

Feasible Synthesis of N, O-Bidentate Difluoroboron Chromophores through Direct Functionalization of Quinoxalin-2(1H)-ones with Ketones in One Shot

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Abstract

Organic difluoroboron complexes is a kind of potential platforms for a wide range of applications owing to their excellent photo-physical properties. Herein, we have explored a simple and direct synthesis methodologies for a library of N,O-Bidentate difluoroboron complexes from quinoxalin-2(1H)-ones and ketones in one shot. The photophysical properties of the generated com-plexes were evaluated and the application potential of these compound on subcellular was also explored.

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Feasible Synthesis of N, O-Bidentate Difluoroboron Chromophores through Direct Functionalization of Quinoxalin-2(1H)-ones with Ketones in One Shot

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Keywords

N, O-Bidentate Difluoroboron | Chromophores | Quinoxalin-2(1H)-ones | Ketones | Green Chemistry |

Comprehensive Summary

Organic difluoroboron complexes is a kind of potential platforms for a wide range of applications owing to their excellent ph

Background and Originality Content

Green chemistry is a pressing concern for chemists, as the increasing pollution and waste generated during chemical processes have become a major environmental issue. The demand for environmentally-friendly processes in organic synthesis has spurred interest in developing efficient and sustainable reactions for the synthesis of valuable organic compounds. Since the discovery of boron dipyrromethenates (BODIPYs) in 1968,^[1] organic difluoroboron complexes have occupied an increasingly important position in organic chem-

istry and material science owing to their superior photophysical properties, such as high fluorescent quantum yield, tunable structure and emission, as well as robust photo- and chemical stability.^[2-5] Especially in the last decade, a large number of difluoroboron complexes have been explored and applied in fluorescent sensing, laser dyes, organic light-emitting devices, bioconjugates components, bio-imaging,^[6-10] and even singlet-oxygen generators for photodynamic therapy.^[11, 12] According to the difference of the ligands, organic difluoroboron complexes can be categorized into three types: N,N-bidentate type, O,O-bidentate type, and N,O-bidentate type. BODIPYs,^[3, 13, 14] including azo-BODIPYs,^[15] and 1,3-dioxa-2-borane have been well studied with plenty of publications,^[16] which could be regarded as the typical representatives of the prior two types of organic difluoroboron complexes compounds. Whereas, the research on N,O-bidentate organic difluoroboron complexes is relatively lagging behind.^[17, 18] The scope and function of N,O-bidentate organic difluoroboron complexes are still rarely involved but promising region worthy further exploration.

Compared to the significant progresses in the expansion of the structure and application for organic difluoroboron complexes, the innovation in the synthetic strategy for these compounds is few and far between. Generally, the process to prepare an organic difluoroboron complex can be divided into two stages: 1) synthesis of corresponding organic bidentate ligand; 2) complexation with boron sources, in most cases is boron trifluoride diethyl etherate (Scheme 1a).^[19-26] Despite of the drawbacks of tedious synthetic steps and low efficiency,^[23-26] the structural diversity of the organic difluoroboron complexes is also limited by the deficiency in effective synthetic methods with broad functional groups tolerance. Recently, as the prosperity of transition-metal-catalyzed C-H bond activation reactions, Glorius group developed two pioneering samples to construct the organic ligands and difluoroboron complexes in one shot via copper-mediated C-H bond activation strategy (Scheme 1b).^[27, 28] These protocols not only provided efficient and rapid assemble solution for organic difluoroboron complexes, but also enriched the inventory of N,O-bidentate products. Apart from the copper tetrafluoroborate ($\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$) employed as catalyst and boron source, stoichiometric silver salts were also necessary as oxidant, which impaired the green chemical scores of these protocols in some extent. With the attention to expand the scope and function of N, O-bidentate organic difluoroboron complexes further, and also from the perspective of green chemistry and sustainable development, novel efficient synthetic method is always of continuing interest.^[29-31] In this paper, we have established a straightforward synthesis of N,O-bidentate organic difluoroboron chromophores from quinoxalin-2(1H)-ones and readily available ketones (Scheme 1c). The reaction showcases excellent step and atom economy, broad functional group tolerance and operational convenience. A vast array of N, O-bidentate organic difluoroboron complexes are synthesized via our protocol. Furthermore, the photophysical properties and application of these compounds in bio-imaging are also explored in several dimensions.

