Synthetic Methods

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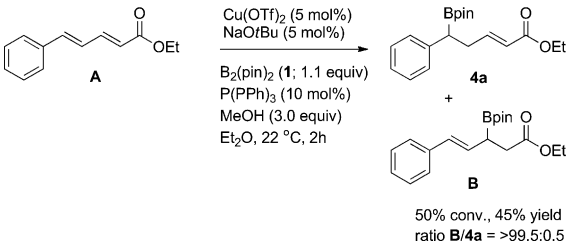
One-Pot Three-Component Catalytic Enantioselective Synthesis of Homoallylboronates**

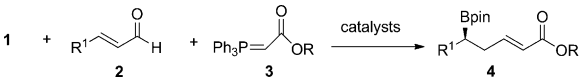
Ismail Ibrahem, Palle Breistein, and Armando Córdova**

The synthesis of enantioenriched α-chiral organoboron compounds has received significant attention in chemical synthesis because the C–B bond can be converted into C–O, C–N, and C–C bonds in a stereospecific fashion.[1] Thus, the design of efficient catalytic protocols for asymmetric synthesis of boron-containing compounds is of utmost interest for organic synthesis.[2,3] In this context, homoallyl- and allylboronates are highly useful since additional derivatization using the alkene moiety as well as the boron group gives rapid access to multifunctional chiral compounds. They can also be used as chiral nucleophiles for additions to either aldehydes and ketones, or imines to give the corresponding alcohols or amines, respectively.[1b1] The metal-mediated enantioselective hydroboration of alkenes is an important method for the preparation of chiral organoboron compounds.[3] With respect to the synthesis of enantioenriched homoallylboronates, Ito and co-workers disclosed an elegant protocol for the synthesis of enantioenriched cyclic homoallylboronates by copper-catalyzed regioselective asymmetric monoborylation of 1,3-dienes using bis(pinacolato) diboron (B_2pin_2; **1**).[4] B_2pin_2 (**1**) has also been successfully employed as the boryl reagent in chiral copper phosphine complexes[5] or bidentate N-hetrocyclic carbene copper complexes to catalyze[6] enantioselective conjugate additions to α,β-unsaturated carbonyl compounds, alkenes, alkynes, and dienes. However, the regioselective and enantioselective 1,6-addition of **1** to 2,4-dienaote esters such as **A** to give the corresponding homoallylboranes **4** has, to the best of our knowledge, not been disclosed (see Eq. (1) for structures).[7] This reaction is challenging and is more likely to render the 1,4-addition product **B** or a mixture of both compounds. In fact, performing the copper-catalyzed addition of **1** to phenyl-2,4-dienaote **A** using PPh_3 (**7a**) as the ligand gave exclusively the 1,4-addition product **B** after 2 hours (50% conv., 45% yield) [Eq. (1)].



(1)

Multicomponent reactions that involve the formation of multiple C–C and carbon–heteroatom bonds in a highly chemo- and stereoselective fashion in one pot is an important research field within chemical synthesis. In particular, the development of catalytic asymmetric multicomponent reactions is a difficult task.[8] Based on the importance of discovering new enantioselective multicomponent reactions, we envisioned an alternative route to the enantioenriched homoallylboronates **4** by a one-pot catalytic asymmetric borane conjugate addition/Wittig reaction sequence using **1**, the α,β-unsaturated aldehydes **2**, and 2-(triphenylphosphoranylidene)acetate esters **3** [Eq. (2)].



