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Nickel-Catalyzed Boron Insertion into the C2−O Bond of Benzofurans

Hayate Saito, Shinya Otsuka, Keisuke Nogi, and Hideki Yorimitsu*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

Supporting Information

ABSTRACT: Treatment of benzofurans with bis(pinacolato)diboron and Cs_2CO_3 under nickel-NHC catalysis resulted in the insertion of a boron atom into the C2−O bond of benzofurans to afford the corresponding oxaborins. The scope of benzofuran substrates is wide, and the reactions proceeded without loss of functional groups such as fluoro, methoxy, and ester that are potentially reactive under nickel catalysis. The boron-inserted products proved to be useful building blocks and subsequently underwent a series of transformations, one of which led to the synthesis of fluorescent π-expanded oxaborins.

Organoboron compounds are definitely important in modern organic chemistry due to their various roles such as synthetic building blocks,[1] functional materials,[2] and bio-related agents.[3] Especially, π-conjugated boracycles have been attracting increasing attention. Some of them can serve as fascinating "boron-doped" organic materials that utilize the vacant *p* orbital of boron for dramatic electronic alteration (Figure 1a).[4] Others find medicinal or biological applications as

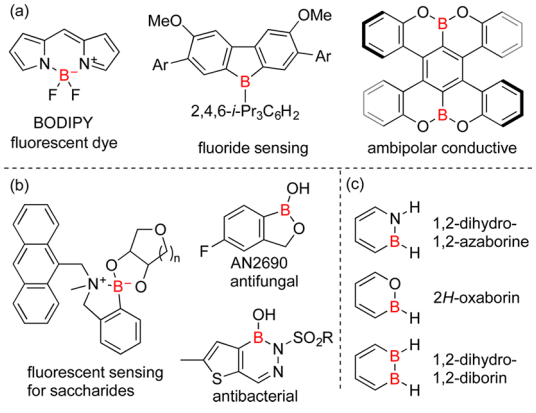

Figure 1. Representative π-conjugated boracycles.

exemplified by saccharide sensors or antimicrobial agents (Figure 1b).[5] From an organometallic viewpoint, borabenzene derivatives, generally called borins, also constitute an intriguing class of π-conjugated boracycles (Figure 1c).[6−8] Among them, 2*H*-oxaborins[7] are emerging as new attractive boracycles also as synthetic intermediates,[7h−l] and fluorescent materials.[4d,7m−p]

Despite the ever-expanding utility of π-conjugated boracycles, methods to implant a boron atom into a π-system remain still limited, undesirably requiring highly Lewis acidic boron halides and/or reactive organometallic reagents as well as harsh conditions and laborious synthetic procedures.[7] New strategies to construct π-conjugated boracyclic skeletons have been demanded.

Recently we have been interested in "aromatic metamorphosis", which represents a transformation of one aromatic system to another cyclic skeleton through partial disassembly of the starting aromatic ring.[9,10] In this context, here we report nickel-catalyzed boron insertion into the C2−O bond of benzofurans to construct benzoxaborin skeletons in one step. This is the first example of a catalytic introduction of a boron atom into a heteroaromatic ring through breaking its aromaticity. Such insertion of a boron atom into a heteroaromatic skeleton would represent an ideally straightforward approach to π-conjugated boracycles.

Furan derivatives are known to undergo catalytic ring-opening arylation and alkylation with organometallic reagents.[11] Although heteroaromatic cores including benzofuran have never been utilized for ring-opening borylation, the recent progress of the Miyaura *ipso*-borylation[12,13] of inert bonds such as C−F,[14] C−O,[15] and C−S[16] bonds encouraged us to tackle this challenge.[17]

After optimization of reaction conditions (*vide infra*), the borylation of the C2−O bond of benzofuran (**1a**) was conducted in the presence of $NiCl_2(PPh_3)IPr$[18] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as a catalyst, bis(pinacolato)diboron ($B_2(pin)_2$), and Cs_2CO_3 in toluene at 100 °C (Scheme 1). After acidic workup, a boron-inserted product, oxaborin **2a**, was obtained as the sole identified product. The structure of **2a** was confirmed by ^1H and ^{13}C NMR, HRMS, and X-ray crystallographic analysis (see Supporting Information (SI)). Importantly, (*E*)-2-[2-(pinacolatoboryl)ethenyl]phenol, which would be a possible borylation product according to the previous alkylation and arylation,[11a,e] was not observed at all.