Scheme 1 Progress in the synthesis of organic difluoroboron complexes.

Results and Discussion

At first, the reaction was conducted between 1-methylquinoxalin-2(1H)-one (**1a**) and acetophenone (**2a**) as shown in Table 1. The desired product **3a** could be obtained with 0.5 equiv of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ as catalyst and BF_2 source (Table 1, Entry 1). The yield could be increased to 65% with 2.0 equiv of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (Table 1, Entry 2-3). When we increased the amount of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ to 2.5 equiv, no better outcomes were obtained (Table 1, Entry 4). Next, we turn to examine the combination of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and other BF_2 sources, and 82% product was generated with 0.5 equiv of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and 2 equiv of HBF_4 (Table 1, Entry 5-7). A series of solvents were also tested and the results indicated that DCE is the proper choice (Table 1, Entry 8-15). When we conducted the reaction at lower temperature, the yield was reduced to 59% (Table 1, Entry 16). To our delight, even 58% of product could be generated without the use of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$. The amount of HBF_4 and the reaction temperature were screened in the absence of Cu salt, and the highest yield was obtained with 2 equiv. of HBF_4 at 80 °C (Table 1, Entry 19-23).

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst (0.5 equiv)	BF ₂ source (2.0 equiv)	Solvent	Yield ^b
1	Cu(BF ₄) ₂ ·6H ₂ O	/	DCE	43
2	Cu(BF ₄) ₂ ·6H ₂ O (1 equiv)	/	DCE	62
3	Cu(BF ₄) ₂ ·6H ₂ O (2 equiv)	/	DCE	65
4	Cu(BF ₄) ₂ ·6H ₂ O (2.5 equiv)	/	DCE	65
5	Cu(OAc) ₂	BF ₃ ·Et ₂ O	DCE	39
6	Cu(BF ₄) ₂ ·6H ₂ O	BF ₃ ·Et ₂ O	DCE	46
7	Cu(BF ₄) ₂ ·6H ₂ O	B(OH) ₃	DCE	78
8	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	DCE	82
9	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	H ₂ O	Trace
10	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	Toluene	48
11	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	MeCN	27
12	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	DCM	56
13	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	DMF	Trace
14	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	DMSO	Trace
15	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	THF	31
16 ^c	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄	DCE	59
17	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄ (1.2 equiv)	DCE	72
18	Cu(BF ₄) ₂ ·6H ₂ O	HBF ₄ (1.5 equiv)	DCE	78
19 ^c	/	HBF ₄	DCE	58
20 ^c	/	HBF ₄ (2.5 equiv)	DCE	59
21 ^c	/	HBF ₄ (1.5 equiv)	DCE	46
22 ^c	/	HBF ₄ (1.2 equiv)	DCE	35
23 ^d	/	HBF ₄	DCE	48

^a Reaction conditions: **1a** (0.20 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), catalyst (0.5 equiv), BF₂ source (2 equiv), solvent (3 mL), 110°C; ^b Isolated yields; ^c The reaction was performed at 80°C; ^c The reaction was performed at 60 °C

With the optimized reaction conditions established, we explored the scope and generality of the present process (Table 2). At the outset, a series of ketones including aryl and alkyl ketones were examined. The electromeric effect of the substituents at the C4-position of the phenyl ring of acetophenone has negligible influence on the yield of the reaction, substrates with simple electron-donating groups substituents (eg., -Me, -OMe, -NH₂) and electron-withdrawing groups (eg., -Br, -I) offer corresponding products (**3ab -3ag**) in the yield of about 68%. When the substituent was changed to bigger morpholine, the product was also synthesized in 62% (**3ah**) yield respectively. Next, acetophenone with substituent at other position and multi-substituted samples were tested, and the products were obtained in the yields of 57% to 69% (**3ai -3al**). When the phenyl group of **2** was changed with naphthyl, anthryl, and N-protected car-

