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Ring expansion of benzocyclobutenols toward benzo[*b*]furans

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An efficient 4-to-5 ring expansion through aryne intermediates is disclosed. A wide variety of iodo-substituted benzo[*b*]furans are prepared from benzocyclobutenols via unusual oxyiodination of aryne intermediates. The great transformability of the resulting aryl iodides enables access to diverse highly functionalized benzo[*b*]furans.

Benzocyclobutene (BCB) derivatives constitute versatile scaffolds that can be transformed into a variety of frameworks through cleavage of the strained cyclobutene C–C bonds under diverse conditions.^{1,2} For example, various transformations involving dearomatization of BCBs by thermal ring opening followed by subsequent bond formations such as cycloadditions have been developed (Figure 1A).^{2a} Advances in modern organometallic chemistry have enabled ring expansion of BCBs to provide a range of fused bicyclic frameworks including naphthalene- and indane-type cores (Figures 1B and 1C).^{2b,2c} Herein, we disclose a new ring expansion that converts the four-membered cyclobutene ring into a five-membered furan ring accompanied by iodination (Figure 1D).

In the course of our studies on synthetic aryne chemistry, we discovered a 4-to-5 ring expansion that enables cyclobutene-to-furan conversion with concomitant iodination.^{3–8} Recently, modular synthetic methods for the preparation of α -aryl carbonyl compounds from 1,3-bis(triflyloxy)-2-iodobenzene have been developed via the sequential generation of arynes **Ia** and **II** (Figure 1E).^{6,7} In particular, we found that aryne **II** was generated from cyclobutenols **4** through base-mediated selective C–C cleavage, and that subsequent trapping with various arynophiles smoothly afforded diverse α -aryl ketones.⁷ In addition, Li

reported an elegant transformation of BCB **5** via the generation of aryne **III** through fluoride-promoted C–C bond cleavage (Figure 1F).⁸

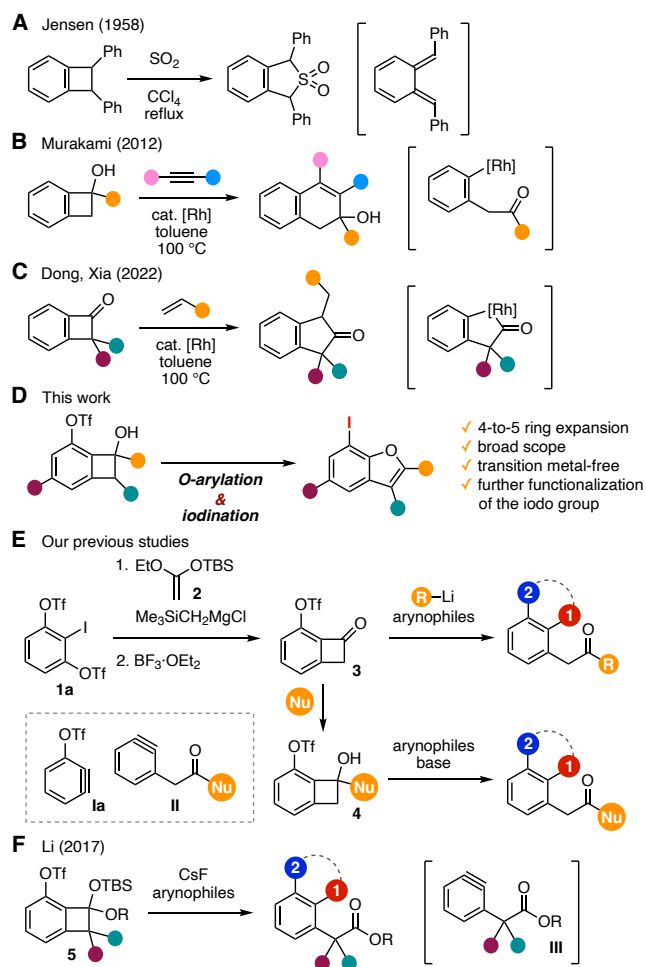


Fig. 1 (A) Jensen's pioneering study. (B) Dihydronaphthalene synthesis. (C) Indane synthesis. (D) This work. (E) Our previous studies. (F) Li's study.