(2)

The key to success for the one-pot synthesis of the homoallylboranes **4** is the ability to control and develop the challenging catalytic enantioselective β-boration step of the enal component **2** to give the corresponding enantioenriched β-boryl aldehyde intermediate **5** prior to the Wittig step (Scheme 1). However, this type of transformation can be plagued by 1,2-addition to give the product **5'** as well.[8] In this context, our previous research has shown that it is possible to achieve highly selective conjugate additions of silyl[10a] and carbon nucleophiles (organozinc reagents)[10b] to enals **2** by combining transition-metal and aminocatalysts.[10–13] Thus, retrocatalytic analysis suggests that the ability of a chiral amine to lower the LUMO of the enal component **2** by iminium activation[14] in combination with copper-catalyzed conjugate addition[15] of the Bpin to this intermediate may favor enantioselective 1,4-addition over 1,2-addition to predominantly give the intermediate **5** (Scheme 1). Its subsequent Wittig reaction with **3** would give the enantioenriched homoallylicboronate product **4**.

[*] Prof. Dr. I. Ibrahem, P. Breistein, Prof. Dr. A. Córdova
Department of Natural Sciences, Engineering and Mathematics
Mid Sweden University, SE-851 70 Sundsvall (Sweden)
E-mail: ismail.ibrahem@miun.se
armando.cordova@miun.se
Prof. Dr. A. Córdova
Department of Organic Chemistry, The Arrhenius Laboratory
Stockholm University (Sweden)
E-mail: acordova@organ.su.se
Prof. Dr. A. Córdova
The Berzelii Center EXSELENT, Stockholm University (Sweden)

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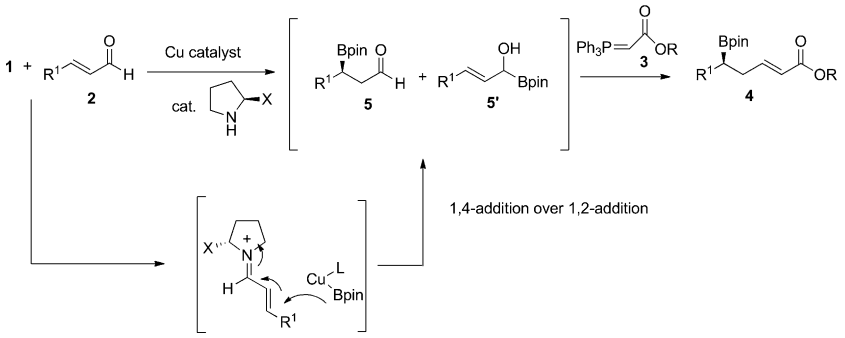
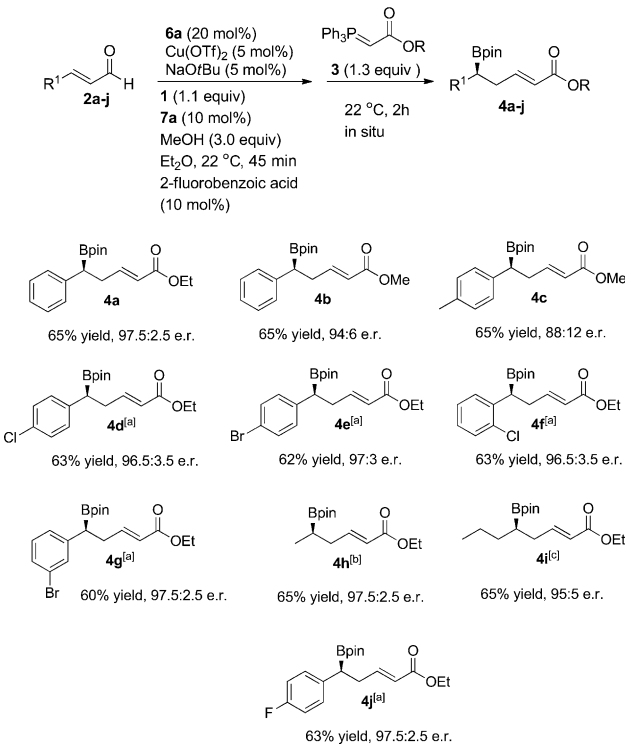


Scheme 1. Proposed reaction sequence. L = ligand.