Table 2 Scope of the reaction. ^{a, b}

^a Standard conditions **A**: substrates **1** (0.2 mmol), substrates **2** (0.4 mmol, 2.0 equiv.), Cu(BF₄)₂·6H₂O (0.1 mmol, 50 mol%), and HBF₄ (0.4 mmol, 2.0 equiv.) in DCE (3.0 mL), at 110°C for 48 h. Standard conditions **B**: **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), and HBF₄ (0.4 mmol, 2.0 equiv.) in DCE (3.0 mL), at 80°C for 48 h. ^b Isolated yields, the yields of the relevant products obtained under Condition **B** are marked in blue. ^c Absorption maxima of the complexes in DCM (2×10⁻⁵ M). ^d Emission maxima of the complexes in DCM (10⁻⁷ M).

bazole, the desired products (**3am -3ao**) were prepared in 59%-65% yields. Except for these aromatic ketones, acetone can also react smoothly to give **3ap** in 53% yield. Next, we sought to examine the limitation of quinoxalin-2(1H)-ones. In the beginning, N-benzyl and N-acetate group were compatible with the standard conditions, offering the desired products (**3ea**, **3fa**) in 76% and 70% respectively. Next, the N-protecting group were displaced with a range of aryl groups, the products were synthesized in 59% to 72% yields (**3ba -3da**). To our delight, when the N-protecting group was removed, the reaction performed smoothly offering corresponding product in over 50% yields (**3ga -3ha**). To demonstrate the efficiency of this procedure further, the reaction was carried out at 10 mmol scale, and **3aa** was prepared in 65% yield at the gram scale. In consideration of the cost and environment factors, the reactions were also evaluated under conditions **B** without $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$, and the yields of the products were provided in the Table 2 marked in blue.

Just as documented, organic difluoroboron complexes display marvelous photoluminescence. When the synthesized products were put under UV light irradiation (365 nm), bright fluorescence emission from green to red were observed not only in solution but also in solid state (Figure 1a, b). Next, a series of studies were carried out to get more understanding about the photophysical properties of these compounds. According to the Uv-vis and fluorescence spectra of **3aa** in multiple solvents (Figure 2c), the dichloromethane solution of **3aa** exhibit the highest quantum yield of up to 0.548 (using naphthacene [$\Phi_F = 0.6$ ($\lambda_{ex} = 443$ nm)] as the standard).

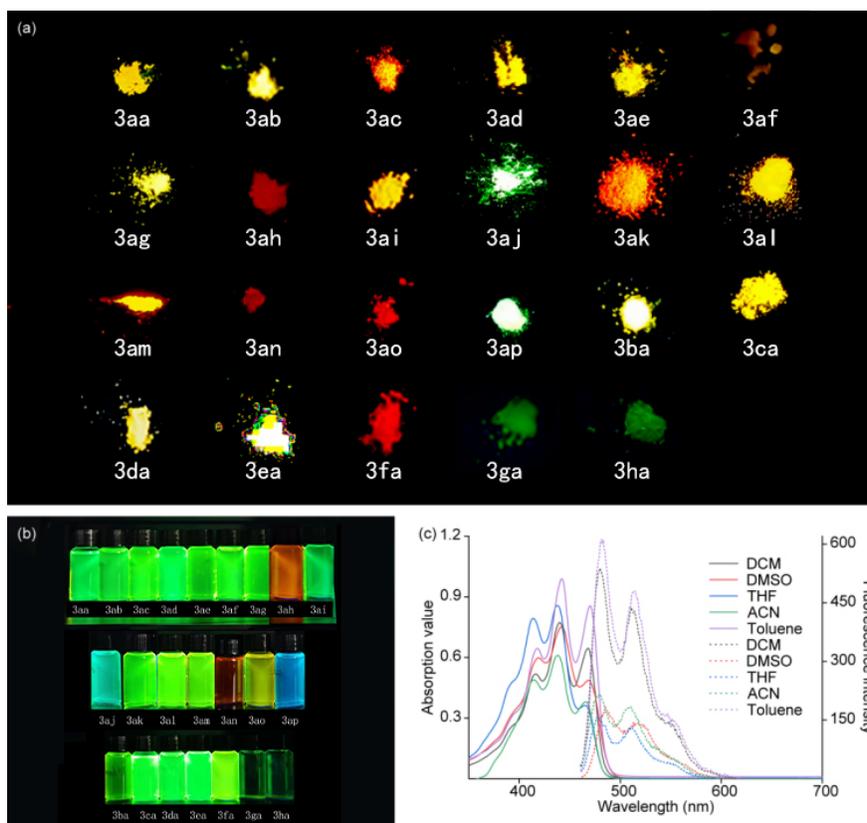


Figure 1 Fluorescence photographs and spectra of the generated organic difluoroboron complexes. ^a Fluorescence photographs of solid powder of representative difluoroboron complexes under UV light irradiation (365 nm). ^b Fluorescence photographs of representative complexes in DCM (2×10^{-5} M) under UV light irradiation (365 nm). ^c Absorption (2×10^{-5} M) and emission (10^{-7} M) spectra of **3aa** in different solvents.