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On the basis of this background, we envisaged that intramolecular *O*-arylation of 3-(acylmethyl)benzynes **II** would proceed in the absence of external arylophilic reagents (Figure 2A).⁹ Subsequent protonation of the resulting aryl anion, followed by deprotonation at the α -position, would trigger a 4-to-5 ring expansion to furnish benzo[*b*]furans **6**. Although bond formation between an sp^2 carbon and a carbonyl oxygen is generally difficult to achieve under conventional conditions, such as cross-coupling reactions, because of the weak nucleophilicity of the carbonyl oxygen, the remarkable electrophilicity of aryne intermediates was expected to enable this challenging C–O formation. Thus, treatment of benzocyclobutenol **4a** with potassium carbonate in acetonitrile at room temperature resulted in the formation of 2-arylbenzo[*b*]furan **6a** in moderate yield (Figure 2B).^{7c} After screening electrophiles for trapping the carbanion intermediate generated in situ, we found that 2,3,4,5,6-pentafluoro-1-iodobenzene promoted efficient oxyiodination of 3-(acylmethyl)benzynes **II** to provide 2-aryl-7-iodobenzo[*b*]furan **7a** in good yield (Figure 2C).^{10–12}

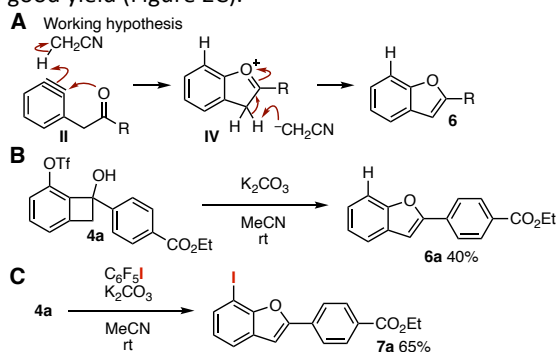


Fig. 2 (A) Working hypothesis. (B) Benzofuran formation involving protonation. (C) Benzofuran formation involving iodination.

The 4-to-5 ring expansion of benzocyclobutenols **4** enabled the efficient synthesis of a wide range of multisubstituted benzo[*b*]furans **7** (Figures 3A and 3B). For example, we achieved the synthesis of 7-iodobenzo[*b*]furans **7b–7f** in good yields with methyl, methoxy, dimethylamino, 1,3-benzodioxole-5-yl, and fluoro groups remaining intact. It is worth noting that gram-scale synthesis of 2-aryl-7-iodobenzo[*b*]furan **7b** was accomplished without any decrease in yield, clearly showing the practical simplicity of this transition-metal-free procedure. The utility of this method was further demonstrated by the preparation of **7g** and **7h** bearing bromo and iodo substituents, motifs that are not straightforwardly assembled by conventional benzo[*b*]furan syntheses. In these products, the retained halo groups can serve as orthogonal reactive handles for downstream transformations, including transition-metal-catalyzed cross-coupling reactions.¹¹ In addition, butyl- and (ethoxycarbonyl)methyl-substituted benzo[*b*]furans **7i** and **7j** were synthesized without damaging the iodo, alkyl, and ester moieties.^{7b} The preparation of 2-aryl-3-methyl-7-iodobenzo[*b*]furan **7k** was also accomplished from the corresponding benzocyclobutenols, which were prepared from a methyl-substituted ketene silyl acetal. After the synthesis of 5-methyl-1,3-bis(triflyloxy)-2-iodobenzene, [2+2] cycloaddition

of the 3-(triflyloxy)aryne intermediate, hydrolysis of the resulting silyl acetals followed by addition of organomagnesium reagents, and subsequent 4-to-5 ring expansion enabled the synthesis of 5-methyl-substituted benzo[*b*]furan **7l** in moderate yield.

