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# Single-Pot Access to Bisorganoborinates: Applications in Zweifel Olefination

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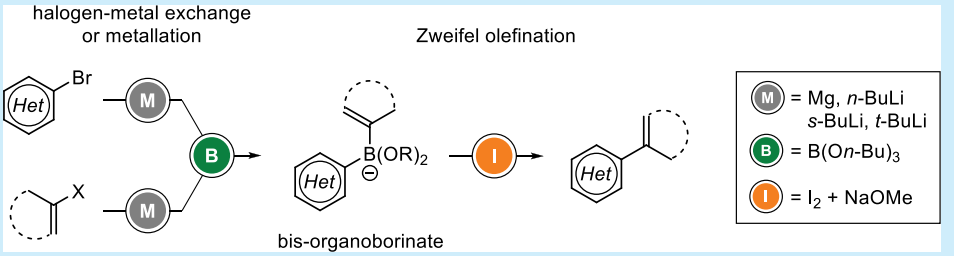
Supporting Information




**ABSTRACT:** Zweifel olefination is a catalyst-free reaction that serves alkene functionalization. While most methods employ commercially available boron pinacol esters, we have assembled a sequence in which the two partners of the formal coupling reaction are installed successively, starting from inexpensive boron alkoxides. The in situ formation of bisorganoborinates was accomplished by consecutive reaction of two different organometallic species. This single-pot procedure represents a great advancement in the generation of organoborinates and their involvement in C−C bond formation.

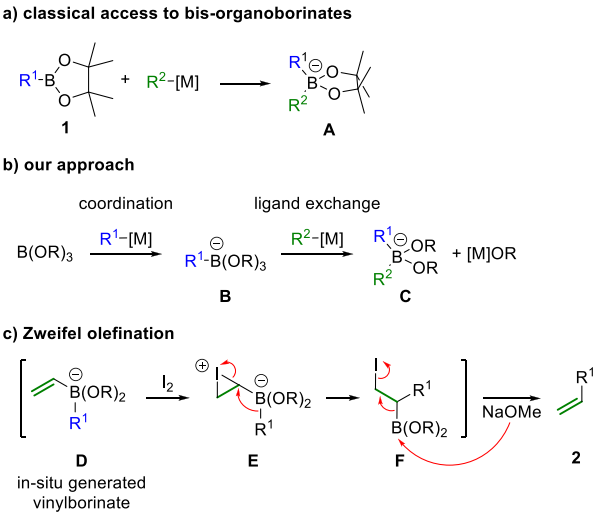
The use of boron in synthesis has spanned the community of organic chemists for a few decades. Boron-based reagents have been employed in quite a number of transformations such as stereo- and regioselective hydroborations,[1] highly functional group tolerant Suzuki cross-coupling reactions,[2] stereospecific homologations pioneered by Matteson,[3] and recently revisited by the group of Aggarwal,[4] and Zweifel olefinations.[5]

With dependable boron-related strategies in hand, we previously set out to tackle challenging strained ring-system syntheses. While boron homologations were employed to stereoselectively access alkylidenecyclobutanes[6] and cyclopropanes,[7] stable boronate complexes enabled the formation of scarcely described substituted cyclobutenes and 2-azetines.[8]

Although Zweifel olefination is an established transformation, for which we recently developed alternative organocerium reagents,[9] most reports describe the use of commercial organoboron pinacol esters **1**.[10] However, this strategy is currently limited by the availability of those reagents and their price. To overcome the need of using boron pinacol esters **1**, we thought of employing in situ generated trialkoxyorganoboronates **B** as intermediates for the formation of bisorganoborinates **C**, considering the pseudometallic character of boron to displace one of the alcoholate ligands (Scheme 1b).

Given that organoboronates **A** and **B** can be generated quantitatively by addition of boron alkoxides to organometallic species ($R^1$−[M]),[11] such a protocol would constitute a solid base as the first step in the in situ formation of bisorganoborinates **C**. With the possibility of performing a ligand exchange on the intermediate organoboronates, an economic alternative to the use of commercially available

**Scheme 1. Our Approach to Bisorganoborinates**[a]




[a]Counter-cations have been omitted for more clarity.