Herein we disclose the unprecedented one-pot three-component enantioselective catalytic reaction between **1**, α,β-unsaturated aldehydes, and (triphenylphosphoranylidene)-acetate esters, thereby giving the corresponding homoallylborane products in good yields and up to 97.5:2.5 e.r. This method employs readily available transition metals and chiral amines as co-catalysts.

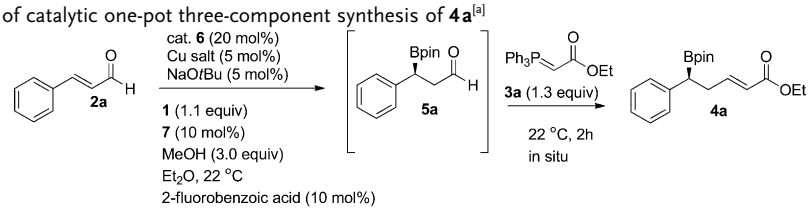
We began our investigation by studying the catalytic one-pot three-component reaction between **1**, cinnamic aldehyde (**2a**), and the phosphorane **3a** using different copper salts, chiral amines (**6**), and phosphine ligands (**7**). Key results are shown in Table 1. We found that performing the one-pot reaction without the use of a chiral amine catalyst (**6**) gave low 1,4-selectivity in the initial β boration of the enal **2a**, which gave both racemic aldehyde **5a** and **5a′** in a 67:33 ratio as determined by ^{1}H NMR analysis of the crude reaction mixture prior to the addition of the Wittig reagent **7a** (entry 1). The reaction without the copper(II) triflate ($Cu(OTf)_2$) catalyst but in the presence of the chiral amine **6a** gave a small amount (< 2% conv.) of **5a** (entry 2). To our delight, the homoallylicboronate **4a** was assembled in an asymmetric fashion when commercially available chiral amines **6a**–**6d** were used as catalysts in combination with $Cu(OTf)_2$ (5 mol%) as the transition-metal co-catalyst and Ar_3P (**7**) as the ligand in diethyl ether at 22°C. MeOH (3 equiv) was added to maintain the copper-catalyzed activation of the borane reagent **1**. It is noteworthy that we were able to isolate the aldehyde **5a** intermediate (the e.r. could only be determined after conversion of **5a** into **4a**). However, it was hard to purify since it decomposes (e.g., elimination) during silica gel column chromatography to give the starting enal **2a**, which has the same R_f value. The addition of an organic acid additive leads to significant improvement of both the 1,4- and enantioselectivity of the asymmetric β-boration step (entries 7 and 9). In fact, only β boration occurred when 2-fluorobenzoic acid was used as the additive. Thus, the protic acid additive accelerated the catalytic cycle of the iminium formation and as a consequence the chemoselectivity was directed towards 1,4-addition. Of the investigated chiral amines **6**, the highest reactivity and enantioselectivity of the B–C bond-forming step was achieved when the chiral amine **6a**[16] was employed as the catalyst and the corresponding homoallylicboronate product **4a** was isolated in 65% yield with 97.5:2.5 e.r. (entry 7).

