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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 (Fig. 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 (Fig. 1B and C).[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 (Fig. 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** (Fig. 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 (Fig. 1F).[8]

On the basis of this background, we envisaged that intramolecular *O*-arylation of 3-(acylmethyl)benzyne **II** would proceed in the absence of external arynophiles (Fig. 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 (Fig. 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)benzyne **II** to provide 2-aryl-7-iodobenzo[*b*]furan **7a** in good yield (Fig. 2C).[10–12]

The 4-to-5 ring expansion of benzocyclobutenols **4** enabled the efficient synthesis of a wide range of multisubstituted benzo[*b*]furans **7** (Fig. 3A and B). 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

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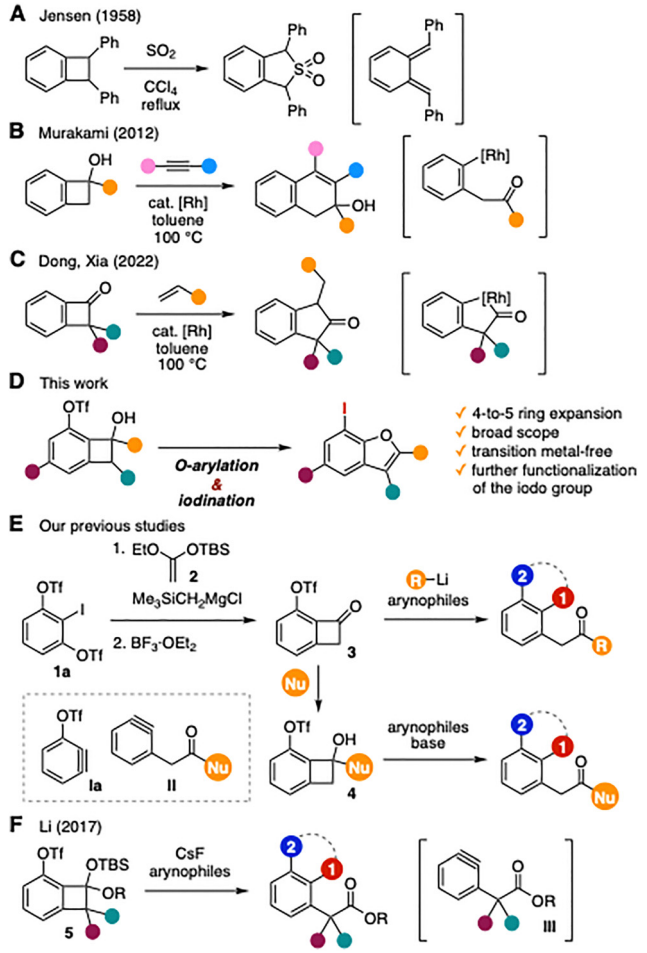

Fig. 1 (A) Jensen's pioneering study. (B) Dihydronaphthalene synthesis. (C) Indane synthesis. (D) This work. (E) Our previous studies. (F) Li's study.

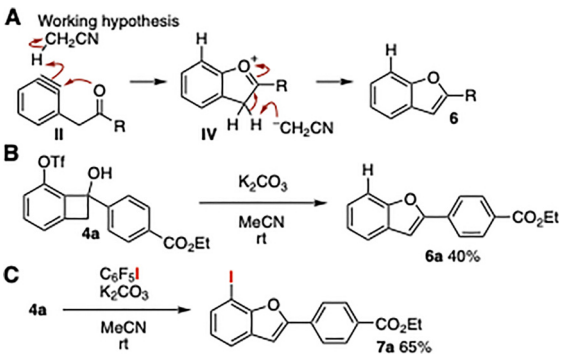

Fig. 2 (A) Working hypothesis. (B) Benzofuran formation involving protonation. (C) Benzofuran formation involving iodination.

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.