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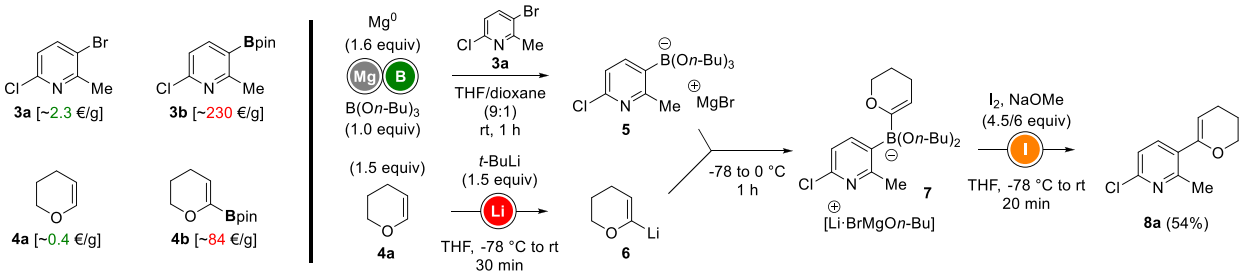
**Scheme 2. Proof of Concept: Coordination–Ligand Exchange–Zweifel Olefination Sequence**[11]




boron pinacol esters **1** (Scheme 1a) would be unlocked with inexpensive boron alkoxides.

In the Zweifel olefination, an alkenyl-organoborinate **D** (Scheme 1c) reacts with iodine, giving an intermediate iodonium species **E** that triggers a 1,2-metalate rearrangement toward the neutral compound **F**, upon which the addition of a base promotes a $\beta$-elimination that ultimately leads to the olefin **2**.[12] The efficient formation of **D** stands as a key step in this transformation. We describe herein a one-pot sequence toward alkenyl-organoborinates **D** and their subsequent involvement in Zweifel olefination reactions.

As a proof of concept, we envisioned the formation of a $Csp^2$–$Csp^2$ bond between a pyridine moiety **3** and a 3,4-dihydropyran **4** (Scheme 2).

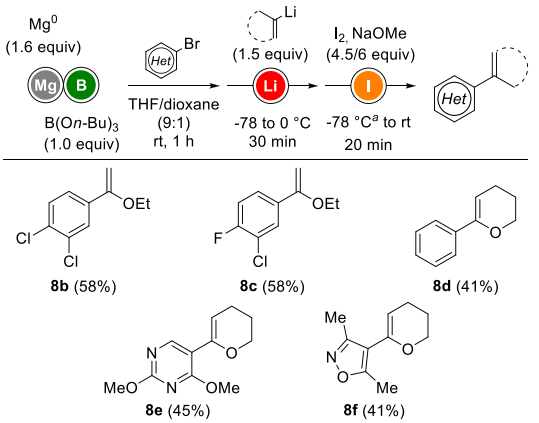
Via known strategies, the reaction requires the use of expensive boron pinacol esters (either **3b** or **4b**), while our method enables the use of cheaper substrates such as **3a** and **4a**. The intermediate 3-pyridylboronate **5** is generated by adding **3a** to a suspension of magnesium in the presence of boron *n*-butoxide (0.15 €/g),[11c,13] the reaction proceeding through metal insertion followed by coordination to the boron atom at room temperature. The presence of dioxane during this step proved to be essential to avoid formation of undesired boron species.[14,15] An ex-situ prepared solution of (3,4-dihydro-2*H*-pyran-6-yl)lithium **6**[16] is added to perform the ligand exchange, releasing an equivalent of butylate salt and giving access to the alkenylborinate **7** (Scheme 2). The intramolecular alkenylation proceeds upon addition of iodine, furnishing the heterocyclic compound **8a** in 54% yield.