Next, the absorption and emission spectra of these products in dichloromethane were investigated sufficiently,

the absorption and emission maxima of these solution vary from 403 nm to 504 nm, and 463 nm to 598 nm with strong substituent-dependency (Table S1). The Stokes shift is a fatal parameter for fluorophore associated closely with their applicational potential. Fluorophores with large Stokes shifts, which possess few spectral overlaps between the absorption and the emission, are desirable for bio-imaging and bio-Sensing due to their higher sensitivity by eliminating of self-absorption. Herein, the largest Stokes shifts of these synthesized complexes was evaluated to reach up to 184 nm (**3an**), which provide promising potential fluorescent probe for bio-sensing. The extraordinary Stokes shifts of **3an** may be attributed to its high degree of charge separation caused by the electron donating, and accepting effect between the electron-deficient difluoroboron motif and the electron-rich naphthalene group. Since the solid state has a significantly difference luminescence performance from the solution state influenced by the aggregation state of the molecules, **3ak** and **3ba** were selected for the solid-state fluorescence test, and the emission maxima of these complexes vary from 580 nm to 600 nm, and the quantum yield of **3ba** is as high as 61.3% (Table S2). These results elucidate the dual-phase emission properties of the complexes. Moreover, to explore the application of the compounds in cell bio-imaging, **3ad** was selected based on the structure of the complex for lysosome-targeting experiments (for details, see Supplementary Materials Figure S1).

Conclusions

We have developed a straightforward and sustainable synthetic methodology to construct N,O-Bidentate difluoroboron complexes from quinoxalin-2(1H)-ones and ketones without transition-metal-catalyst. This approach benefits from easily available starting materials, excellent step and atom economy, and good functional group compatibility. In addition, most of these complexes have broad and intense absorption and emission bands, and display bright and intensive fluorescence in dual-phase. The results of colocalization experiments of the selected product also demonstrated the specificity for lysosomes targeting, indicating potential applications for cell tracking related to lysosomes function. Ongoing research including further mechanistic details and applicational exploration are currently underway.

Experimental

Reaction condition **A** : Quinoxalin-2(1H)-ones **1** (0.2 mmol, 1.0 equiv), methyl ketone **2** (0.4 mmol 2 equiv), $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.5 equiv), HBF_4 (2.0 equiv) and DCE (3.0 mL) were added to a 35.0 mL sealed tube. The reaction mixture was heated to 110°C for 48 hours. When the reaction was finished, 20 mL saturated ammonium chloride solution was added and the residue was extracted with DCM (3×5.0 mL). The pure product was obtained by flash chromatography on Aluminum oxide using petroleum ether and Dichloromethane as the eluent (PE/DCM = 5:1 to 1:3).

Reaction condition **B** : Quinoxalin-2(1H)-ones **1** (0.2 mmol, 1.0 equiv), methyl ketones **2** (0.4 mmol 2 equiv), HBF_4 (2.0 equiv) and DCE (3.0 mL) were added to a 35.0 mL sealed tube. The reaction mixture was heated to 80°C for 48 hours. When the reaction was finished, 20 mL saturated ammonium chloride solution was added and the residue was extracted with DCM (3×5.0 mL). The pure product was obtained by flash chromatography on Aluminum oxide using petroleum ether and Dichloromethane as the eluent (PE/DCM = 5:1 to 1:3).

Supporting Information

The supporting information for this article is available on the WWW under <https://doi.org/10.1002/cjoc.2023xxxxx>.

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Entry for the Table of Contents

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A rapid and green synthetic protocol for N,O-bidentate difluoroboron chromophores was achieved via cascade C-H functiona