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Dual 1,2-Migration-Enabled β-Boryl Amide Synthesis

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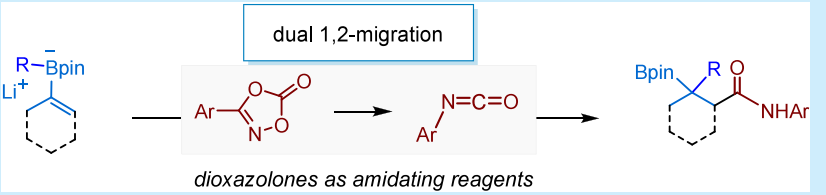

ABSTRACT: A metal-free approach for the synthesis of multisubstituted β-boryl amides is achieved via the couplings of dioxazolones with readily accessible vinyl boronate complexes. The dioxazolones undergo a Curtius-type rearrangement, in situ generating electrophilic isocyanates that subsequently react with vinyl boronate complexes. This mechanistically distinct approach enables the efficient construction of structurally diverse β-boryl amides featuring a borylated quaternary carbon center. The synthetic versatility of this protocol is further demonstrated through multiple downstream transformations of both the boron and carbonyl moieties.

Amides are pervasive units in nature and technology.[1] They serve as the backbone of proteins[2] and are key structural components in high-performance polymers such as nylons, aramids, and Twaron.[3] Beyond their structural significance, amides also serve as versatile intermediates to construct high value-added amines and ketones.[4] In view of the facts, the formation of amide bonds remains one of the most extensively studied transformations in organic chemistry.[5] Traditional approaches to amide primarily rely on couplings of carboxylic acids[6] and its activated esters[7] with amines. Alternatively, transition-metal-catalyzed cross couplings of Grignard,[8] organozinc,[9] organoboron,[10] and alkyl bromide[11] with isocyanates have also been developed to fuse amide bonds (Scheme 1a). Despite their high efficiency, these methods often suffer from stoichiometric complex coupling reagents, tedious substrate preactivation, or toxic isocyanates and metal catalysts. Aside from economic and environmental concerns, the preparation of multisubstituted amides with a reactive boron moiety as a transform handle from current condensations and couplings is still recognized to be a long-standing challenge due to the undesired side reaction of the boron group. While challenging, amides bearing a β-boryl group are important intermediates to construct various functionalized core scaffolds of bioactive compounds. Although boron conjugate addition has emerged as a powerful strategy for delivering β-boryl carbonyl compounds,[12] its application to the synthesis of multisubstituted β-boryl amides remains underexplored. Consequently, it is highly desirable to unveil new efficient and safe strategies for the direct assembly of such architectures.

Vinyl boronate complexes, readily prepared from reaction of organolithium and organobron, represent a class of highly versatile nucleophiles.[13] These complexes readily undergo electrophile-,[14] transition metal-,[15] and radical-mediated 1,2-migrations,[16] enabling the construction of diverse C−C bonds bearing boron functional groups. Notably, Morken and coworkers demonstrated the efficacy of 1,2-migration through a palladium-catalyzed conjunctive cross coupling of alkenyl boronates with carbamoyl chlorides, which afforded tertiary β-boryl amides in high yields with excellent chemoselectivity.[17] Inspired by the progress, we envisioned that isocyanate could serve as a competent electrophile to trigger a Zweifel-type 1,2-migration of vinyl boronate complexes, thereby forming multisubstituted β-borylated amides (Scheme 1b). However, the inherent toxicity of isocyanate poses significant safety and handling challenges, which led us to explore an alternative surrogate. Dioxazolones, a class of nontoxic and bench-stable cyclic carbonates, have emerged as promising candidates. Beyond being an acyl nitrene transfer reagent,[18] dioxazolones are demonstrated to facilely undergo the Curtius-type 1,2-rearrangement to release isocyanates and CO_2 as the sole stoichiometric byproduct.[19] We considered that the in situ generation of isocyanate via dioxazolone rearrangement could be employed to prepare β-boryl amides in combination with 1,2-migration of vinyl boronate complexes, thus avoiding the direct handling of hazardous reagents directly. Herein, we