IPr was found to be the best ligand and other *N*-heterocyclic carbenes and phosphines worked yet with lower efficiencies (Table S1 in SI). The pre-coordinated $NiCl_2(PPh_3)IPr$ complex proved to be superior to mixing $Ni(cod)_2$ and IPr·HCl *in situ*. Cs_2CO_3 was the most suitable activator and other bases served with less efficiencies (Table S2). The choice of $B_2(pin)_2$ was crucial, and other diboron reagents such as bis(neopentylglycolato)diboron and bis(catecholato)diboron were totally ineffective (Table S3). Nonpolar toluene is the best solvent among tested (Table S4). Ethereal solvents gave marginal results and polar solvents such as DMF and acetonitrile suppressed the reaction.

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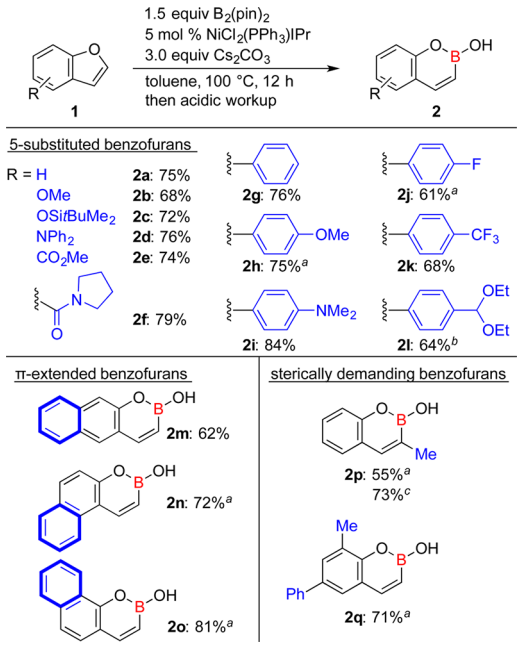
Scheme 1. Scope of Benzofurans

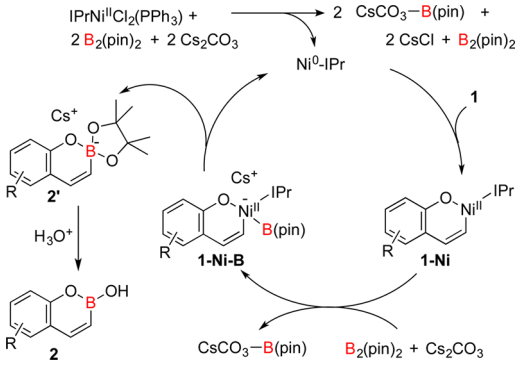


[a]10 mol% of catalyst was used. [b]Product **2l** was obtained as the corresponding aldehyde after acidic workup. [c]10 mol % of $Ni(cod)_2$ and IMes·HCl were used as a catalyst.

With the optimal conditions in hand, we investigated the scope of benzofurans **1** (Scheme 1).[19,20] Notably, the boron insertion reactions of **1b**, **1e**, **1h**, and **1j** proceeded smoothly without loss of their functional groups such as methoxy, ester, and fluoro that are potentially reactive under nickel catalysis. A *tert*-butyldimethylsilyl ether protection satisfactorily resisted possible C−O bond cleavage as well as desilylation to yield **2c**. A diethyl acetal unit also survived under the borylation conditions, and after acidic workup, the corresponding 4-formylphenyl-substituted oxaborin **2l** was obtained in good yield. Unfortunately, a benzofuran with an unprotected formyl group did not undergo the reaction. Furthermore, π-extended naphthofurans **1m**−**1o** were also applicable to the boron insertion to afford tricyclic naphthoxaborin cores. Although steric hindrance at the 2-position of the benzofuran ring in **1p** lowered reactivity, employing less bulky 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) as a ligand instead of IPr improved the yield of **2p**. Although a methyl group at the 7-position in **1q** slightly decreased the yield of **2q**, 2-fold catalyst loading (10 mol %) gave a favorable result. Attempts to convert 3-substituted benzofurans resulted in poor yields.

