Deconstructive Cycloaromatization Strategy towards N,O-Bidentate Ligands and Their Four-Coordinate Organoboron Complexes

Jinlei Zhou  
Guangdong Pharmaceutical University

Xiaotian Shi  
Guangdong Pharmaceutical University

Huitao Zheng  
Guangdong Pharmaceutical University

Guangxian Chen  
Guangdong Pharmaceutical University

Chen Zhang  
Guangdong Pharmaceutical University

Xiang Liu  
Guangdong Pharmaceutical University

Hua Cao (caohua@gdpu.edu.cn)  
Guangdong Pharmaceutical University

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Abstract

The innovative construction of novel N,O-bidentate ligands and N,O π-conjugated four-coordinate organoboron complexes represent a long-standing challenge for chemists. Here, we report an unprecedented and straightforward approach for the construction of N,O-bidentate ligands and their organoboron complexes via the merge of ring deconstruction with cycloaromatization of indolizines and cyclopropenones. Without any catalysts, our method is able to deliver a series of polyaryl 2-(pyridin-2-yl)phenol ligands, N,O π-conjugated organoboron (BF₂ and BAr₂) complexes with good functional-group compatibility which are difficult or even impossible to synthesize with previous methods. Importantly, the formed N,O-bidentate ligands were easy to scale up and derive with valuable drugs and active molecules. In addition, the photoluminescence measurements and the HOMO/LUMO gap have been investigated, the results have revealed that N,O π-conjugated tetracoordinate boron complexes display bright fluorescence, large Stokes shifts, and good quantum yields (Φ_lum = 0.15–0.45). The method proposed by the paper will inspire the development of various N,O-bidentate metal and boron complexes, which is expected to move the area of catalysis chemistry and material science forward.

Introduction

Bidentate ligands and their organoboron complexes represent one of the most important classes of organic compounds, which are extensively utilized in medicinal chemistry, homogeneous catalysis, materials chemistry, and so on. In particular, N,N-bidentate ligands and their organoboron (BF₂, BAr₂) complexes have been thoroughly developed for their readily available, good catalytic activity, and chemselectivity. For example, N,N-bidentate organic BF₂ complexes boradipyrromethene (BODIPY) are considered as outstanding representatives. They have successfully provided significant contributions to the development of many applications such as fluorescent indicators, biological fluoroprobes, organic light-emitting devices (OLED), and photosensitizers, because of the particular properties related to high fluorescence intensity, quantum yields, and exceptional stability (Scheme 1a, left).

Scheme 1 | Access to N,O-bidentate ligands and their organic boron complexes.

N,O-bidentate organoboron (BF₂, BAr₂) complexes that are nonetheless reckoned to be underexplored should also have significant advances in optical material and labeling reagents (Scheme 1a, right). However, the synthesis of these fluorescent N,O-bidentate ligands and their organic boron (BF₂, BAr₂) complexes are extremely difficult owing to the lack of efficient methods, which makes their development far behind that of N,N-bidentate organic BF₂ complexes BODIPY. Thus, the development of convenient transformation to prepare those fluorescent compounds with functional diversity is still highly desirable. In this regard, 2-(pyridin-2-yl)phenol is a class of important N,O-bidentate ligand accompanied with tremendous development potential. Generally, the synthesis of such BF₂ complexes with 2-(pyridin-2-yl)phenol ligands require multi-step sequence transformation (Suzuki coupling, deprotection, and coordination) from the prefunctionalized procedures pyridinyl halides/surrogates and aryl organometallic
reagents (Scheme 1b).\textsuperscript{[38--40]} Recently, Jiao successfully achieved PdCl\(_2\) and N-hydroxyphthalimide cocatalyzed C\(_{sp2}\)-H hydroxylation of 2-phenylpyridine by dioxygen activation.\textsuperscript{[41]} Glory developed copper-catalyzed one-shot synthesis of N,O-bidentate organic BF\(_2\) complexes from 2-phenylpyridine derivatives (Scheme 1b).\textsuperscript{[42]} But there are still some limitations needed to be addressed: 1) Multi-step synthesis is needed, and some precursors need complex pre-functionalization; 2) Metal catalysts are necessary, and metal- and oxidant-free systems have not been established; 3) Relatively narrow substrate scope. More challenging structures such as fluorescent polyaryl 2-(pyridin-2-yl)phenol ligands and their BF\(_2\) and BAr\(_2\) complexes cannot be synthesized. To meet these challenges, we proposed a deconstructive cycloaromatization strategy, which could quickly access polyaryl 2-(pyridin-2-yl)phenol ligands and their four-coordinate organoboron complexes.