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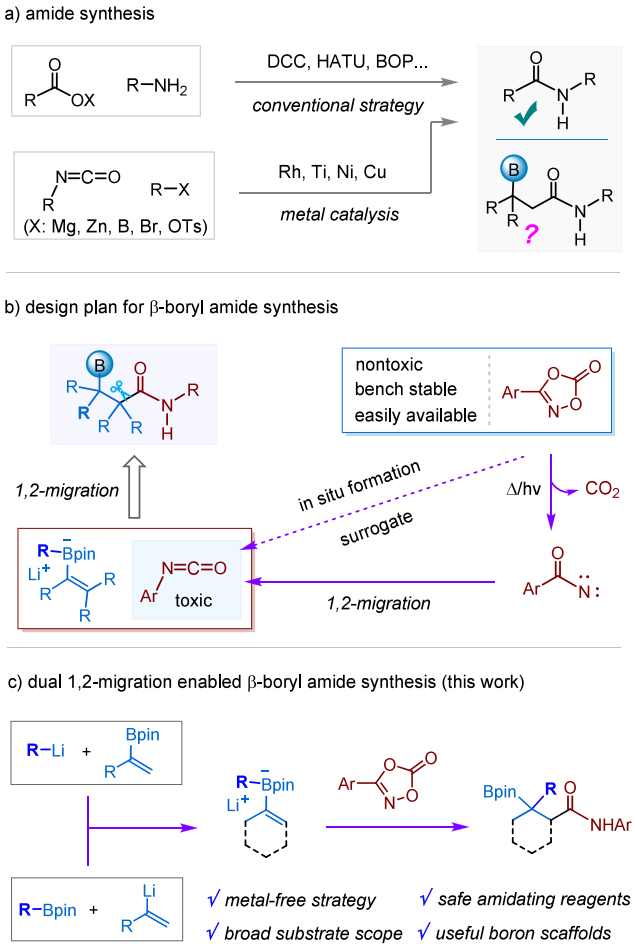
Scheme 1. Functionalized Amide Synthesis

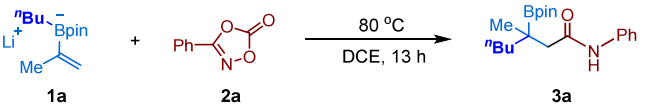


report our findings on the dual 1,2-migration-enabled efficient *β*-boryl amide synthesis (Scheme 1c).

Based on the design, we initiated the investigation by reacting vinyl boronate complex **1a** with dioxazolone **2a**. The boronate complex **1a** was prepared by the complexation of 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.3 mmol) with *n*-butyl lithium (0.33 mmol) in dry diethyl ether at 0 °C for 1 h (Table 1). Following the solvent switch, the subsequent reaction sequence was performed in DCE solvent at 80 °C for 13 h, and the desired *β*-boryl amide product was obtained in 65% yield (entry 1). A systematic solvent screening revealed that 1,4-dioxane is the optimal medium for this transformation, while other solvents such as toluene, acetone, DCM, $CHCl_3$, and THF yielded inferior results (entries 2−7). The yield of **3a** improved to 73% when the loading of **2a** was increased to 2.5 equiv (entry 8). Lowering the reaction temperature to 60 °C gave the desired amides in 49% yield, while performing the reaction at 100 °C afforded the product in 59% yield (entries 9 and 10).[20] Irradiation of the reaction mixture under blue LEDs instead of thermal conditions failed to give any product (entry 11).

After the establishment of optimal conditions, the substrate generality of this metal-free amidating reaction was investigated, which was summarized in Scheme 2. The vinyl boronate complexes used in the studies could readily form via the reaction of vinyl boronic esters with organolithium (method A). Alternatively, the vinyl lithium obtained from the lithium-halogen exchange of vinyl bromides could also

Table 1. Condition Optimizations[c]



1a 2a 3a

Entry	Variation from the standard conditions	Yield (%)[a]
1	None	65
2	Toluene instead of DCE	55
3	Acetone instead of DCE	0
4	DCM instead of DCE	40
5	$CHCl_3$ instead of DCE	57
6	THF instead of DCE	35
7	1,4-Dioxane instead of DCE	69
8[b]	1,4-Dioxane instead of DCE	73
9	60 °C	49
10	100 °C	59
11	Blue LED instead of 80 °C	0

[a]Isolated yield. [b]2.5 equiv of **2a** was used. [c]Reaction condition: **1a** (0.3 mmol), **2a** (0.6 mmol), solvent (2.0 mL), under inert atmosphere, 13 h.