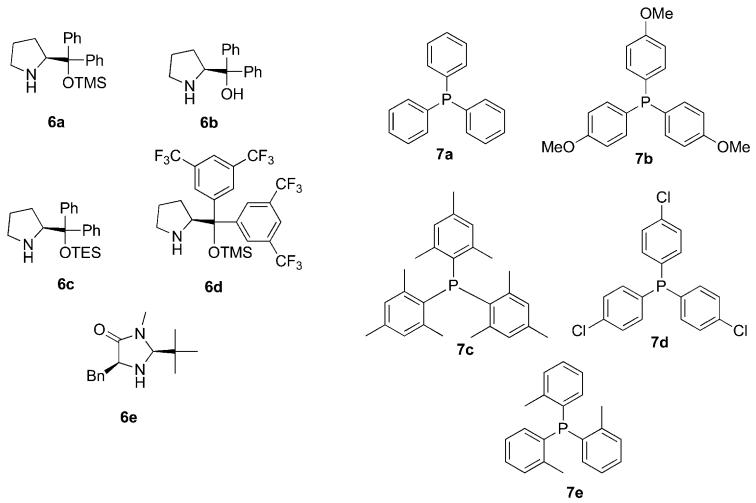
With these results in hand, we decided to probe the scope of the catalytic one-pot three-component enantioselective reaction using $Cu(OTf)_2$ as the metal catalyst, **6a** as the chiral amine, and **7a** as the phosphine additive in diethyl ether at 22°C (Scheme 2). The three-component reactions were efficient and proceeded with excellent 1,4-selectivity in the β-boration step and the corresponding homoallylboronates **4a**–**4j** were assembled in an asymmetric fashion in good yields and high enantiomeric ratios through the conjugate boron addition/Wittig sequence. The reaction tolerated enals with both aryl and aliphatic substituents at their β position. Moreover, cinnamic enals **2** with an electron-withdrawing group at the *para*, *ortho*, or *meta* position exhibit higher reactivity in the β-boration step (Scheme 1). For example, the β boration of enals **2d**–**2g** and **2j** was completed within 35 minutes as determined by ^{1}H NMR analysis. The subsequent addition of the Wittig reagents **3** gave the corresponding homoallylboranes **4d**–**4g** and **4j** with 96.5:3.5–97:5:2.5 e.r. after 2 hours. The yields were in the range of 60–67% because the intermediates decomposed through elimination during the Wittig step to give the enals **2**. Thus, a small amount of the corresponding diene **A** was also formed. We also investigated the reactions with enals **2** wherein either R was heterocyclic or **2** was β substituted. However, the reactions were slower and the corresponding products **4** were formed with lower e.r. values



Scheme 2. [a] 35 min. [b] **2h** (3 equiv), 60 min. [c] 4°C, 45 min.

Table 1: Initial examination of catalytic one-pot three-component synthesis of **4a**[a]