A plausible reaction mechanism is shown in Scheme 2. As the initial step, $B_2(pin)_2$ should reduce the Ni(II) precatalyst to IPrNi(0) species mediated by Cs_2CO_3. Oxidative addition of the C2−O bond of benzofuran **1** to IPr-Ni(0) would give oxanickelacycle **1-Ni**.[21,22] This regioselective pseudovinylic C−O bond cleavage was in accordance with the known Ni-catalyzed arylation reactions of benzofurans.[11] Subsequent transmetalation with $B_2(pin)_2$ would generate cyclic nickelate intermediate **1-Ni-B**. C−B bond-forming reductive elimination followed by intramolecular B−O bond formation would furnish the corresponding spirocyclic borate **2′** and regenerate the IPr-Ni(0). Another possible mechanism consists of oxidative addition of diboron to nickel, borylnickelation of the C2−C3 double bond of benzofuran, and β-oxygen elimination. As

Scheme 2. Presumable Reaction Mechanism

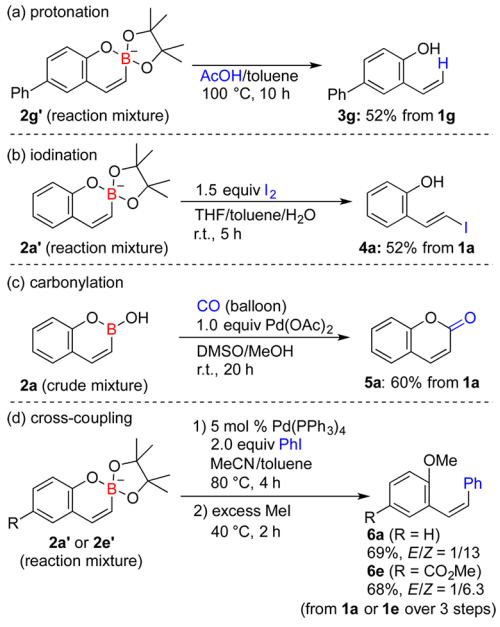


oxidative addition of a B−B bond to Ni(0) is unknown, we are tempted to support the mechanism shown in Scheme 2. Hydrolysis of **2′** upon acidic workup should give benzoxaborin **2**. Ionic borate **2′** indeed precipitated out of the reaction medium and could be collected by filtration before aqueous workup, which allowed us to characterize **2a′** by the ^1H NMR analysis of **2a′** in CD_3CN.[23]

The products, oxaborins **2** or spirocyclic borates **2′**, underwent a variety of transformations as shown below, which highlights their synthetic utility.

Oxaborins **2** are fairly stable under acidic conditions at room temperature due to their cyclic structure. However, protonolysis proceeded at 100 °C upon addition of acetic acid, for instance, to the reaction mixture including **2g′** to provide *o*-vinylphenol **3g** (Scheme 3a). This two-step transformation corresponds to formal hydrogenolysis of the C2−O bond of benzofuran.

Scheme 3. Transformations of Oxaborins



Iodinolysis[24] of the C−B bond of **2a′** proceeded in the presence of I_2, affording (*E*)-*o*-hydroxy-β-iodostyrene (**4a**) with inversion of the stereochemistry[25] (Scheme 3b).

Palladium-assisted carbonylation reaction of the C−B bond of **2a** under a CO atmosphere took place and following intramolecular cyclization gave coumarin (**5a**) in 60% yield based on **1a** (Scheme 3c).[26,27] The coumarin synthesis via oxaborin **2a** is

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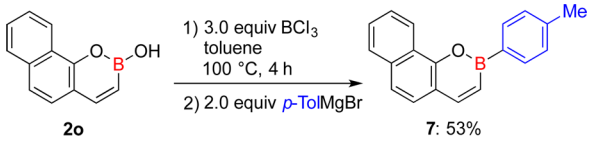
considered to be formal carbonyl insertion into benzofuran and is important as a proof-of-concept.

