Letter

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Silver-Assisted, Iridium-Catalyzed Allylation of Bis[(pinacolato)boryl]methane Allows the Synthesis of Enantioenriched Homoallylic Organoboronic Esters.

Miao Zhan‡, Ren-Zhe Li‡, Ze-Dong Mou‡, Chao-Guo Cao‡, Jie Liu*, Yuan-Wei Chen*, Dawen Niu*

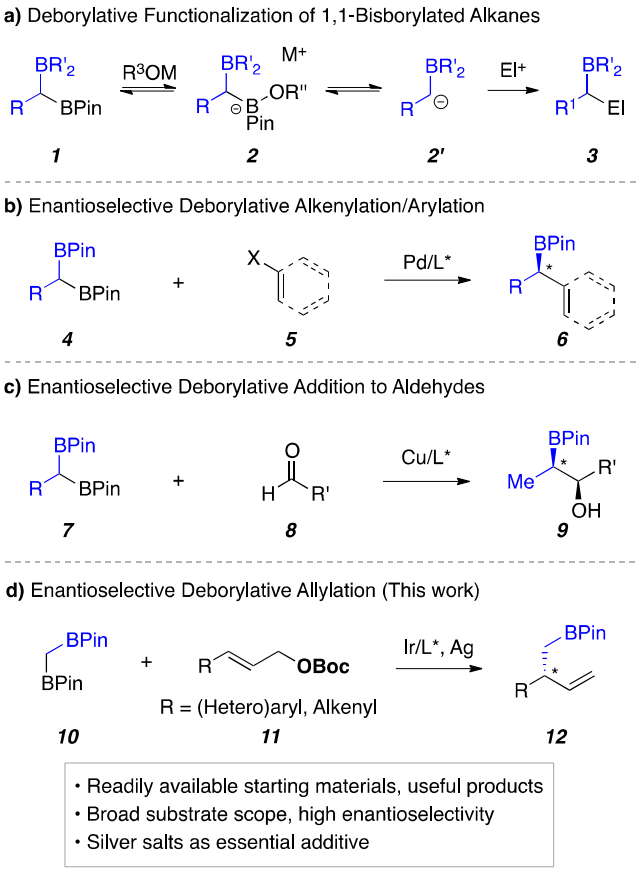
Department of Emergency, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center for Biotherapy, Chengdu 610041, China

ABSTRACT: Described here is an enantioselective approach of making chiral, β-substituted homoallylic organoboronic esters. In the presence of LiOtBu and a catalytic amount of silver salt, commercial bis[(pinacolato)boryl]methane participated in the iridium catalyzed asymmetric allylation reactions, delivered a '$CH_2B(pin)$' group, and yielded the title compounds from allylic carbonates. The synthetic utility of the prepared chiral organoboronates was demonstrated by their conversion into other important classes of compounds.

KEYWORDS: Boronic Esters, Bis[(pinacolato)boryl]methane, Iridium, Silver, Enantioselective Allylation, Catalysis.

Organoboronic acid derivatives [$RB(OR')_2$] are a significant class of compounds in chemistry.[1] With chemical stability and synthetic versatility,[2] $RB(OR')_2$ are deemed as attractive intermediates for constructing complex natural products or diversified chemical libraries. In addition, some of these compounds possess important biological activities[3] and are used as anticancer agents.[4] As a result, general and selective methods of making $RB(OR')_2$ are desirable and have been actively pursued by the synthetic community. Over the last few decades, tremendous efforts have been devoted to the development of catalytic, asymmetric methods for their preparation, with substantial progress achieved. Many of the reported methods are based on asymmetric hydroboration,[5] diboration,[6] or borofunctionalization[7] of unsaturated organic compounds or nucleophilic substitution of boryl anions.[8] These methods produce chiral organo-boronic esters by addition of one or more boryl [$B(OR)_2$] groups.[9,10]