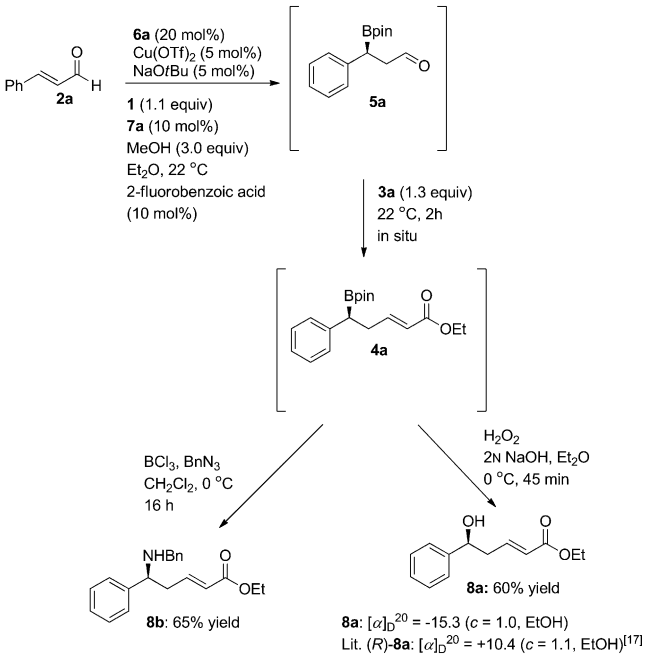


Entry[a]	Amine	7	Cu salt	*t* [h]	Conv. [%][b]	e.r.[c]
1[d]	–	**7a**	$Cu(OTf)_2$	1	60	50:50
2	**6a**	**7a**	–	7	<2	n.d.
3	**6a**	**7a**	CuCl	4	<2	n.d.
4	**6a**	**7a**	CuBr	4	<2	n.d.
5	**6a**	**7a**	CuI	4	<2	n.d.
6	**6a**	**7a**	CuOAc	4	<2	n.d.
7	**6a**	**7a**	$Cu(OTf)_2$	1	98	97.5:2.5
8	**6a**	**7a**	$CuOCl_2$	4	<2	n.d.
9[e]	**6a**	**7a**	$Cu(OTf)_2$	1	98	69:31
10	**6a**	**7b**	$Cu(OTf)_2$	4	70	90:10
11	**6a**	**7c**	$Cu(OTf)_2$	4	24	63:37
12	**6a**	**7d**	$Cu(OTf)_2$	4	70	85:15
13	**6a**	**7e**	$Cu(OTf)_2$	4	30	80:20
14	**6b**	**7a**	$Cu(OTf)_2$	1	80	55:45
15	**6c**	**7a**	$Cu(OTf)_2$	2	95	72:28
16	**6d**	**7a**	$Cu(OTf)_2$	1	85	53:47
17	**6e**	**7b**	$Cu(OTf)_2$	7	20	n.d.

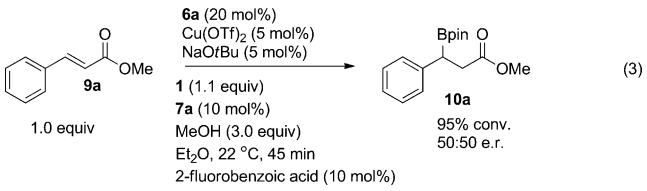
[a] Under N_2 atmosphere. See the Supporting Information for details of the reaction conditions. [b] Conversion into aldehyde **5a** as determined from the ^{1}H NMR spectra of the crude reaction mixture. [c] Determined by HPLC analysis of **4a** on a chiral stationary phase. [d] Without the addition of the chiral amine catalyst **6a**, the 1,4-/1,2-addition ratio was 67:33, as determined by ^{1}H NMR analysis of the crude reaction mixture prior to the Wittig step. [e] Without the addition of 2-fluorobenzoic acid, the 1,4-/1,2-addition ratio was 75:25, as determined by ^{1}H NMR analysis of the crude reaction mixture prior to the Wittig step. n.d. = not determined, TES = triethylsilyl, TMS = trimethylsilyl.

(60:40–65:35). To establish the absolute configuration of the homoallylicboronates **4** and show the synthetic utility of our asymmetric multicomponent reaction, we investigated a one-pot transformation for the assembly of the valuable homoallylic alcohol **8a** (Scheme 3).[17,18] The one-pot reaction was successful and we were able to isolate the corresponding homoallylic alcohol **8a** in 60% yield. Comparison with the literature revealed that the stereochemistry at C5 was *S* ($[\alpha]_D^{20} = -15.30\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0\ g\,cm^{-3}$, EtOH); Lit. (*R*)-**8**: $[\alpha]_D^{20} = +10.40\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.1\ g\,cm^{-3}$, EtOH).[17] Thus, the absolute configuration of the homoallylboronates **4** is *S* (R = aryl). We also broadened the scope of the strategy by synthesizing homoallylic amine **8b** in 65% yield.[19]

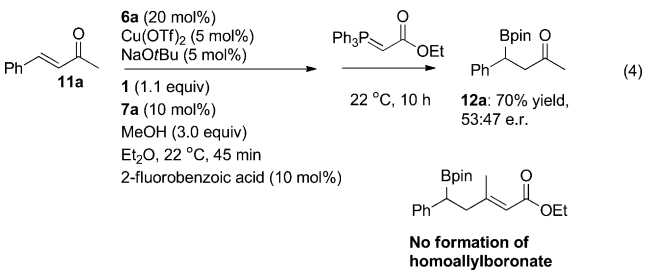
The presence of chiral iminium intermediates derived from the reaction of the catalyst **6a** and enal **2a** in the β-boration step of our one-pot three-component reaction was confirmed by ^{1}H NMR and HRMS analysis of the crude reaction mixture. In addition, subjecting the cinnamic ester **9a** to the same reactions conditions that were used for the synthesis of homoallylboronate **4a** gave the corresponding racemic β-borylated product **10a** [Eq. (3)]. Furthermore,



