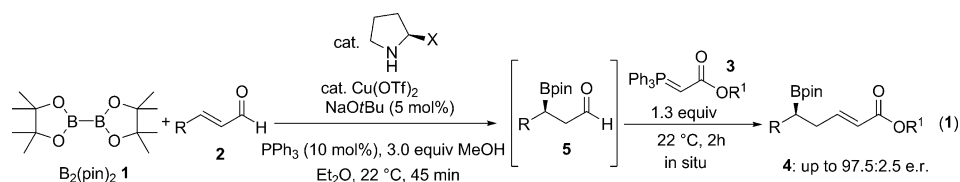


One-Pot Three-Component Highly Selective Synthesis of Homoallylboronates by Using Metal-Free Catalysis

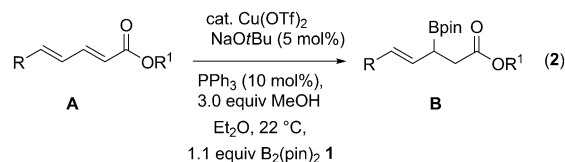
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The development of catalytic multicomponent and tandem reactions that involve the formation of C–C and C–heteroatom bonds in one-pot is an important research field within organic synthesis.^[1] These types of transformations serve as versatile tools for constructing valuable molecules as well as reducing multiple isolation steps, generation of waste, and solvents. In this context, the catalytic Petasis reaction, which is the multicomponent transformation between an aldehyde, an amine, and a vinyl or aryl boron reagent, is a very useful reaction for the synthesis of functional amines.^[2] Moreover, organoboron compounds such as homoallyl- and allylboronates represent valuable synthetic organic intermediates and has received significant attention in chemical synthesis.^[3] For example, homoallyl-^[3k–n] and allylboronates are useful nucleophiles and important starting materials for the synthesis of alcohols and amines by addition to aldehydes and imines, respectively.^[3b–c] Thus, the development of efficient catalytic methods for the synthesis of boron-containing compounds is an important research field in chemical synthesis.^[4,5] In this context, the metal-catalyzed conjugate addition of diborons to electron-deficient olefins is one of the dominated methods for the synthesis of chiral organoboron compounds.^[3k,5–8] The development of metal-free methodologies is an important task in organic synthesis.^[9] On the other hand metal-free boron additions to electron-deficient

alkenes are rare. In pioneering work, Hoveyda and co-workers first disclosed the metal-free catalytic β -boration of α,β -unsaturated ketones and esters.^[10] Later Fernández reported another metal-free system for this transformation.^[11] However, the metal-free catalytic conjugate borane addition to enals has not been reported. In this context, we recently disclosed a catalytic one-pot three-component enantioselective homoallylborane synthesis aided by a combination of copper and chiral amine catalysts [reaction (1)].^[12]



This one-pot three-component reaction between bis(pinacolato)diboron ($B_2(\text{pin})_2$) **1**, enals **2**, and Wittig compounds **3** is an alternative for a possible selective 1,6-addition of **1** to **A** to give homoallylboranes **4**. However, the direct copper-catalyzed addition of **1** to 2,4-dienoate esters **A** gives exclusively the 1,4-addition products **B** [reaction (2)].^[12]



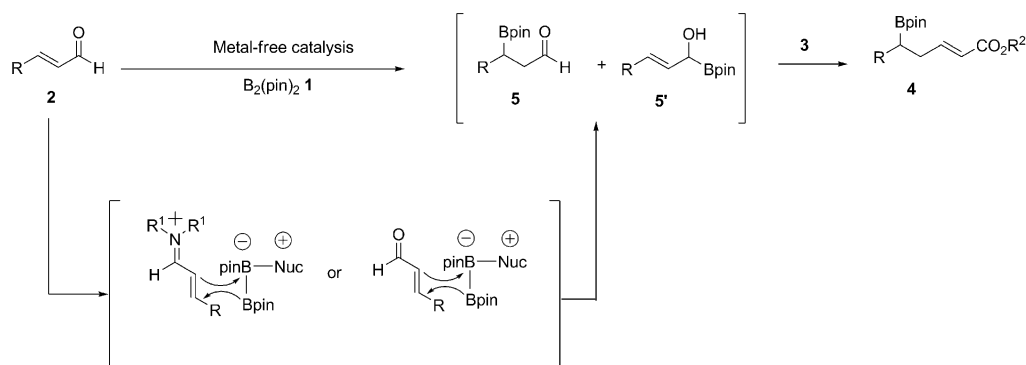
Based on the importance of development of metal-free technologies and our research interest in this field, we wanted to investigate and develop a metal-free version of the one-pot three-component reaction between bis(pinacolato)diboron ($B_2(\text{pin})_2$) **1**, α,β -unsaturated aldehydes **2**, and 2-(triphenylphosphoranylidene)acetate esters **3** (Scheme 1). However, the catalytic β -boration of enals **2** can either undergo 1,4-addition or 1,2-addition to form **5** or **5'**, respectively (Scheme 1). High 1,4-selectivity had to be acquired to achieve a useful protocol for the one-pot three-component synthesis of homoallylboranes **4**. We envisioned that this could be possible by using a small organic nucleophile (e.g., N-heterocyclic carbene (NHC), PPh_3 and amine) for the activation of the B–B bond of **1** towards conjugate boron addition to α,β -unsaturated aldehydes **2** (nucleophilic activation).^[10,11] In addition, it could be possible to improve the