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 (Fig. 3C and D).[13,14] In the synthesis of **8a** bearing an electron-deficient aryl group, we

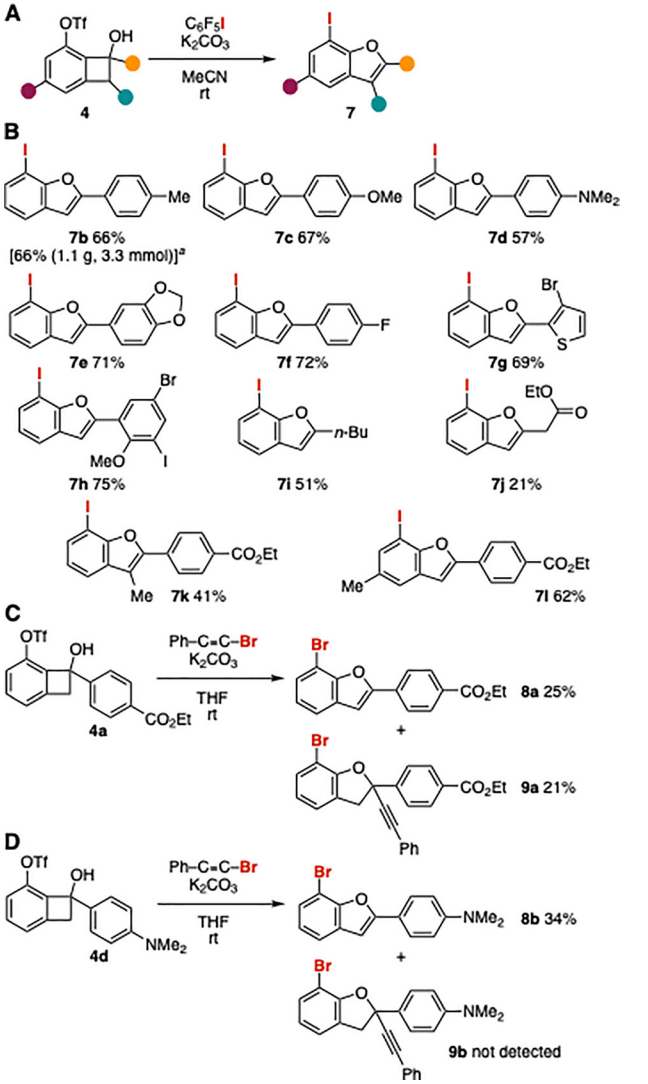

Fig. 3 (A) General scheme for the synthesis of various benzo[*b*]furans **7**. (B) Structures and yields of products. (C) Synthesis of **8a**. (D) Synthesis of **8b**. [a]The reaction was performed in 5.0 mmol scale. For details, see the SI.

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 Fig. 4A. First, 3-(acylmethyl)benzyne **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 sp^2-hybridized oxygen atom is uncommon,[16] the high electrophilicity of aryne intermediate **II** would enable formation of oxonium intermediate **V**.

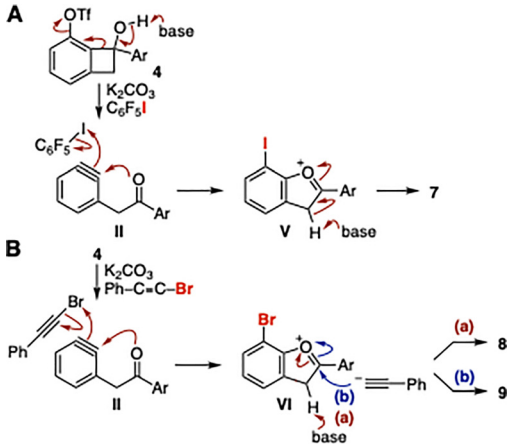

Fig. 4 (A) A plausible reaction mechanism for the synthesis of **7**. (B) Plausible reaction mechanisms for the formation of **8** and **9**.

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 (Fig. 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.

