Brønsted Acid-Catalyzed Stereospecific Dearomative Spirocyclization of Benzothiophenyl Analogues of Tertiary *cis*-*β*-Benzylstyrenes

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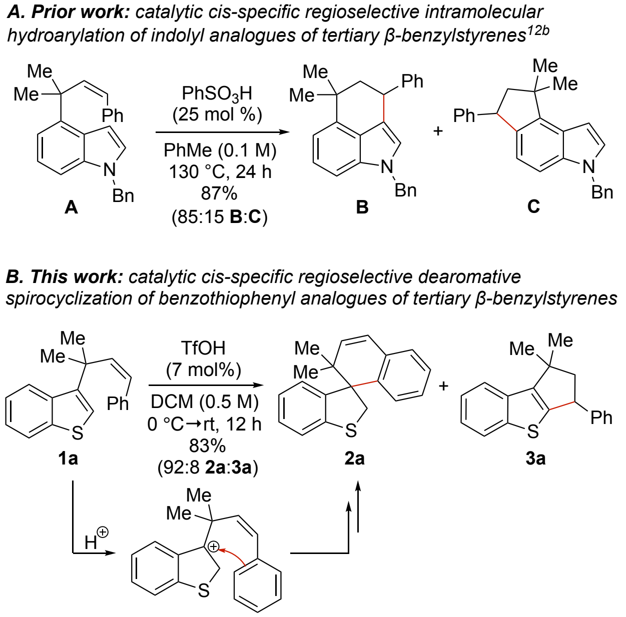
ABSTRACT: 3-Substituted benzothiophenyl analogues of tertiary *cis*-*β*-benzylstyrenes undergo triflic acid-catalyzed dearomative spirocyclization to afford vicinal quaternary center-containing compounds at room temperature. Hydroarylation of the styrene is a competing process that could be selected for in substrates possessing electron-rich styrenyl alkenes, or an indole in place of the benzothiophene.

The construction of quaternary carbons is an area of intense research interest in organic synthesis due to both the prevalence of quaternary centers in biologically active natural products and pharmaceutical agents as well as the challenge of forging congested C–C bonds.[1–3] Synthetically, quaternary carbons can enhance rates of cyclization reactions and associated selectivity outcomes thereof.[4] Medicinally, quaternary carbons are relatively metabolically stable.[5] Among quaternary carbon-containing molecules, spirocycles have garnered particular medicinal attention in recent years[6] and may be considered a privileged molecular motif in drug discovery as diversifying lynchpins and thanks to their improved pharmaceutical properties compared to aspirocyclic or planar aromatic molecules.[7] Dearomatization is likely the most common strategy by which spirocycles are prepared,[8,9] including a few examples of Brønsted acid-catalyzed approaches.[10] Syntheses of spirocycles are constrained by functional group incompatibility and the consequent limited functionality available for subsequent synthetic manipulation.[11] Additionally, spirocyclizations that furnish vicinal all-carbon quaternary centers have not been reported to the best of our knowledge.

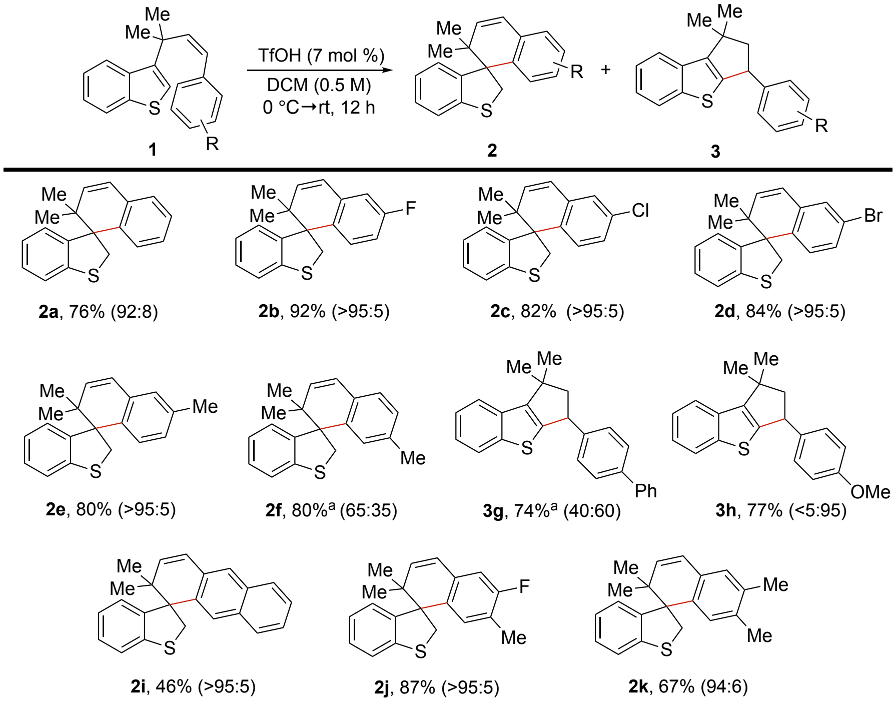
Stemming from our interest in catalytic intramolecular arylations of congested alkenes,[12] particularly the *cis*-specific behavior of indole **A** (Scheme 1A),[12b] we observed that a benzothiophenyl analogue (**1a**, Scheme 1B) underwent dearomative spirocyclization to form **2a** with high chemoselectivity over styrene hydroarylation products including **3a**, although styrene hydroarylation is favored for electron-rich styrenes. Herein, a variety of spiroheterocycles bearing vicinal quaternary centers and an intact alkene are prepared from the *cis*-configured isomers of benzo[*b*]thiophene derivatives of **1a** through dearomative spirocyclization at room temperature with catalytic triflic acid.