As described by the group of Aggarwal,[5g] no excessive amount of alkenyllithium reagent was required for full consumption of the intermediate trialkoxyboronate as shown by $^{11}B$ NMR measurements.[15]

With a proof of concept in hand, we started exploring the in situ formation of bisorganoborinates through magnesium insertion/trapping reaction and further ligand exchange with alkenyllithium. Reasonable yields were obtained for insertions onto aromatic and heteroaromatic derivatives, in combination with acyclic (**8b–c**) and cyclic (**8d–f**) alkenyl ethers (Scheme 3).

However, when the ligand exchange of the second step was performed using organomagnesium reagents, an excess of the latter was required for the Zweifel product to be obtained with maximum efficiency. Three equivalents were needed in order to generate a proposed tetrakis–organoboron complex containing three alkenyl groups. $^{11}B$ NMR studies also demonstrated that the intermediate organoboronate species such as **B** (Scheme 1b) would remain unconsumed with lower excesses of organomagnesium reagents.[14] The boron-relayed room-temperature magnesium insertion/trapping reaction was performed on a wide range of aryl and heteroaryl bromides and

**Scheme 3. Mg Insertion/Ligand Exchange with Alkenyllithium Reagents/Zweifel Olefination Sequence**[a]




[a]Conducting the addition of iodine at 0 °C resulted in lower yields.

followed by exchanges of alkoxide ligands with alkenylmagnesium species (Scheme 4). The scope of the reaction was evaluated with vinyl (**9a–f**), isopropenyl (**9g–q**), and $\alpha$-styrylmagnesium reagents (**9r–v**) in 45 to 89% yield. Interestingly, valuable heteroaromatic derivatives were successfully engaged in this procedure, affording sophisticated structures such as alkenyl pyrazole **9q** (50%) or pyrimidines **9n**, **9s**, and **9v** (48 to 74%).

Next, we envisioned that a Br/Li exchange (instead of Mg insertion) as a first step could be used in the formation of intermediate organoboronates (Scheme 5). *n*-Butyllithium was introduced at −78 °C on different aryl bromides, and—after formation of the organoboronate species via addition of boron butylate—the sequence was continued as above, with further introduction of 3 equiv of ex situ generated alkenylmagnesium stock solutions.

Phenanthryl, naphthyl, and carbazolyl substrates led to olefins **10a–c** in good yields up to 80%, validating the process to work with a first step of organolithium addition. The transformation being quite efficient, we pushed the challenge further and set out to perform a double, yet unprecedented Zweifel olefination on bisbrominated substrates. Double Br/Li exchange was undertaken using 2 equiv of *n*-BuLi at −78 °C. Twice the amount of further reagents was subsequently needed to drive the reaction to completion, affording bisolefinated products **10d–f** in good yields (up to 63%).