convert to the corresponding boronate complexes by addition to organoboronic esters (method B). We first examined the reaction scope of the dioxazolones. With procedure A, it was found that effective reactions could be observed for a number of dioxazolones. The installation of electron-donating methoxy (**3b**), methyl (**3c**), and *tert*-butyl (**3d**) groups at the *para*-position underwent the amidation smoothly, giving the corresponding products in good yields. When electron-withdrawing trifluoromethoxy (**3e**), halogen atoms (**3f** and **3g**), carboxylic ester (**3h**), phenyl (**3i**), and trifluoromethyl (**3j**) groups were equipped, acceptable yields of *β*-boryl amides were also obtained. Methyl and fluoro substituents orientated at the *meta*- or *ortho*-site led to a marginal effect on this reaction (**3k** and **3l**). Dioxazolones bearing disubstituted groups, including 3,4-dimethoxy, 3,5-dimethoxy, and naphthyl groups, were all applicable candidates to give the desired products in 50−57% yields (**3m**−**3o**). It is worth noting that dioxazolones with a heterocycle such as furan and thiophene groups can be employed as substrates successfully under the current conditions to furnish the products in good yields (**3p** and **3q**). Unfortunately, alkyl dioxazolones failed to give any product. Besides *n*-butyl lithium, other organolithiums such as *t*-butyl lithium, methyl lithium, phenyl lithium, and (2-methylprop-1-en-1-yl)lithium were also compatible with the reaction system (**3r**−**3u**). Interestingly, when using *α*,*β*-disubstituted vinyl boronic ester (**3v**) and cyclic vinyl boronic esters (**3w** and **3x**) as substrates, multisubstituted *β*-boryl amides formed in good yields with moderate diastereoselectivity. This dual 1,2-migration-indcued amide synthesis initiated by reacting vinyl lithium with alkyl boronic esters (method B) was also demonstrated to be an effective procedure. For example, the complexation of *α*-methyl vinyl lithium with ethyl (**3y**), isopropyl (**3z**),[21] but-3-en-1-yl (**3aa**),[21] 3-phenylpropyl (**3ab**), and 4-methylpentyl (**3ac**) boronic esters could steadily form boronate complexes which successively underwent cross coupling with dioxazolones efficiently. In addition, alkyl boronic esters containing ether and silyl ether groups survived sequential amidation, delivering the products in good yields (**3ad** and **3ae**). Importantly, several labile functional groups including alkyl bromide and esters survived both the boronate complex formation and cross

