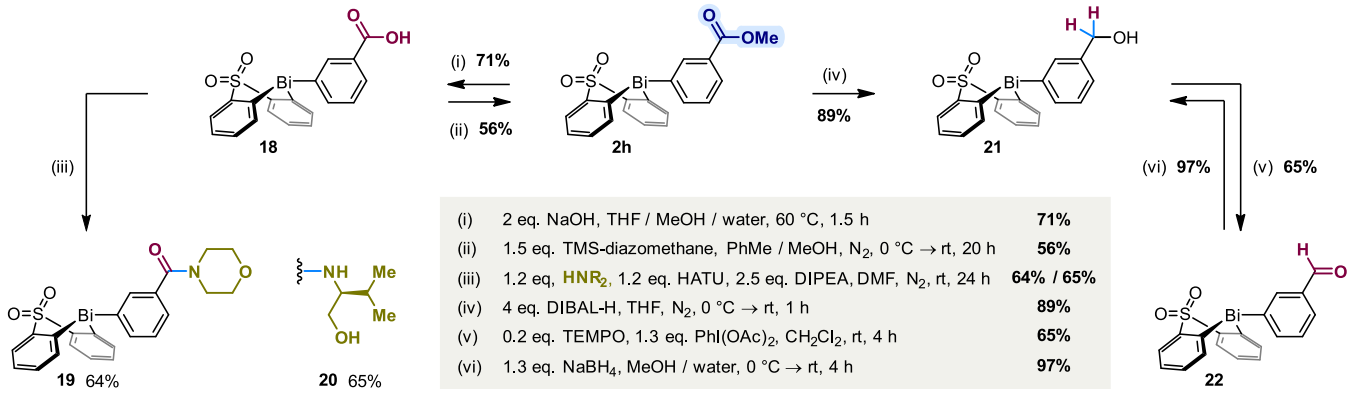
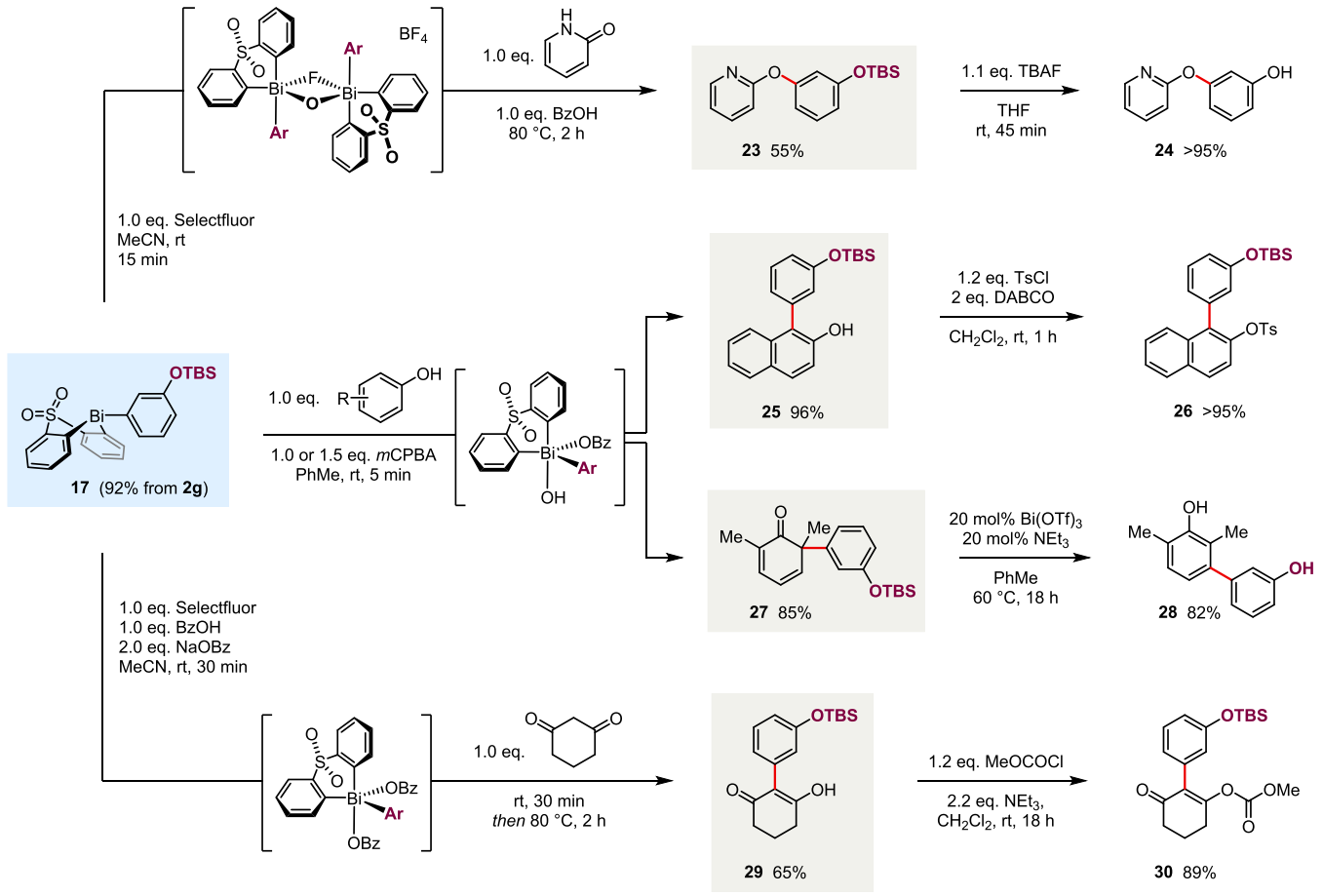
**Scheme 6. Functional Group Interconversions of Aryl Esters**




**Scheme 7. Applications of Functionalized Aryl Bismacycles to Electrophilic Arylation**




potential issues with previously established synthetic routes, namely, (1) the availability of boronic acids or (2) low transmetallation rates. We anticipate that the present study will prove a valuable addition to the growing number of tools available to organobismuth chemistry and that it will expedite the adoption of bismuth-mediated arylation in both industrial and academic target-oriented synthesis.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00361.

Experimental procedures; spectra; and optimization data (PDF)

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## Notes

The authors declare no competing financial interest.

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