Deconstructive functionalization has long been an integral part of organic synthesis, allowing rapid construction of scaffolds of complex molecular via ingenious cleavage and reorganization of chemical bond, which widely serves as a momentous synthetic strategy for multifarious fields.\textsuperscript{[43--52]} In particular, the ring deconstruction-rearomatization reaction is considered to be a challenging chemical transformation, also known as "scaffold hopping" (Scheme 1c).\textsuperscript{[53--54]} To date, the sequence deconstruction-cycloaromatization of indolizines has never been proposed,\textsuperscript{[55--62]} though several complexes and valuable molecules can be constructed through this strategy (Scheme 1c). Considering the great applicative prospects of N,O-bidentate ligands and their organic boron complexes, we disclose unprecedented metal-free deconstructive cycloaromatization between indolizines and cyclopropenones that can furnish a three-carbon unit as a key building block,\textsuperscript{[63--68]} providing practical polyaryl N,O-bidentate ligands and their organic BX\(_2\) (X = F, Ar) complexes in one-pot. Of note, some representative four-coordinate organoboron complexes show interesting photophysical properties.

### Results And Discussion

#### Condition optimization.

We have long been committed to developing new methods to construct nitrogen-containing heterocyclic derivatives.\textsuperscript{[69--73]} Thus, easily available 2-phenylindolizine and diphenylcyclopropenone were chose as the model substrates to conduct the reaction under 120 °C in DCM for 18 h (Table 1). Surprisingly, the sequence deconstructive recycloaromatization product was secured with a prominent yield (95%) without any catalysts and additives (Table 1, entry 1). Lowering the reaction temperature to 100 °C and 80 °C resulted in decreasing yields of polyaryl N,O-bidentate ligand (Table 1, entry 2). These results indicated that deconstructive aromatization was driven by heat. Then, a series of solvents, such as DCE, toluene, and DMSO were tested and they showed worse results than standard conditions (Table 1, entry 3). Performing the reaction at nitrogen atmosphere affected the reaction efficiency slightly and afforded the polyaryl 2-(pyridin-2-yl)phenol in 88% yield (Table 1, entry 4). Finally, the radical inhibitor TEMPO and BHT were added to the reaction, respectively, the hardly changed yields indicated that a free radical process was not involved in the transformation.
**Synthesis of polyaryl N,O-bidentate ligands.**

With the optimal conditions in hands, we began to evaluate the substrate adaptability of this deconstructive-cycloaromatization reaction, as summarized in Scheme 2. Firstly, various substituted indolizines were applied to get the target products under the optimized conditions. The 2-phenylindolizine with substituents at its pyridine ring, such as methyl, methoxy, ethyl, and ester, could give the desired N,O-bidentate ligands 3b-3e in 68%-93% yields. To our delight, products 3f and 3g were also obtained with high yields when alkyls replaced aryl group at C-2 position of indolizines. Both electron-donating and electron-withdrawing groups at para-position of benzene were well tolerated to deliver the corresponding N,O-bidentate ligands 3h-3r with moderate to high yields, in which product 3r was detected by single-crystal X-ray diffraction to figure out its concrete structure (CDCC 2101314). Similarly, when the meta- and ortho- positions of phenyl ring were equipped with various substituents, regardless of whether mono- or di-substituted, products 3s-3aa were all achieved in satisfactory yields (70%-91%). And the reaction was not severely affected by the service of 2-(4-fluorophenyl)-7-methylindolizine and 2-(4-chlorophenyl)-8-methylindolizine (3ab, 85%; 3ac, 86%). It was found that thienyl-, furyl-, and pyridyl-substituted indolizines was effectively leading to 70-81% yields of 3ad-3af. Then several cyclopropenones were entrusted with the mission to complete this deconstructive-cycloaromatization reaction. In comparison to the model substrate, cyclopropenones with methyl and methoxyl group on phenyl ring also offered the ideal products 3ag-3ai in nice yields. When it came to dithienylcyclopropenone, the reaction result made us amused with 82% yield of 3aj. It was worth mentioning that dithienylcyclopropenone and 2-(thiophen-2-yl)indolizine proved to be successful substrates for the procedure of deconstructive-cycloaromatization under metal- and oxidant-free conditions, affording N,O-bidentate ligand 3ak in 60% yield.