Scheme 1. Brønsted Acid-Catalyzed Stereospecific Intramolecular Hydroarylation Reactions of Heteroaromatic Analogues of Tertiary *β*-Benzyl Styrenes.


A. Prior work: *catalytic cis-specific regioselective intramolecular hydroarylation of indolyl analogues of tertiary β-benzylstyrenes[12b]*

B. This work: *catalytic cis-specific regioselective dearomative spirocyclization of benzothiophenyl analogues of tertiary β-benzylstyrenes*

Reaction optimization (see the Supporting Information for details) revealed that spirocyclization could be accomplished in good yield using trifluoromethanesulfonic acid (TfOH) as a catalyst after 12 hours at ambient temperature in dichloromethane. We examined the substrate scope by decorating with various functional groups (Table 1). Catalytic triflic acid afforded dearomative spirocyclized products in good or excellent yield in many cases. For example, *meta*-substituted styrenes bearing F, Cl, Br or Me (**1b**–**1e**) afforded dearomative spirocycles **2b**–**2e** in high yield with the new bond formed *para* to the functional group. Of note, *m*-fluoro substrate **2b** afforded the best yield and chemoselectivity that we observed in this study.[13] Variation of substituents *para* to the alkene revealed that the chemoselectivity could be inverted by electronic enrichment. Specifically, *p*-methyl substrate **1f** afforded a 65:35 mixture of **2f** and **3f**, while *p*-phenyl analogue **1g** afforded a 40:60 ratio of **2g** and **3g**, and most impressively *p*-methoxy substrate **1h** selectively afforded the styrene hydroarylation product **3h** in 77% isolated yield. Naphthyl analogue **1i** afforded 46% yield of **2i** at the less sterically hindered position. We also



2a, 76% (92:8) **2b**, 92% (>95:5) **2c**, 82% (>95:5) **2d**, 84% (>95:5)

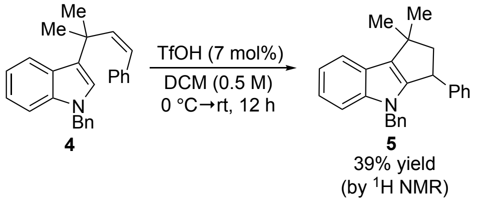
2e, 80% (>95:5) **2f**, 80%[a] (65:35) **3g**, 74%[a] (40:60) **3h**, 77% (<5:95)

2i, 46% (>95:5) **2j**, 87% (>95:5) **2k**, 67% (94:6)

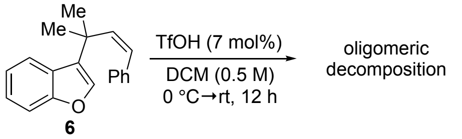
Table 1. Reaction Scope. Reactions were conducted on 0.3 mmol scale in a closed vial. The substrates were fully consumed in all cases. Unless otherwise noted, yields refer to the isolated amount of the indicated major product. Isomeric ratios (**2**:**3**, indicated in parentheses) were determined by ^{1}H NMR analysis of the crude reaction mixture. [a] Combined isolated yield of inseparable regioisomers.

evaluated two disubstituted styrenes, and fluoromethyl substrate **1j** afforded **2j**, which possesses the new C–C bond *para* to the F group. The 3,4-dimethyl analogue **1k** afforded 67% yield of **2k**.

The analogous 3-substituted indole and benzofuran analogues of benzothiophene do not undergo spirocyclization appreciably. Rather, indole substrate **4** afforded the hydroarylation product **5** in 39% NMR yield (eq 1), while benzofuran **6** decomposed unproductively (eq 2).



(1)



(2)

In summary, we have developed a Brønsted acid-catalyzed intramolecular dearomative hydroarylation of benzothiophenyl analogues of tertiary *cis*-*β*-benzylstyrenes to access spirocyclic benzocycloalkanes. This is the first example of a spirocyclization furnishing vicinal quaternary centers that we are aware of. Hydroarylation of the styrene is a competing process that predominates for electron-rich styrenyl alkenes.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was sponsored by the University of California, Merced and an award from the Hellman Faculty Fellows Fund.

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