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Scheme 1.

rate and selectivity of the 1,4-addition step by merging this activation mode with catalytic iminium activation (Scheme 1).^[12,13]

Herein we disclose a highly regioselective metal-free catalytic synthesis of homoallylboranes **4** by using N-heterocyclic carbenes (NHC) and amines as catalysts.

In initial experiments, we found that it was important to have a bulky amine (e.g., **6a**) as a catalyst for the copper co-catalyzed β -boration of enal **2a** to achieve high 1,4-selectivity (see the Supporting Information). Thus, we began the investigation of the metal-free β -boration of **2a** using racemic **6a** as the catalyst (Table 1).

The **6a**^[14]-catalyzed boron conjugate additions proceeded with high conversion and gave the corresponding Michael product **5a** and **5a'** in a ratio of up to 75:25 (Table 1, entries 1 and 2). To our delight, we found that we were able to significantly improve the 1,4-selectivity (95:5) and reactivity of the amine **6a**-catalyzed β -boration of **2a** when heterocyclic salt **7a** was chosen as the NHC pre-co-catalyst (Table 1, entries 3 and 4). In fact, this was the most efficient catalytic system. However, removing the amine **6a** and just having the NHC **7a'** as the catalyst did not significantly decrease the reaction rate and the 1,4-selectivity was unaffected (Table 1, entry 3). Thus, we also decided to probe the use of N-heterocyclic salts (catalysts **7b** and **7c**) as pre-catalysts for the β -boration of **2a** without the presence of **6a** (Table 1, entries 7 and 8). However, the 1,2-addition product **5a'** was formed in a 1:1 ratio as compared to the Michael product **5a**. The use of phosphine **7d** as the catalyst gave higher 1,4-selectivity under certain reaction conditions (**5a/5a'** 85:15; Table 1, entry 9). We also observed that the 1,4-selectivity was temperature dependent (Table 1, entries 11 and 12). Lowering the catalyst loading of **7a** to 5 and 1 mol%, respectively, decreased the rate and conversion of these reactions (Table 1, entries 13 and 14). Simple bases such as KO t Bu and Cs₂CO₃ could also promote the β -boration transformation, however the 1,4/1,2-selectivity was 64:36

Table 1. Metal-free catalytic β -boration of **2a**.^[a]

Entry	7	Base	<i>t</i> [h]	Conv. [%] ^[b]	5a/5a' ^[b]
1	–	KO t Bu	1	90	65:35
2	–	Cs ₂ CO ₃	2	70	75:25
3	7a	KO t Bu	0.75	99	95:5
4	7a	Cs ₂ CO ₃	0.75	99	95:5
5 ^[c]	7a	KO t Bu	1	95	95:5
6 ^[c]	7a	Cs ₂ CO ₃	1	90	95:5
7 ^[c]	7b	KO t Bu	0.33	98	50:50
8 ^[c]	7c	KO t Bu	0.33	98	50:50
9 ^[c]	7d	KO t Bu	1	62	85:15
10 ^[c]	7d	Cs ₂ CO ₃	4	45	50:50
11 ^[c,d]	7a	KO t Bu	1	50	75:25
12 ^[c,e]	7a	KO t Bu	18	17	50:50
13 ^[c,f]	7a	KO t Bu	12	35	95:5
14 ^[c,g]	7a	KO t Bu	24	35	95:5
15 ^[c]	–	KO t Bu	2	90	64:36
16 ^[c]	–	KO t Bu	1	56	80:20

[a] Under N₂ atmosphere, **6a** (20 mol%), **7** (10 mol%), KO t Bu (35 mol%), 70°C.