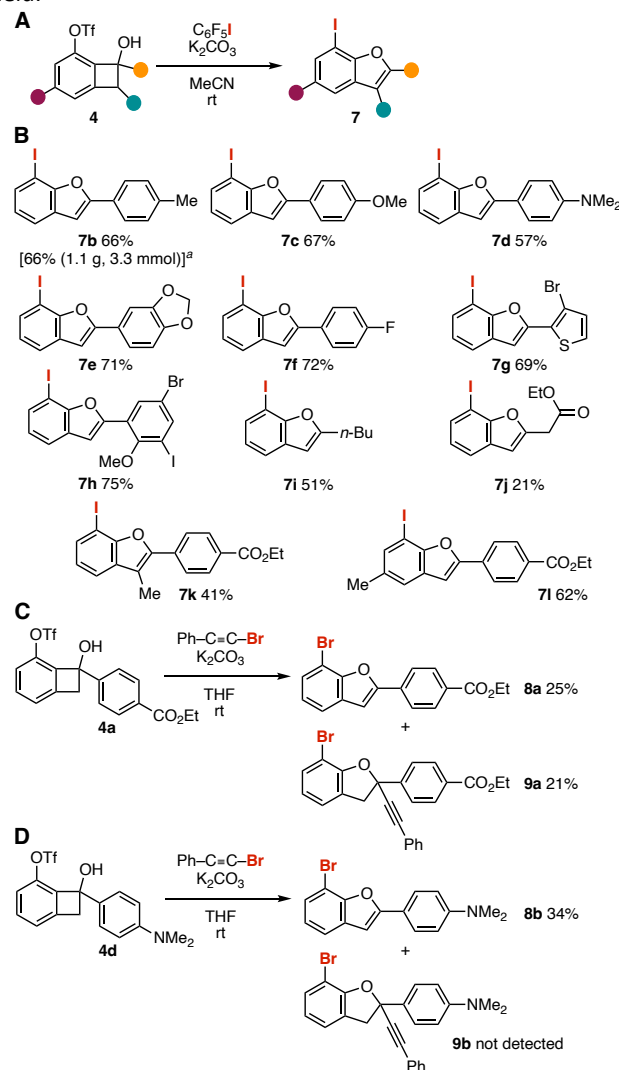


Fig. 3 (A) General scheme for the synthesis of various benzo[*b*]furans **7**. (B) Structures and yields of products. (C) Synthesis of **8a**. (D) Synthesis of **8b**. *The reaction was performed in 5.0 mmol scale. For details, see the Supporting Information.

In the presence of 1-bromo-2-phenylacetylene, 2-aryl-7-bromobenzo[*b*]furans **8a** and **8b** were obtained through C–O formation followed by bromination (Figures 3C and 3D).^{13,14} In the synthesis of **8a** bearing an electron-deficient aryl group, we found that 2-alkynyl-2-aryl-substituted 7-bromo-2,3-dihydrobenzofuran **9a** was also formed as a side product.¹⁵ In contrast, the benzofuran formation from **4d** bearing an electron-rich 4-dimethylaminophenyl group proceeded smoothly to provide **8b** in moderate yield, and the corresponding alkynylated side product **9b** was not detected. These results suggest that the alkynylation pathway is facilitated by the presence of the electron-withdrawing ester moiety.



A plausible reaction mechanism for the formation of 7-iodobenzo[*b*]furans is shown in Figure 4A. First, 2-(acylmethyl)benzynes **II** is generated from benzocyclobutenols **4** through deprotonation, C–C cleavage accompanied by carbonyl formation, and elimination of the triflate ion.⁷ Next, intramolecular *O*-arylation with concomitant iodination furnishes oxonium intermediate **V**. Although nucleophilic attack at an sp²-hybridized oxygen atom is uncommon,¹⁶ the high electrophilicity of aryne intermediate **II** would enable formation of oxonium intermediate **V**. Subsequent deprotonation of **V** triggers aromatization and completes the five-membered ring formation to provide 7-iodobenzo[*b*]furan **7**. Although no direct spectroscopic evidence was obtained, the involvement of oxonium intermediate **V** is supported by the formation of side product **9a** during oxybromination of aryne intermediate **II**, followed by trapping with the resulting phenylacetylide (Figure 4B).¹³ The inductive effect of the bromo substituent would enhance the electrophilicity of oxonium intermediate **VI**, thereby promoting nucleophilic addition. In contrast, adduct **9b** was not obtained from benzocyclobutenol **4d** bearing an electron-donating dimethylamino group, suggesting that the electron-deficient nature of oxonium intermediate **VI** would facilitate nucleophilic attack by acetylides. The formation of side product **9a** also argues against a pathway involving enolization followed by *O*-arylation and iodination for the formation of benzo[*b*]furans.