The synthetic advantage of the 7-iodobenzo[*b*]furans **7** was showcased by various transformations of the iodo group (Fig. 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 (Fig. 5A, upper).[17] We also achieved the palladium-catalyzed amination of 7-iodobenzo[*b*]furan **7b** in good yield (Fig. 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 (Fig. 5A, bottom).[19]

We accomplished the synthesis of cicerfuran analog **13** from benzo[*b*]furan **7e** (Fig. 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]

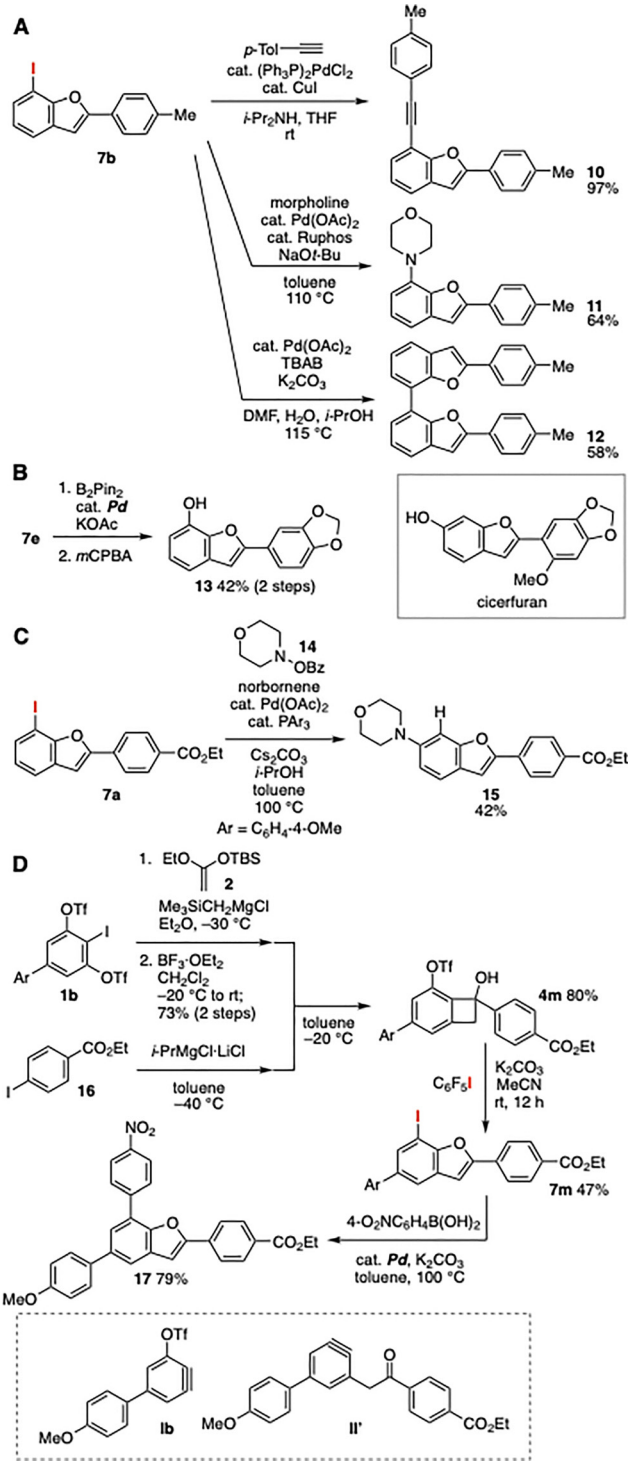

Fig. 5 (A) Transition-metal-catalyzed coupling reactions of **7b**. (B) Synthesis of cicerfuran derivative **13**. (C) Synthesis of **15**. (D) Modular synthesis of **17**. For details, see the SI. Ruphos = 2-(2,6-$(MeO)_2C_6H_3$)C_6H_4P(*c*-Hex)$_2$. TBAB = Bu_4NBr.

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 (Fig. 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 (Fig. 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.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information contains supplemental data, experimental details, and characterization data of all new compounds. See DOI: https://doi.org/10.1039/d6cc01989g.

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