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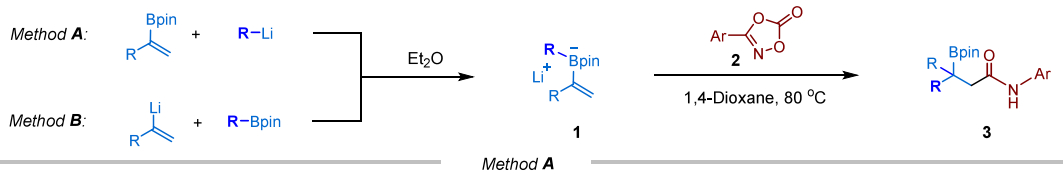
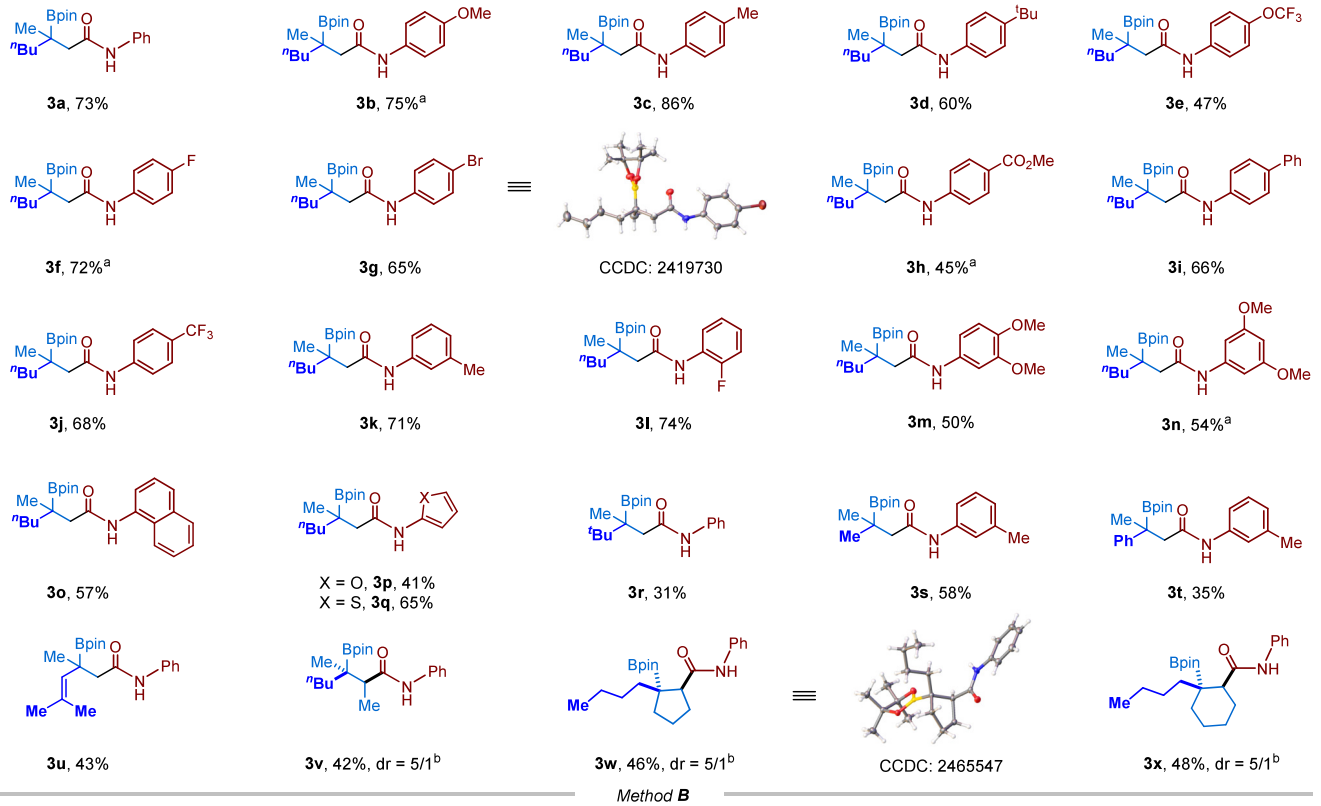
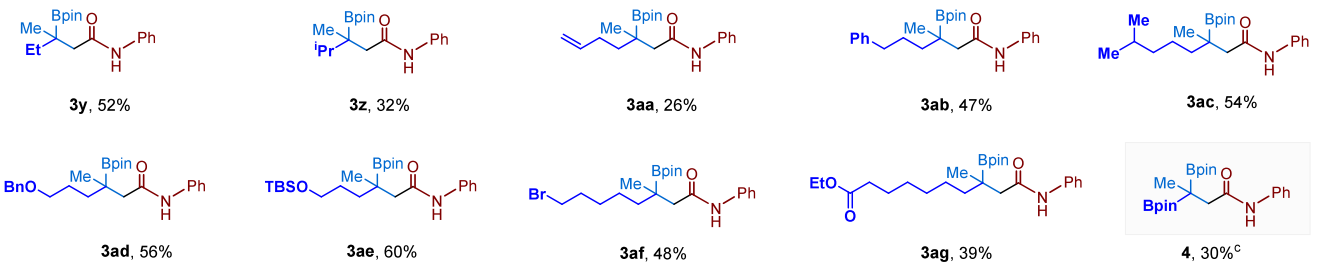
Scheme 2. Substrate Scope[d]



Method A



Method B



[a]Isolated yield after oxidation. [b]Dr was determined by ^{1}H NMR analysis. [c]B_2Pin_2 was used. [d]Reaction condition: **1** (0.3 mmol), **2** (0.75 mmol), 1,4-dioxane (2.0 mL), nitrogen atmosphere, 80 °C for 13 h, isolated yield.

coupling with dioxazolones and afforded the corresponding products with useful levels of reaction efficiency (**3af** and **3ag**). Lastly, it should be pointed out that the coupling of the boronate complex generated by B_2pin_2 and α-methyl vinylmagnesium bromide with dioxazolone also is effective, giving the amide **4** bearing a β-*gem*-diboron group.