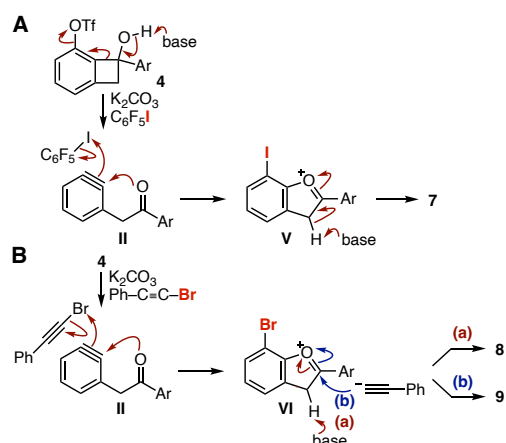


Fig. 4 (A) A plausible reaction mechanism for the synthesis of **7**. (B) Plausible reaction mechanisms for the formation of **8** and **9**.

The synthetic advantage of the 7-iodobenzo[*b*]furans **7** was showcased by various transformations of the iodo group (Figure 5A). For example, Sonogashira cross-coupling of **7b** with 4-tolylacetylene took place smoothly in the presence of palladium and copper catalysts to afford diaryl acetylene **10** in excellent yield (Figure 5A, upper).¹⁷ We also achieved the palladium-catalyzed amination of 7-iodobenzo[*b*]furan **7b** in good yield (Figure 5A, middle).¹⁸ Furthermore, bi(benzo[*b*]furan) **12** was efficiently prepared from 7-iodobenzo[*b*]furan **7b** by reductive dimerization catalyzed by palladium in the presence of isopropyl alcohol (Figure 5A, bottom).¹⁹