[b] Conversion to aldehyde **5a** as determined by the ¹H NMR spectra of the crude reaction mixture. [c] Reaction performed without **6a**. [d] At 50°C. [e] At 22°C.

[f] 5 mol% of **7a**. [g] 1 mol% of **7a**. Pin = pinacolato.

and 80:20, respectively (Table 1, entries 15 and 16). Notably, the catalytic metal-free addition of **1** to **A1** did not exhibit regioselectivity and **4a** and **B1** was formed in a 1:1 ratio [reaction (3)].

With these results in hand, we decided to probe the scope of the one-pot, three-component catalytic metal-free reaction between **1**, enals **2**, and Wittig reagents **3** by using the

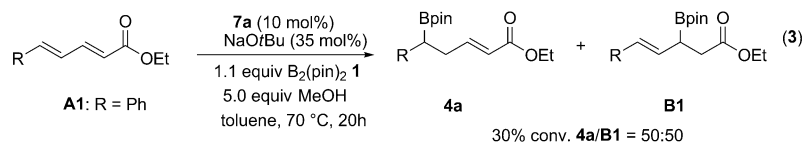
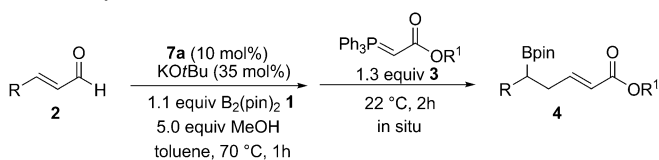


Table 2. Metal-free NHC-catalyzed one-pot three-component synthesis of homoallylboronates **4**.^[a]



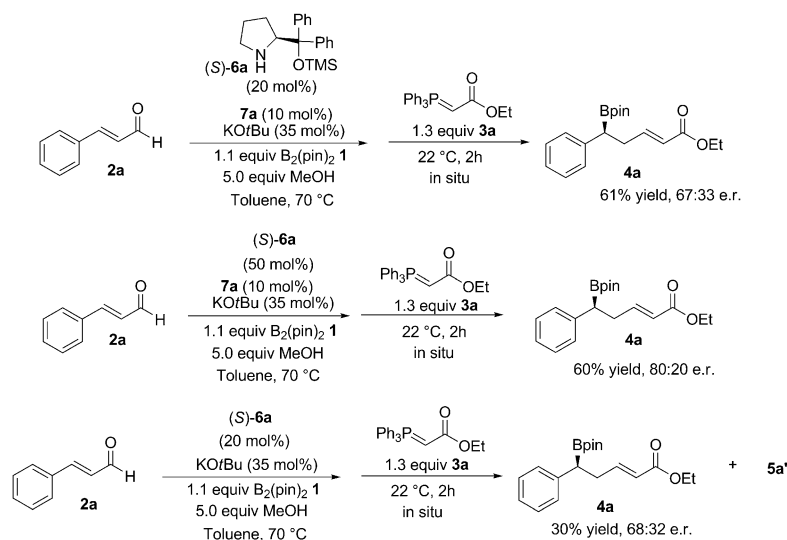
Entry	R	R ¹	Product	Yield [%] ^[b]	5a/5a' ^[c]
1 ^[d]	Ph	Et	4a	61	95:5
2	Ph	Et	4a	60	95:5
3	Ph	Me	4b	61	95:5
4	4-MeC ₆ H ₄	Et	4c	60	95:5
5	4-MeC ₆ H ₄	Me	4d	61	95:5
6 ^[e]	4-ClC ₆ H ₄	Et	4e	60	97:3
7 ^[e]	4-BrC ₆ H ₄	Et	4f	60	97:3
8 ^[e]	4-FC ₆ H ₄	Et	4g	59	97:3
9 ^[f]	<i>n</i> Pr	Et	4h	61	90:10
10 ^[f]	<i>n</i> Bu	Et	4i	62	90:10
11 ^[f]	Et	Et	4j	61	90:10
12 ^[f,g]	Me	Et	4k	60	90:10