To evaluate the practicability of this protocol, we successfully scaled up the preparation of compounds **3a** and **3k**, obtaining the corresponding products in 59% and 56% isolated yields, respectively (Scheme 3). These β-boryl amide products proved to be versatile intermediates for the preparation of useful scaffolds. Oxidation of the boron moiety enabled facile access to β-hydroxyl amide **5** in 85% yield, whereas chemoselective reduction of amide with $LiAlH_4$ gave γ-amino boronic ester **6** in 51% yield. N-Methylation of **3a** followed by Zweifel olefination efficiently furnished β-vinyl amide **8** in good yield. Additionally, treatment of amide **3a** with Lawesson's reagent provided the corresponding thioamide **9** in 56% yield.

To gain insight into the reaction process, we conducted several control experiments. As shown in Scheme 4, the addition of TEMPO to the reaction system did not decrease the reaction efficiency, which rules out the possibility of a radical pathway. When aryl isocyanate **10** was used as the amidating reagent, the desired product formed in 61% yield under the standard conditions. In contrast, alkyl isocyanate did

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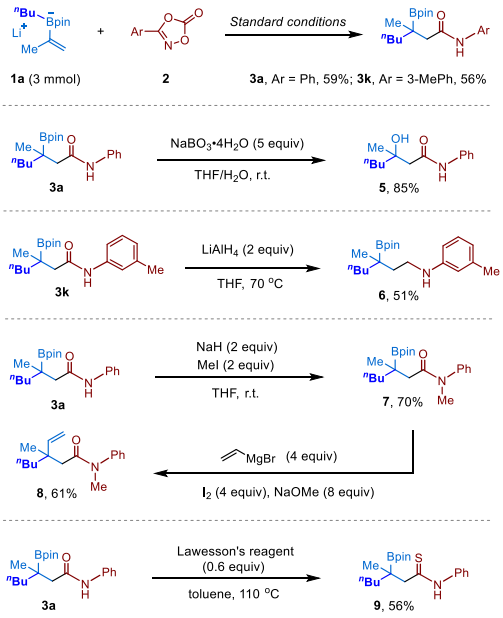
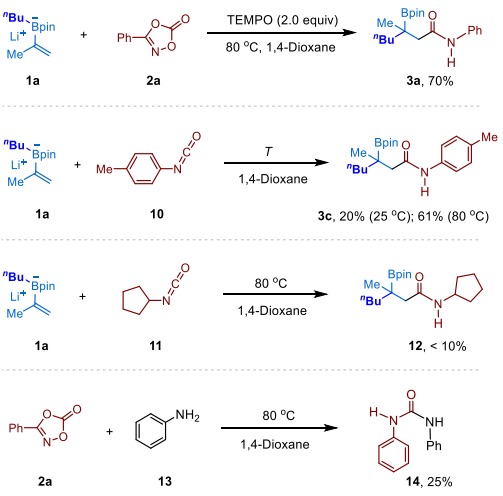
Scheme 3. Product Transformations



Scheme 4. Mechanistic Studies



not give any desired product, which accounts for the low reactivity of alkyl dioxazolones. In addition, aniline was subjected to the dioxazolone solution under the standard conditions, and the corresponding urea derivative was detected. All these experimental observations demonstrate that isocyanate may serve as a reactive intermediate in this transformation.

In summary, we have realized a dual 1,2-migration-induced amidation through a formal coupling of vinyl boronate complexes with dioxazolones, offering a rapid and green route for synthesizing multisubstituted β-boryl amides. This process displays several features, including metal-free conditions, bench-stable amidating reagents, as well as excellent substrate generality. Mechanistic studies support the presence of an isocyanate intermediate that is generated in situ from the Curtius-type rearrangement of dioxazolone. Moreover, the resulting borylated amides are highly synthetically useful precursors that might enable access to important biologically active compounds via the diverse post-transformations of boron and carbonyl groups.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c02107.

Experimental details, characterization of all new compounds, the X-ray crystal structure, computational results and NMR spectra (PDF)

Accession Codes

Deposition Numbers 2419730 and 2465547 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(20) *n*-Butylboronic acid pinacol ester was observed as a major side product at 100 °C, suggesting that the vinyl boronate complexes may undergo accelerated decomposition at higher temperatures.

(21) In some cases, alkyl boronic acid pinacol esters were formed as major side products, significantly reducing the yield of the desired products.

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