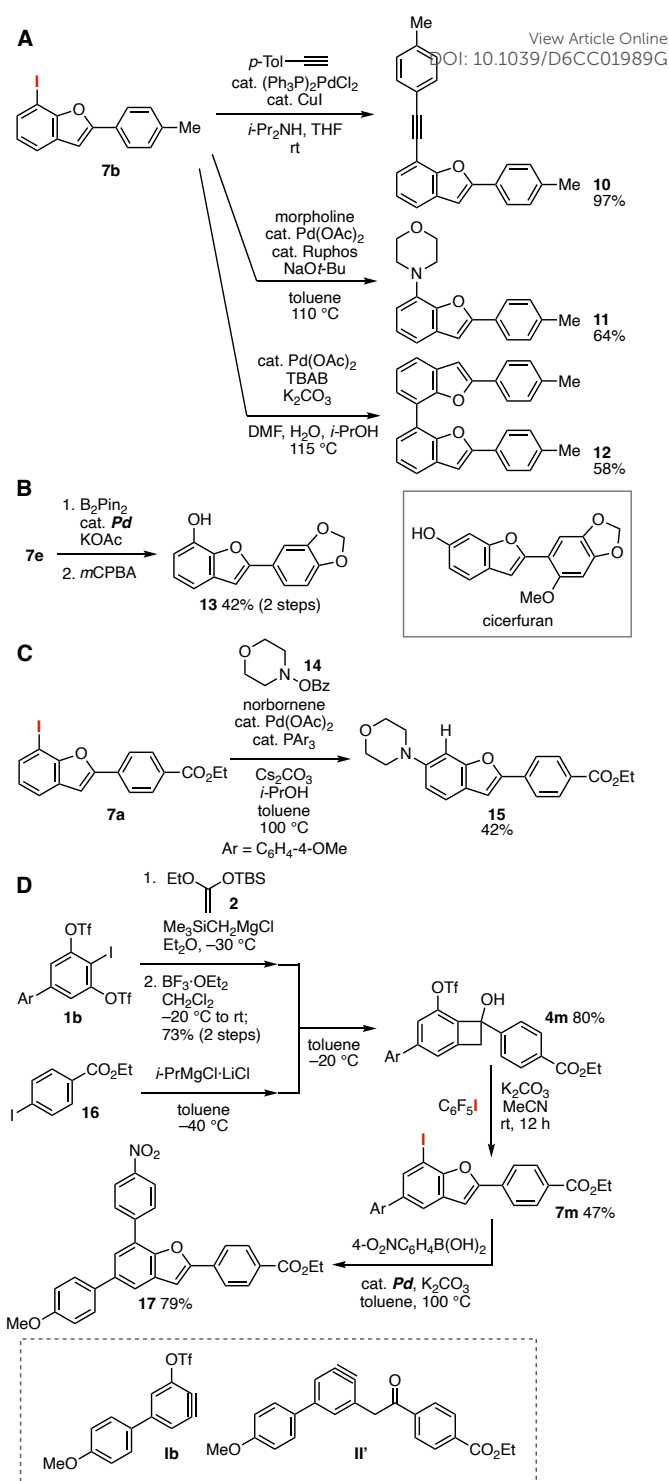


Fig. 5 (A) Transition-metal-catalyzed coupling reactions of **7b**. (B) Synthesis of cicerfuran derivative **13**. (C) Synthesis of **15**. (D) Modular synthesis of **17**. For details, see the Supporting Information. Ruphos = 2-(2,6-(MeO)₂C₆H₃)C₆H₄P(*c*-Hex)₂. TBAB = Bu₄NBr.

We accomplished the synthesis of cicerfuran analog **13** from benzo[*b*]furan **7e** (Figure 5B). Palladium-catalyzed Miyaura borylation of 7-iodobenzo[*b*]furan **7e** followed by oxidation with *m*CPBA proceeded smoothly to provide cicerfuran analog **13**.^{20,21} Because the 1,3-benzodioxole-5-yl unit was introduced from 5-bromo-1,3-benzodioxole via the corresponding Grignard reagent, this modular approach to 2-aryl-7-



hydroxybenzo[*b*]furans from readily available starting materials should enable the facile synthesis of diverse cicerfuran analogs, thereby facilitating detailed structure–activity relationship studies of cicerfuran derivatives with respect to bioactivities such as antimicrobial activity.²²

Functionalization of **7a** was achieved not only at the 7-position but also at the 6-position by the Catellani reaction in the presence of norbornene (Figure 5C).²³ Indeed, 6-morpholino product **15** was formed from 7-iodobenzo[*b*]furan **7a** along with protonation at the 7-position.

The selective synthesis of triaryl benzo[*b*]furan **17** was accomplished from readily available modules including **1b**, **2**, aryl iodide **16**, and 4-nitrophenylboronic acid (Figure 5D). Indeed, after preparation of a benzocyclobutenone derivative from **1b** and **2** followed by hydrolysis, an aryl Grignard reagent prepared from aryl iodide **16** was added to the resulting ketone to furnish benzocyclobutenol **4m** in high yield. Then, 4-to-5 ring expansion in the presence of 2,3,4,5,6-pentafluoro-1-iodobenzene resulted in the formation of 2,5-diaryl-7-iodobenzo[*b*]furan **7m**. Furthermore, we succeeded in the efficient Suzuki–Miyaura cross-coupling of the resulting aryl iodide **7m** to afford triaryl benzo[*b*]furan **17**. Thus, the synthesis of triaryl benzo[*b*]furan **17** was completed from readily available starting materials through 4-to-5 ring expansion with concomitant iodination.

In conclusion, we have developed an efficient skeletal editing method that transforms a four-membered cyclobutene ring into a five-membered furan ring via unusual oxyiodination of aryne intermediates with the carbonyl oxygen under mild basic conditions. A significant advantage of this method over conventional benzo[*b*]furan syntheses lies in its modular access to halo-functionalized and even polyhalogenated benzo[*b*]furans from readily available modules. Since polyhalogenated benzo[*b*]furans are difficult to prepare in a concise and site-selective manner by conventional approaches, this method provides a useful platform for the synthesis of highly functionalized benzo[*b*]furans through divergent transition-metal-catalyzed transformations of the resulting aryl halides. Further studies, including expansion of the electrophile scope, applications to the synthesis of bioactive benzo[*b*]furans, and theoretical investigation of the detailed reaction mechanism, are currently underway in our research group.

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Data Availability Statement

The data supporting this article have been included as part of the ESI.

Conflicts of interest

There are no conflicts to declare.

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