The Suzuki–Miyaura coupling of **2a′** or **2e′** in the reaction mixture with iodobenzene was successful in one pot with retention of stereochemistry to selectively yield (*Z*)-**6a** or (*Z*)-**6e** after subsequent methylation of the reactive hydroxy group (Scheme 3d). This one-pot transformation proceeded with mild reagents and is thus advantageous over the known ring-opening arylation of benzofurans with organolithium or magnesium reagents.[11]

Interest in π-extended oxaborins has been surging due to their intriguing photophysical properties.[4d,7m−p] According to Lerner's report,[7p] 9-aryl-10,9-oxaboraphenanthrenes bearing an exocyclic aryl-boron bond serve as luminescent fluorophores. Thus, we expected that replacement of the hydroxy group on the boron atom of **2** with an aryl group would be an attractive method for the synthesis of oxaborin-based fluorescent molecules. Chlorination of the B–OH bond of naphthoxaborin **2o** smoothly took place with BCl_3, followed by arylation with arylmagnesium bromide provided **7** (Scheme 4). Although **2o** did not display fluorescence, **7** exhibited strong blue fluorescence with a quantum yield of 40% (see SI, Figure S1). DFT calculations of **7** (Figure S1) show that the naphthoxaborin core and the tolyl substituent are coplanar at the optimized structure and well conjugated. The HOMO and LUMO of **7** were calculated to be widely delocalized, ranging from the naphthalene core to the tolyl group through the oxaborin unit.

Scheme 4. Exocyclic Arylation of 2o



In conclusion, we have developed the first example of catalytic boron insertion into an aromatic core, taking advantage of a Ni-NHC catalyst. The boron insertion has proved to show reasonable chemoselectivity while this nickel catalysis breaks the aromaticity of benzofuran. The resulting organoboron compounds underwent various transformations such as carbonylation and arylation, thereby being synthetically useful building blocks. Replacement of the exocyclic hydroxy group of **2** with an aryl group resulted in the synthesis of a new blue-emitting compound. In light of the unparalleled importance of organoboron compounds as synthetic intermediates as well as functional materials and bioactive compounds, this boron insertion strategy will be a powerful means to create new and/or useful boracycles of importance.[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10255.

Optimization of conditions, experimental procedures, characterization data, and photophysical property and computational details of **7** (PDF)

X-ray crystallographic data for **2a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*yori@kuchem.kyoto-u.ac.jp

ORCID

Hideki Yorimitsu: 0000-0002-0153-1888

Notes

The authors declare no competing financial interest.

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(19) Hydroxyoxaborins and their anhydrides are known to be in equilibrium in organic solvents. For this equilibrium, see ref 7g. Because of this unavoidable equilibrium, the NMR spectra of **2** always showed additional signals that originate from the anhydride as "impurity". For more details, see SI. The yields of boron-inserted products were based on the molar weights of **2**, without considering the possible presence of their anhydrides.

(20) Moderate yields, except for **2p** (low conversion), resulted from generations of several unidentified byproducts and from some loss of the products during purification due to their high affinity to silica gel. Benzofurans **1** were almost fully converted.

(21) We performed a stoichiometric reaction of **1g** with $Ni(cod)_2$/IPr without $B_2(pin)_2$ and Cs_2CO_3 followed by acidic workup. The expected *o*-vinylphenol **3g** was not detected, and most of benzofuran **1g** was recovered.

(22) The boron insertion reaction of benzofuran (**1a**) in the presence of phenyl vinyl ether resulted in recovery of **1a**, formation of an only 4% yield of **2a**, and formation of a considerable amount of phenol that implies the generation of the volatile and somewhat unstable vinylboronate. Phenyl vinyl ether is proved to be more reactive than benzofuran under the borylation conditions.

(23) The vinylic protons of **2a′** moved upfield compared with **2a** due to the increased electron density of the oxaborin core. In addition, the two singlets corresponding to the methyl groups of the pinacol moiety were observed (see SI).

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(27) Methyl *trans-o*-hydroxycinnamate was obtained as a byproduct in 11% yield.

(28) Attempts to insert a boron atom into dibenzofuran, 2-benzylfuran, 2,3-dihydrofuran, and 2,3-dihydrobenzofuran under nickel catalysis failed, and no desired products were observed. Attempted boron insertion into benzothiophene resulted in giving a complex mixture. Development of such boron insertion reactions is under investigation in our group.

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