In consideration of previous results, it was expected that a procedure using sequentially two organolithium reagents would lead to desired products, and compounds **11a** and **b** were isolated in moderate yields (Scheme 6). Importantly, such a protocol allowed us to use 2 equiv of the same olefin to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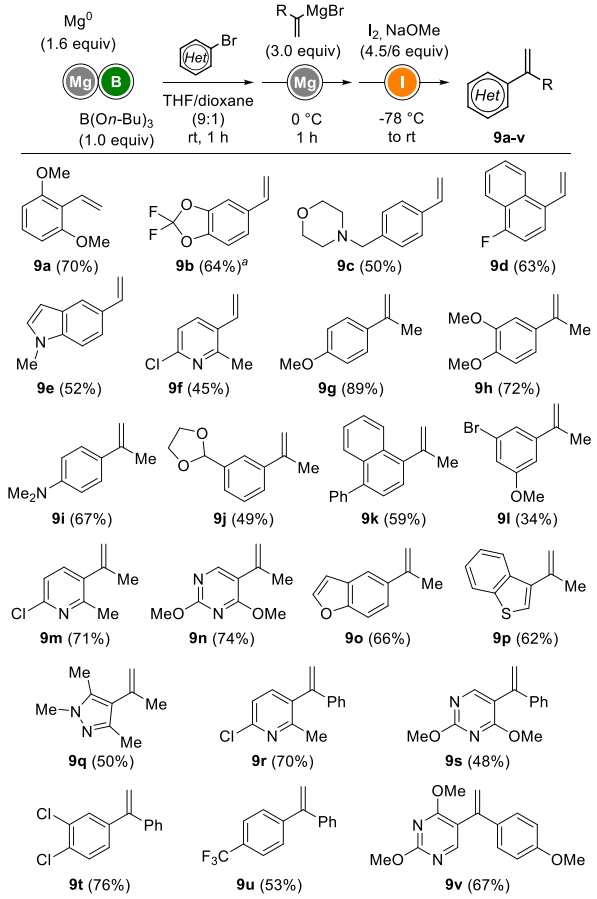
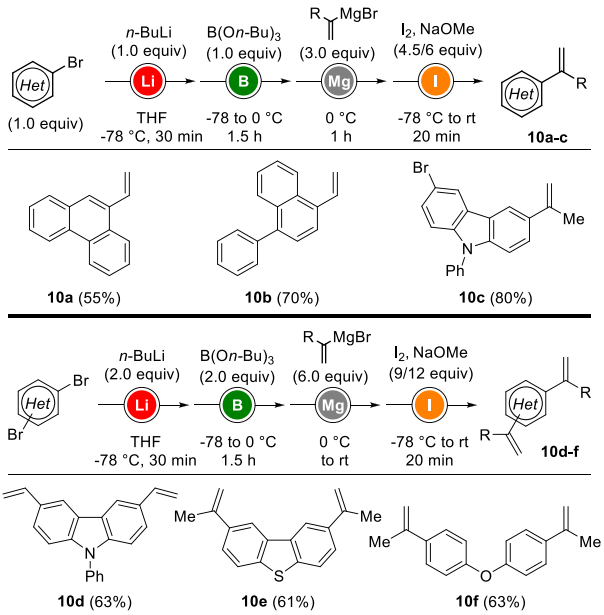
**Scheme 4. Mg Insertion/Ligand Exchange with Alkenylmagnesium Reagents/Zweifel Olefination Sequence**



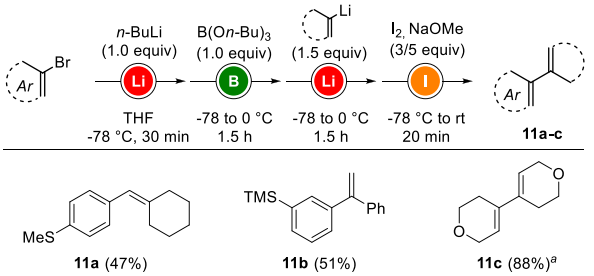

[a]Yield was determined by $^{19}F$ NMR vs $C_6F_6$ as internal standard.

**Scheme 5. Br/Li Exchange/Ligand Exchange with Alkenylmagnesium Reagents/Zweifel Olefination Sequence**




undergo formal dimerization (**11c**) in 88% yield, opening an efficient route toward functionalized dienes.

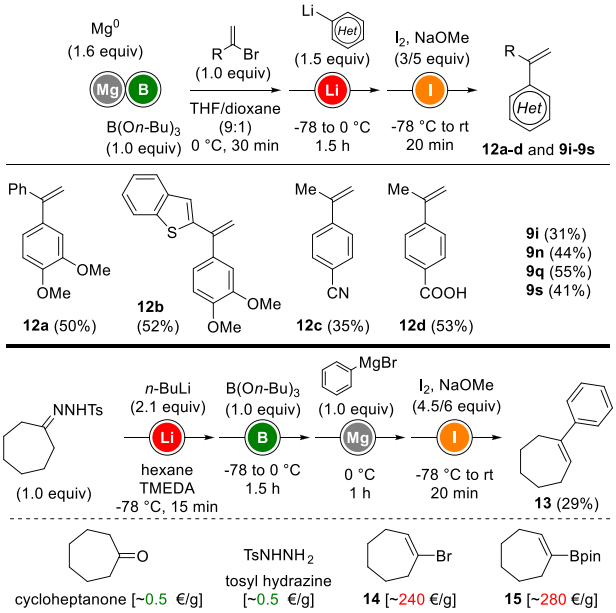
**Scheme 6. Br/Li Exchange/Ligand Exchange with Alkenyllithium Reagents/Zweifel Olefination Sequence**




[a]**11c** was made from 4-(3,6-dihydro-2*H*-pyran)yllithium and 0.5 equiv of B(O*n*-Bu)$_3$ (see SI).