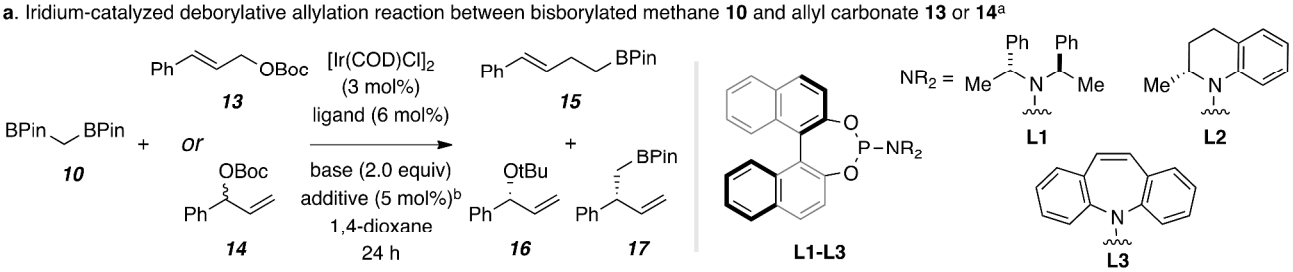
Lately, a novel approach capitalizing on the facile monodeborylation[11,12] of 1,1-bisborylalkanes has emerged, and provided unique accesses to complex organoboron compounds by introducing an α-boroalkyl group (**1** to **3**, Scheme 1a). It is believed that the deborylation process of 1,1-bisborylated alkane **1** is facilitated by the stabilizing effect of the three-coordinate boron atom adjacent to the resulting anionic center (cf. **2'**).[11h, 13] Therefore, this reaction stops at the monodeborylation stage, and one boronic ester group is retained in the product. Within this regime, some enantioselective reactions have been reported. For example, the Morken group has developed palladium-catalyzed enantioselective deborylative arylation[12a] and alkenylation[12b] reactions of 1,1-bisborylalkanes, giving highly valuable chiral benzyl and allyl boronic esters (**4**+**5** to **6**, Scheme 1b). The Hall group later reported an investigation of the effects of different ligands on the palladium-catalyzed deborylative arylation reaction.[12c] In addition, the Meek group has established a copper-based deborylative addition of 1,1-bisborylethane **7** to aldehydes **8**,



Scheme 1. a) Deborylation of 1,1-bisborylalkanes in the synthesis of chiral organoboronates. b) and c) Prior work that inspired this study. d) Deborylative allylation of 1,1-bisborylated methane (This work).

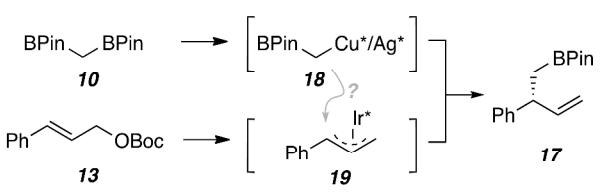
Table 1. a) Condition optimization for iridium-catalyzed deborylative allylation of bis[(pinacolato)boryl]methane (10). b) A hypothetical Ag/Cu assisted deborylative allylation pathway. c) ^{1}H NMR spectrum of the crude reaction mixture obtained from the entry 10 experiment.

a. Iridium-catalyzed deborylative allylation reaction between bisborylated methane **10** and allyl carbonate **13** or **14**[a]