[a] i) N₂ atm, **7a** (10 mol%), KOtBu (35 mol%), MeOH (5.0 equiv.), 70 °C, 1 h. ii) **3** (1.3 equiv.), 2 h. [b] Isolated product yield after column chromatography of pure **4**. [c] The ratio of **5:5'** was determined by ¹H NMR analysis of the crude reaction mixture after the initial conjugate addition step. [d] In the presence of **6a** (20 mol%). [e] i) N₂ atm, **7a** (10 mol%), KOtBu (35 mol%), MeOH (5 equiv.), 70 °C, 30 min; ii) **3** (1.3 equiv.), 2 h. [f] i) N₂ atm, **7a** (10 mol%), NaOtBu (35 mol%), MeOH (5.0 equiv.), 70 °C, 2.0 h; ii) **3** (1.3 equiv.), 2 h. [g] **2k** (3 equiv.).

imidazolium salt **7a** as the pre-catalyst, KOtBu (35 mol%) as the base and MeOH (5 equiv) in toluene (Table 2). The reactions were also performed with or without amine **6a** as the co-catalyst.

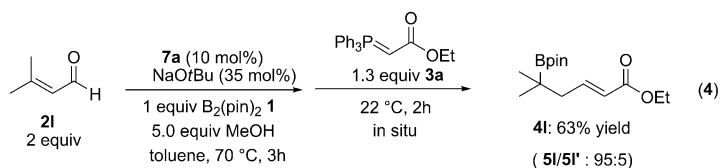
We found that the corresponding homoallylboronates **4** could be synthesized in good yields with high 1,4-selectivity (90:10–97:3) by using the catalytic β-boration/Wittig tandem reaction. The use of amine **6a** as the co-catalyst improved the reaction rate; however, the yields of the homoallylboronates **4** were similar to those in which it was omitted from the reaction (Table 2, entries 1 and 2). This is probably due to that the intermediate aldehyde **5** decomposes during the Wittig step giving back the enal **2**,

Scheme 2. Reactions with (*S*)-**6a**.

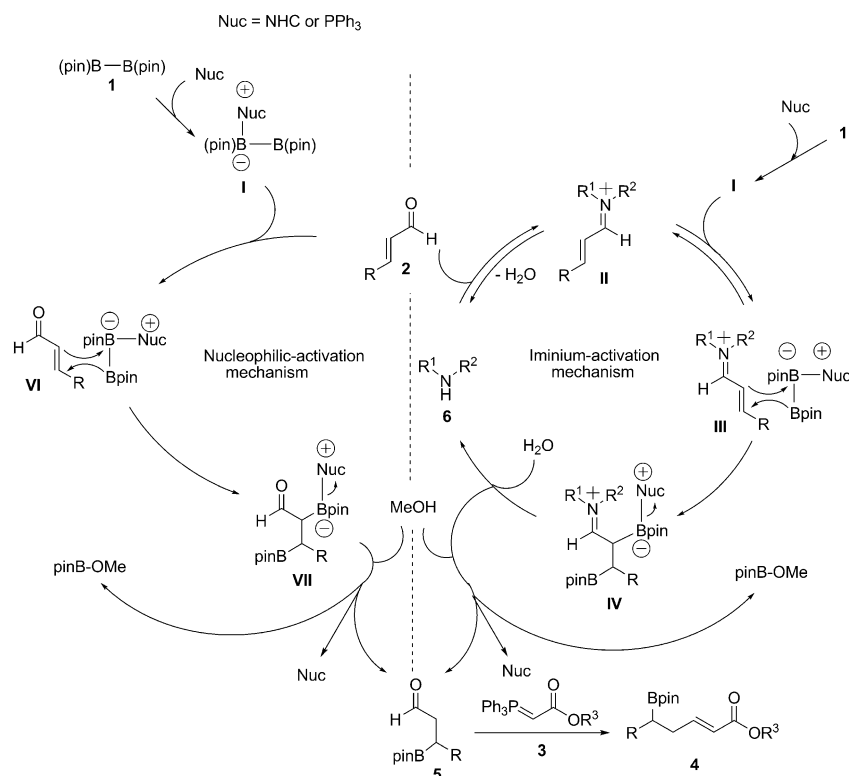


which also reacted to give dienal **A** as a side product. The metal-free transformation tolerated both β-aryl- and aliphatic-substituted enals **2** as the acceptor component. For example, homoallylborane **4i** was

formed in 62% yield (Table 2, entry 10). It is noteworthy that the one-pot three-component co-catalytic metal-free β-boration/Wittig cascade reaction was able to deliver homoallylboronates **4** with a quaternary-substituted carbon atom [reaction (4)], thus giving access to tertiary homoallylalcohols and amines.