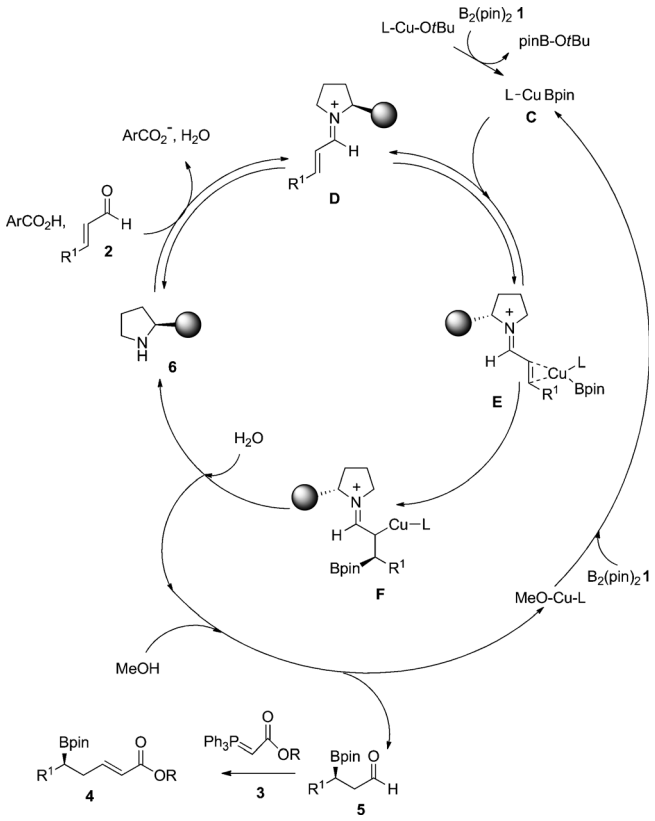
Scheme 3. One-pot catalytic enantioselective synthesis of homoallylic alcohol **8a** and homoallylic amine **8b**.



subjecting α,β-unsaturated ketone **11a**, which is known to not form iminium intermediates with the bulky amino catalyst **6a**,[16] to the reaction conditions used for the β boration of enals **2** gave nearly racemic β-borolyated ketone **12a** [Eq. (4)]. These results indicate that iminium activation is necessary to make the one-pot three-component reaction enantioselective.



Based on the absolute configuration of the products **4**, the above experimental results, and our previous DFT calculations,[10] we propose the reaction mechanism depicted in Scheme 4. The in situ generated L–Cu^{II}–Bpin **C** species approaches the less sterically hindered *Si* face (R = aryl) of the β-carbon atom of the imiunium intermediate **D**. Subsequent C–B formation at the *Re* face of the iminium intermediade **E** gives **F**. Hydrolysis and addition of MeOH regenerates the chiral amine catalyst **6**, thus leading to formation of a reactive MeO–Cu^{II}–L species and the β-borylaldehyde intermediate **5**. Next, the in situ Wittig reaction with **3** gives the final homoallylboronate product **4**.



Scheme 4. Proposed reaction mechanism.

In summary, we have developed an efficient, novel one-pot three-component enantioseelctive reaction between a diboron reagent, α,β-unsaturated aldehydes, and 2-(triphenylphosphoranylidene)acetate esters. The asymmetric multicomponent reaction proceeds through a β boration/Wittig sequence to give the corresponding homoallylboronates with high enantiomeric ratios using simple bench-stable chiral amines and copper catalysts. In addition, the study shows that it is possible to merge the catalytic cycles of transition-metal-catalyzed nucleophilic activation of diboron reagents with amine-catalyzed iminium activation of enals to achieve a highly 1,4- and enantioselective β boration of enals. The one-pot expansion of the co-catalytic three-component reaction to the asymmetric synthesis of homoallylic alcohols was also disclosed. Further development of this type of one-pot multicomponent co-catalytic asymmetric reaction and its application in total synthesis is ongoing in our laboratories.

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