**Scheme 2 | Access to polyaryl N,O-bidentate ligands via deconstructive aromatization.** Reactions were performed in 0.3 mmol scale. 1 (0.30 mmol), 2 (0.33 mmol, 1.1 equiv), DCM (3.0 mL), 120 °C, 18 h.

**Synthesis of organoboron (BF\(_2\) and BPh\(_2\)) complexes.**

Organoboron compounds have important value and are widely used in numerous fields, including organic synthesis, catalysis, drug discovery, materials science, and so on. Among them, organic BF\(_2\) and BAR\(_2\) complexes have gathered much interests. Inspired by the above success on the construction of N,O-bidentate ligand via the merge of ring deconstruction with cycloaromatization of indolizines and cyclopropenones, we continued to expand this one-pot protocol to build valuable N,O-bidentate organic BF\(_2\) and BAR\(_2\) complexes (Scheme 3). For instance, 2-phenylindolizine and diphenylcyclopropenone could proceed smoothly in the presence of BF\(_3\)-OEt\(_2\) and triethylamine, giving N,O-bidentate organic BF\(_2\) complex 4a in 80% yield under metal-free conditions. Moreover, a few indolizine derivatives were subsequently examined for forming N,O-bidentate organic BF\(_2\) complexes 4b-4f, and producing the BF\(_2\) complexes in 60%-82% yields, in which the crystal structure of 4b were obtained (CDCC 2101316). Similarly, different cyclopropenones were proved to be reliable candidates, furnishing the BF\(_2\) complexes 4g and 4h in moderate yields. To our delight, when BPh\(_3\) participated in this reaction with model
reactants, the targeted N,O-bidentate organic BPh$_2$ complexes 5a were achieved in nice yields without any other catalysts and additives. Also, the indolizines bearing various groups, such as different-substituted phenyl, furyl, and pyridyl, could also provide the corresponding BPh$_2$ complexes 5b-5f in good yields (65%-82%). More importantly, we found that a variety of boric acid can also directly participate in the reaction as a boron source, leading to four-coordinate organoboron complexes by one-pot method. The results proved that different substituted phenylboronic acids were tolerable in the presence of K$_3$PO$_4$ and the expected diarylboron complexes (5g-5m) were afforded in good yields (77%-90%). Besides phenyl, other arylboronic acids, such as thienyl, furyl, naphthyl, and carbazolyl boronic acid, could enable to forge target products 5n-5q in 77%-86% yields. The crystal structure of 5q was analyzed (CDCC 2121318). Next, we introduced triphenylamine groups to indolizine and used it to get the corresponding BPh$_2$-complexs 5r and 5s successfully with good yields. Finally, bisindolizine derivative prepared via Suzuki-coupling of iodoindolizine and 1,4-phenylenebisboronic acid finished the deconstructive-cycloaromatization and provided product 5t in 84% yield. Notably, compound 5t contains two four-coordinate organoboron centers.

**Synthesis of polyaryl phenolic esters.**

Then, we turned our attention to put acetic acid into the reaction edifice, the assumed polyaryl 2-(pyridin-2-yl)phenol derivatives were produced in one-pot (Scheme 4). For example, when acetic acid was used, essential 2-(pyridin-2-yl)phenol derivatives 6a-6d were got in 60%-75% yields with variant indolizines, and the crystal structure data of 6c has arrived in our hand (CDCC 2101315). This novel deconstructive aromatization strategy provides a convenient, direct and practical access to synthesize complex N,O-bidentate ligand and their derivatives in one-pot. metal- and oxidant-free conditions.