We next decided to investigate if iminium intermediates were present during the amine **6a**-catalyzed β-borations (Scheme 2). This was indicated by the observed rate acceleration when **6a** was used as the catalyst or co-catalyst as described earlier. The HRMS and ¹H NMR spectroscopic analysis of the crude reaction mixtures confirmed the presence of iminium intermediates during these reaction conditions.^[15] In preliminary mechanistic studies, the one-pot three-component catalytic metal-free reactions using enantiomerically pure (*S*)-**6a** (20 mol%) as the catalyst and enal **2a** as the aldehyde component were investigated (Scheme 2). The **6a**-catalyzed metal-free one-pot three-component β-boration/Wittig cascade reaction between **1**, **2a**, and **3a** gave the corresponding enantioenriched homoallylborane (*S*)-**4a** with up to 68:32 enantiomer ratio (e.r., Scheme 2).^[16] It is noteworthy that when the catalyst loading of (*S*)-**6a** was increased to 50 mol% the corresponding homoallylborane (*S*)-**4a** was



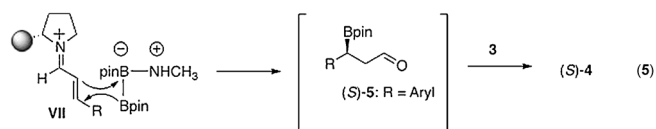
Scheme 3. Proposed reaction mechanism for the metal-free one-pot three-component synthesis of homoallylboranes **4**.

isolated in 60% yield with 80:20 e.r. (Scheme 2). This indicates that a non-enantioselective background reaction reduced the e.r. of **4a** at lower loadings of chiral catalyst **6a**.

The above results together with the HRMS demonstrate that iminium activation is part of the catalytic cycle when amines **6** are present. Thus, we propose the following catalytic mechanism for the formation of homoallylboronates **4** through β -boryl aldehydes **5**, which proceeds by simultaneous nucleophilic and iminium activation pathways when amines **6** and NHC **7'** were used as co-catalysts (Scheme 3).

The base generated NHC catalyst **7a'** will interact with the diboron reagent **1** to form intermediate **I**, which increases the nucleophilicity of the unassociated boron as shown by Hoveyda et al.^[10] Next, the nucleophilic species **I** will either directly attack the enal **2** or the in-situ-generated iminium intermediate **II** to generate species **VI** or **IV**, respectively, via **V** and **III**. Subsequent, hydrolysis and methanolysis will regenerate the amine **6** and NHC **7'** co-catalysts, respectively, and form the β -borylaldehyde **5**. Finally, the Wittig reaction between **3** and **5** will give the corresponding homoallylborane **4**. The stereochemical outcome of the reaction performed with (*S*)-**6a** as the co-catalyst can be explained by a *Re*-facial attack of **I** to iminium intermediate **VII**, which leads to the formation of (*S*)-**4** via (*S*)-**5** [reaction (5)]. This is in accordance with the transition-state theory of chiral amine **6a** and copper co-catalyzed β -boration and silylations, which proceed through iminium activation.^[12]

In summary, we have developed the first metal-free one-pot three-component catalytic selective reaction between a diboron reagent, α,β -unsaturated aldehydes, and 2-(triphenylphosphoranylidene)acetate esters. The multicomponent reactions proceed with high chemo- and regioselectivity through a catalytic β -boration/Wittig sequence, which gives the corresponding homoallylboronates in good yields by using simple bench-stable N-heterocyclic carbenes and amines as catalysts. In addition, a novel merging of the catalytic cycles of NHC nucleophilic activation of diboron reagents and amine-catalyzed iminium activation of enals was disclosed. Further development of this type of one-pot multicomponent catalytic reactions, enantioselective variants, and its application in total synthesis is ongoing in our laboratories.^[17]



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Keywords: aldehydes • boron • conjugate addition • multicomponent reactions • organocatalysis

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