We finally explored the possibility of an inverse procedure in which the alkenyl group would be introduced in the first step (Scheme 7). In this case, considerable savings of alkenylmagnesium reagent—previously required in excess—would be achieved. Such a challenge was undertaken by generating an alkenylboronate from the corresponding alkenyl bromide, in the presence of magnesium and boron *n*-butoxide. An aryllithium species was then added (1.5 equiv), followed by iodine and sodium methoxide. This procedure allowed for the formation of *gem*-bisarylated alkenes **12a** and **b** in moderate yields.

**Scheme 7. Zweifel Olefinations with In Situ Generated Alkenylboronates[11]**




In addition, this reverse alternative provides an access to compounds that could not be obtained via previous routes, such as the nitrile derivative **12c** (35%). A challenging unprotected carboxylic acid was also engaged in in the second step of the olefination reaction. In this case, 2 equiv of *n*-BuLi was used: one to deprotonate the carboxylic acid and one to perform a halogen−metal exchange. **12d** was obtained in 53% yield. To push the methodology further, we employed a Shapiro rearrangement to produce an alkenyllithium reagent to be engaged in the Zweifel olefination. Cycloheptanyl hydrazone was chosen as a representative example, as classical



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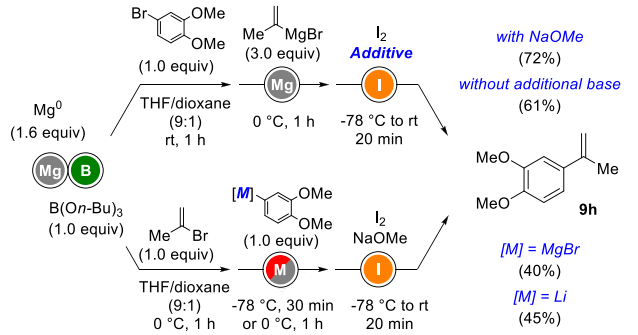
alternatives would require expensive starting materials such as 1-cycloheptenyl bromide **14** or boron pinacol ester **15**. Even though **13** was obtained in 29% yield, only inexpensive cycloheptanone and tosylhydrazine were needed as substrates in this multistep one-pot sequence.

We have shown that different transition-metal-free paths can be taken to synthesize arylated olefins without the need of purchasing expensive boron pinacol esters. In Scheme 8, we summarize and compare some of these methods, having an in situ magnesium insertion/trapping reaction as the first step. Employing classical conditions described in Scheme 4 afforded **9h** in 72% yield.

**Scheme 8. Comparison of Different Methods to Access 9h**




Importantly, when performing the ligand exchange in the second step on the intermediate organoboronate, magnesium butoxide (*n*-BuOMgBr) is released in the reaction mixture, and we hypothesized that this alcoholate could be used as the required base in the elimination step. Avoiding the addition of sodium methanolate confirmed this hypothesis, as **9h** was isolated in 61% yield. Alternatively, the first insertion step could be performed on the alkenyl part, preventing the use of an excessive amount of the corresponding Grignard reagent in the second step. Similar yields were obtained using either arylmagnesium or aryllithium species (40−45%).

In conclusion, we have demonstrated that a stoichiometrically controlled generation of hetero bisorganoborinates could be turned into a powerful tool for C−C bond formation. By unlocking new and complementary paths toward diversely substituted boron species, a wide array of functionalized olefins were developed, employing inexpensive substrates and reagents in combination with catalyst-free Zweifel conditions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00493.

Experimental procedures and characterization (IR, HRMS, and $^{1}H$ and $^{13}C$ NMR data) for all new compounds (PDF)

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### Author Contributions

†A.M. and A.N.B. contributed equally.

### Notes

The authors declare no competing financial interest.

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