As we know, phenol derivatives are not only indispensable components of many drugs, but also good synthetic intermediates. Therefore, the polyaryl 2-(pyridin-2-yl)phenols synthesized by the present method were easily incorporated into several drug molecules and bioactive units via esterification process under mild conditions (Scheme 4). We firstly employed a simple pyrazolecarboxylic acid, which is an intermediate of YW2065 (anti-CRC molecule), and fortunately, the desired esterification product 6e was yielded in 82% yield. Then two approved drugs indometacin and febuxostat with complicated structure could combine with polyaryl 2-(pyridin-2-yl)phenol, generating the corresponding derivatives 6f and 6g in high yields, respectively. Herein, we developed a rapid method for the construction of complex framework polyaryl 2-(pyridin-2-yl)phenols and successfully applied it to the modification of several pharmaceuticals and biologically active molecules.

**Scheme 4 | Synthesis of polyaryl phenolic esters derivatives and incorporation of N,O-bidentate ligand into drugs and active molecules.** Conditions: [a] 1 (0.3 mmol, 1.0 equiv), 2a (0.33 mmol, 1.1 equiv), AcOH (0.36 mmol, 1.2 equiv), DCM (3.0 mL), 120 °C, 18 h. [b] 3 (0.2 mmol), RCOOH (0.3 mmol, 1.5 equiv), DCC (0.3 mmol, 1.5 equiv), DMAP (0.2 mmol, 1 equiv), DCM, r.t., 24 h.

**Further transformations of products.**
In order to further evaluate the practicability and expansibility of this deconstructive aromatization reaction, we expanded the scale of this metal and additive-free transformation to 8 mmol (Scheme 5). Surprisingly, we easily and efficiently acquired the final product 3a in 81% yield (2.6 g) by direct filter and wash with MeOH. The further transformations were studied. When halogenating agents, N-fluorobenzenesulfonimide (NFSI), 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), and N-bromosuccinimide (NBS), were stirred with N,O-bidentate ligand at 80 °C respectively, the corresponding halogenated products 7a-7c were given with 78%-96% yields, which could be purified readily by recrystallization (hexane and DCM). The obtained halogenated N,O-bidentate ligands were easily ordinated with arylboronic acids to produce the corresponding four-coordinate organoboron complexes (8a-8c). Next, three different boric acids were coupled with brominated N,O-bidentate ligand, generating 9a-9c with good yields. Reaction could also occur between N,O-bidentate ligand and perfluorotriphenylborane to cater for product 10 in 90% yield.

**Scheme 5 | Further transformation of N,O-bidentate ligands.** Conditions: [a] 1a (10 mmol), 2a (11 mmol, 1.1 equiv), DCM (25 mL), 120 °C, 18 h.[b] 3a (0.3 mmol), NFSI (0.36 mmol, 1.2 equiv), DCM (3 mL), 80 °C, 12 h. [c] 3a (0.3 mmol), NBS or DCDMH (0.36 mmol, 1.2 equiv), DCM (3 mL), 80 °C, 12 h. [d] 7a, 7b, or 7c (0.3 mmol),Ph-B(OH)₂ (1.5 mmol, 5 equiv), K₃PO₄ (3 mmol, 10 equiv). [e] 8b (0.3 mmol), boric acid (0.45 mmol, 1.5 equiv), Pd(PPh₃)₄ (0.03 mmol, 0.1 equiv), K₂CO₃ (0.6 mmol, 2.0 equiv), THF:H₂O (10:1, 3 mL), 90 °C, 12 h. [f] 3a (0.3 mmol), perfluorotriphenylborane (0.36 mmol, 1.2 equiv), DCM (3 mL), 80 °C, 12 h.

**Photophysical property investigations**

To prove the promising applications as optical material of the four-coordinate organoboron complexes, we next investigated the photophysical properties of N,O-bidentate BPh₂ complexes prepared by this method (Scheme 6 and Table 2). Clearly, the selected four-coordinate organoboron complexes (5a, 5i, 5q, 5t, and 8a) display bright blue fluorescence in DCM, while compounds 9b and 5s display light green fluorescence and 5r displays intensive yellow fluorescence under UV light irradiation (365 nm) (Scheme 6a). The detailed spectra datas were shown in Scheme 6. Absorption spectra of 5a in different solvent shows that DCM is the best solvent for these N,O-bidentate BPh₂ complexes (Scheme 6b). The absorption maximum wavelengths of the selected complexes range from 311 nm to 347 nm in DCM solution (Scheme 6c). In fluorescence emission spectra, their maximum photoluminescence wavelength are concentrated at 473 nm to 570 nm (Scheme 6d). Different substituent groups weakly affect on emission wavelength and fluorescence intensity, while compounds 9b, 5s, and 5r have remarkable red shifts. It is worthy to note that compound 5r displays the emission maxima at 570 nm (Scheme 6d). Interestingly, these organoboron complexes exhibits large Stokes shifts ranging from 139 nm to 223 nm, and such large Stokes shifts makes them appealing in valuable applications (Table 2). Finally, density functional theory (DFT) calculations were conducted at the B3LYP/6-31G(d) level using the Gaussian 03 package for further study the optoelectronic properties.[74] The calculated HOMO and LUMO energy levels of selected compounds (5a, 5r, 5s, 5t, and 9b) were summarized at Scheme 6e and Table 2. The results disclosed
that the HOMO−LUMO gaps of these four-coordinate organoboron complexes are in the range from 2.99 to 3.70 eV.

**Proposed mechanism**

Based on the results of our experiments and previous reports, a plausible mechanism is depicted in Scheme 7. First, a resonance is occurred between cyclopropenone 2a and its ionic form 2a′, which reacts with 2-phenyl indolizine 1a in high temperature to give intermediate I. Then, charge transfer occurs on the nitrogen atom in indolizine to form ion intermediate II. Subsequently, the intermediate III was obtained via the cleavage of C-N bond. Intermediate III isomerized to more stable intermediates IV. Finally, the intramolecular positive and negative ions interact to produce intermediate V, which further undergoes aromatization to obtain the final product 3a. 3a could react with BF₃ and BPh₃ (or arylboronic acid) to give N,O-bidentate organic BF₂ and BAr₂ complexes 4a and 5a.

**Conclusion**

In conclusion, we have developed an efficient and unprecedented access to produce novel polyaryl N,O-bidentate ligands without any metals or other additives via deconstructive cycloaromatization reaction from indolizines and cyclopropenones. Furthermore, this strategy provides a convenient and one-pot synthesis of novel N,O-bidentate organic BF₂ and BPh₂ compounds, in which the optical properties and HOMO/LUMO gap of these tetracoordinate organoboron compounds are explored. Notably, these N,O π-conjugated boron complexes exhibit bright fluorescence, and large Stokes shifts, which could have appealing applications in bioassays and optoelectronic devices. We envision that this work will open new access to the construction of polyaryl N,O-bidentate ligands and inspire the discovery of various N,O-bidentate metal and boron complexes.

**Declarations**

Supporting Information

Supporting Information is available. Experimental details, characterization data and NMR spectra of new compounds.

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**Tables**

Tables 1-2 are available in the Supplementary Files section.

**Figures**

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**a)** N,N-bidentate and N,O-bidentate organoboron (BF₂, BAR₂) complexes

![Diagram](image1)

**b)** Known access to N,O-bidentate ligands and organoboron complexes

1. General approach via multi-step sequence of pre-activation

2. Deactivation to N,O-bidentate ligands and organoboron complexes

**c)** Access to N,O-bidentate ligands and their organic boron complexes via deconstructive aromatization of indolizines and cyclopropenes: this work

- 73 examples, up to 98% yield
- Metal-free, one-pot synthesis
- Easily scale-up, direct filter
- Diverse polyaryl N,O-bidentate ligands and four-coordinate organoboron (BF₂ and BAR₂) complexes
- Excellent photophysical properties (bright fluorescence, large Stokes shifts, and good quantum yield)
Figure 1

Scheme 1 | Access to N,O-bidentate ligands and their organic boron complexes.

![Scheme 1 Diagram]

Figure 2

Scheme 2 | Access to polyaryl N,O-bidentate ligands via deconstructive aromatization. Reactions were performed in 0.3 mmol scale. 1 (0.30 mmol), 2 (0.33 mmol, 1.1 equiv), DCM (3.0 mL), 120 °C, 18 h.
Scheme 3 | One-pot approach to organoboron (BF₂ and BPh₂) complexes via deconstructive aromatization. For 4, Conditions: 1 (0.30 mmol), 2 (0.33 mmol, 1.1 equiv), BF₃•OEt₂ (0.60 mmol, 2.0 equiv), Et₃N (3.0 mmol, 10 equiv), DCM (3.0 mL), 120 °C, 18 h. For 5a-5f, Conditions: 1 (0.30 mmol), 2 (0.33 mmol, 1.1 equiv), BPh₃ (0.60 mmol, 2.0 equiv), DCM (3.0 mL), 120 °C, 18 h; For 5g-5t, Conditions: 1
(0.30 mmol), 2 (0.33 mmol, 1.1 equiv), boric acid (1.5 mmol, 5 equiv), K$_3$PO$_4$ (3 mmol, 10 equiv), 120 °C, 18 h.

Figure 4

Scheme 4 | Synthesis of polyaryl phenolic esters derivatives and incorporation of N,O-bidentate ligand into drugs and active molecules. Conditions: [a] 1 (0.3 mmol, 1.0 equiv), 2a (0.33 mmol, 1.1 equiv), AcOH (0.36 mmol, 1.2 equiv), DCM (3.0 mL), 120 °C, 18 h. [b] 3 (0.2 mmol), RCOOH (0.3 mmol, 1.5 equiv), DCC (0.3 mmol, 1.5 equiv), DMAP (0.2 mmol, 1 equiv), DCM, r.t., 24 h.
Figure 5

Scheme 5 | Further transformation of N,O-bidentate ligands. Conditions: [a] 1a (10 mmol), 2a (11 mmol, 1.1 equiv), DCM (25 mL), 120 °C, 18 h. [b] 3a (0.3 mmol), NFSI (0.36 mmol, 1.2 equiv), DCM (3 mL), 80 °C, 12 h. [c] 3a (0.3 mmol), NBS or DCDMH (0.36 mmol, 1.2 equiv), DCM (3 mL), 80 °C, 12 h. [d] 7a, 7b, or 7c (0.3 mmol), Ph-B(OH)₂ (1.5 mmol, 5 equiv), K₃PO₄ (3 mmol, 10 equiv). [e] 8b (0.3 mmol), boric acid (0.45 mmol, 1.5 equiv), Pd(PPh₃)₄ (0.03 mmol, 0.1 equiv), K₂CO₃ (0.6 mmol, 2.0 equiv), THF:H₂O (10:1, 3 mL), 90 °C, 12 h. [f] 3a (0.3 mmol), perfluorotriphenylborane (0.36 mmol, 1.2 equiv), DCM (3 mL), 80 °C, 12 h.
Figure 6

Scheme 6 | Photophysical property investigations. (a) Picture of representative four-coordinate organoboron complexes (5a, 5i, 5q, 5t, 5r, 5s, 8a, and 9b) under UV light irradiation (365 nm). (b) Absorption spectra of 5a in different solvent. (c) Absorption spectra of N,O-bidentate BPh$_2$ complexes (5a, 5i, 5q, 5t, 5r, 5s, 8a, and 9b) in DCM. (d) Emission spectra of N,O-bidentate BPh$_2$ complexes (5a, 5i, 5q, 5t,
5r, 5s, 8a, and 9b) in DCM. (e) Energy diagram and Kohn–Sham orbital representation of 5a, 5r, 5s, 5t, and 9b.

Figure 7

Scheme 7 | Proposed mechanism.

Supplementary Files

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