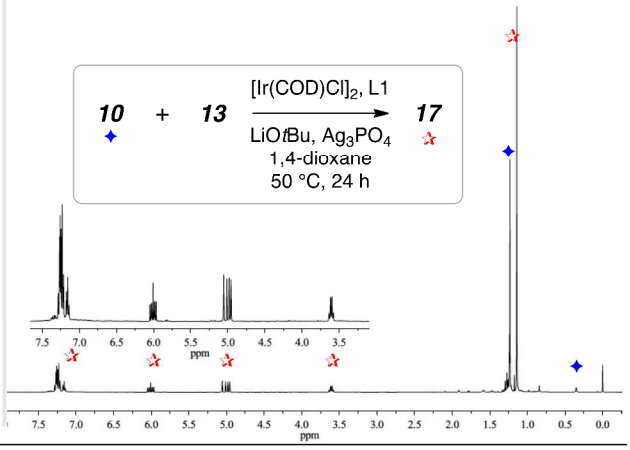


entry[c]	ligand	base	additives	T (°C)	conv.	15:16:17	yield (ee)[d] of 17
1	**L1**	LiOtBu	none	40	69%	0:20:32	32 (93)
2	**L1**	NaOtBu	none	40	58%	0:8:20	20 (na)
3	**L1**	KOtBu	none	40	53%	0:0:0	0 (na)
4[e]	**L1**	LiOtBu	CuBr	40	100%	64:24:4	4 (na)
5	**L1**	LiOtBu	AgOTf	40	95%	0:15:52	52 (93)
6	**L1**	LiOtBu	AgF	40	88%	0:5:78	78 (94)
7	**L1**	LiOtBu	$AgNO_3$	40	92%	0:7:72	72 (92)
8	**L1**	LiOtBu	Ag_2O	40	93%	0:7:81	81 (93)
9	**L1**	LiOtBu	Ag_3PO_4	40	93%	0:3:91	91 (93)
10	**L1**	LiOtBu	Ag_3PO_4	50	100%	0:3:94	94 (93)
11	**L1** (no Ir)	LiOtBu	Ag_3PO_4	50	<10%	0:0:0	na (na)
12	**L2**	LiOtBu	Ag_3PO_4	50	98%	0:1:95	95 (-82)
13	**L2**	LiOtBu	none	50	90%	0:10:45	45 (-47)
14	**L3**	LiOtBu	AgOMs	25	100%	0:1:98	98 (-1)
15[d]	**L3**	LiOtBu	AgOMs	25	100%	0:3:82	82 (90)
16[d]	**L3**	LiOtBu	AgOTf	25	100%	0:na:84	84 (95)
17[d]	**L3**	LiOtBu	none	25	41%	na	7 (na)

b. Proposed iridium-catalyzed allylation assisted by Cu/Ag metal ions



c. ^{1}H NMR spectrum of the crude mixture of the model reaction



[a] For **L1** and **L2**, electrophile **13** was used; for **L3**, electrophile **14** was used. Reactions in this Table were performed on 0.2 mmol scale. [b] 5 mol% based on metal ions. [c] 1.5 equiv of **10** and 1.0 equiv of allyl carbonate were used unless otherwise noted. [d] Yield, product ratio, and conversion were determined by ^{1}H NMR analysis, using 2-methylnaphthalene as internal standard; enantiomeric excess (ee) values were determined by chiral HPLC analysis. [e] Product **15** was formed exclusively in high yield if $[Ir(COD)Cl]_2$ is not used. [f] 1.0 equiv of **10** and 2.1 equiv of **14** were used.

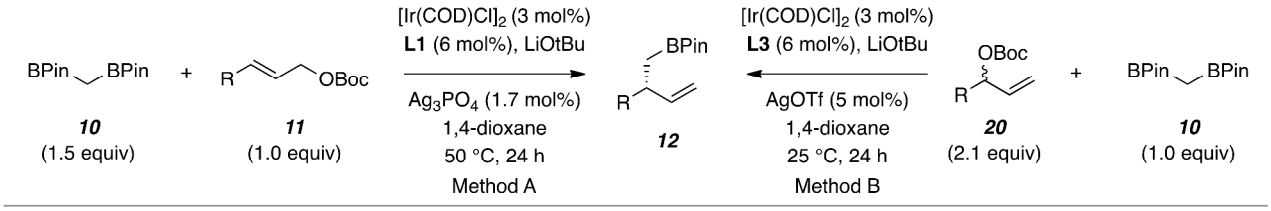
yielding 1,2-hydroxyboronates **9** in good enantio- and diastereoselectivities[12d] (Scheme 1c).

Inspired by these seminal contributions, we contemplated the possibility of uniting such a facile deborylation process of 1,1-bisborylalkanes with the well-established iridium-catalyzed asymmetric allylative substitution (AAS) chemistry[14] as a strategy to prepare chiral, β-substituted homoallylic organoboronic esters (**10**+**11** to **12**, Scheme 1d). Herein we report our development of such a reaction. We established that when in the presence of a suitable silver salt, the easily available bis[(pinacolato)boryl]methane[15] (**10**) is an effective coupling partner in the iridium-catalyzed AAS reaction, and delivers a '$CH_2B(pin)$' group as a derivatizable one-carbon unit.[16] This reaction displayed significant substrate scope and a variety of chiral β-substituted homoallylic organoboronates could be prepared under mild conditions. Since boronic esters could be readily converted to a hydroxyl or amine group,[1,17] this method could also be viewed as an umpolung strategy to make chiral homoallyl alcohol and amines. In this study, we found addition of silver salts[18] to be essential for the reaction efficiency and selectivity. During the preparation of this manuscript, the Cho group[11f], Fu group[11j], and Hoveyda group[12e] have each reported a mechanistically distinct, copper-based approach to achieve the allylation of bis[(pinacolato)boryl]-methane. By using the chiral NHC ligands developed by their group, Hoveyda and coworkers accomplished the enantioselective variant of this reaction and applied it into an elegant total synthesis of rhopaloic acid A. The copper-based approaches developed in these groups require allylic phosphates or halides as electrophiles, while our Ir/Ag catalyzed system permits the use of the less reactive allylic carbonates **11**.[19]

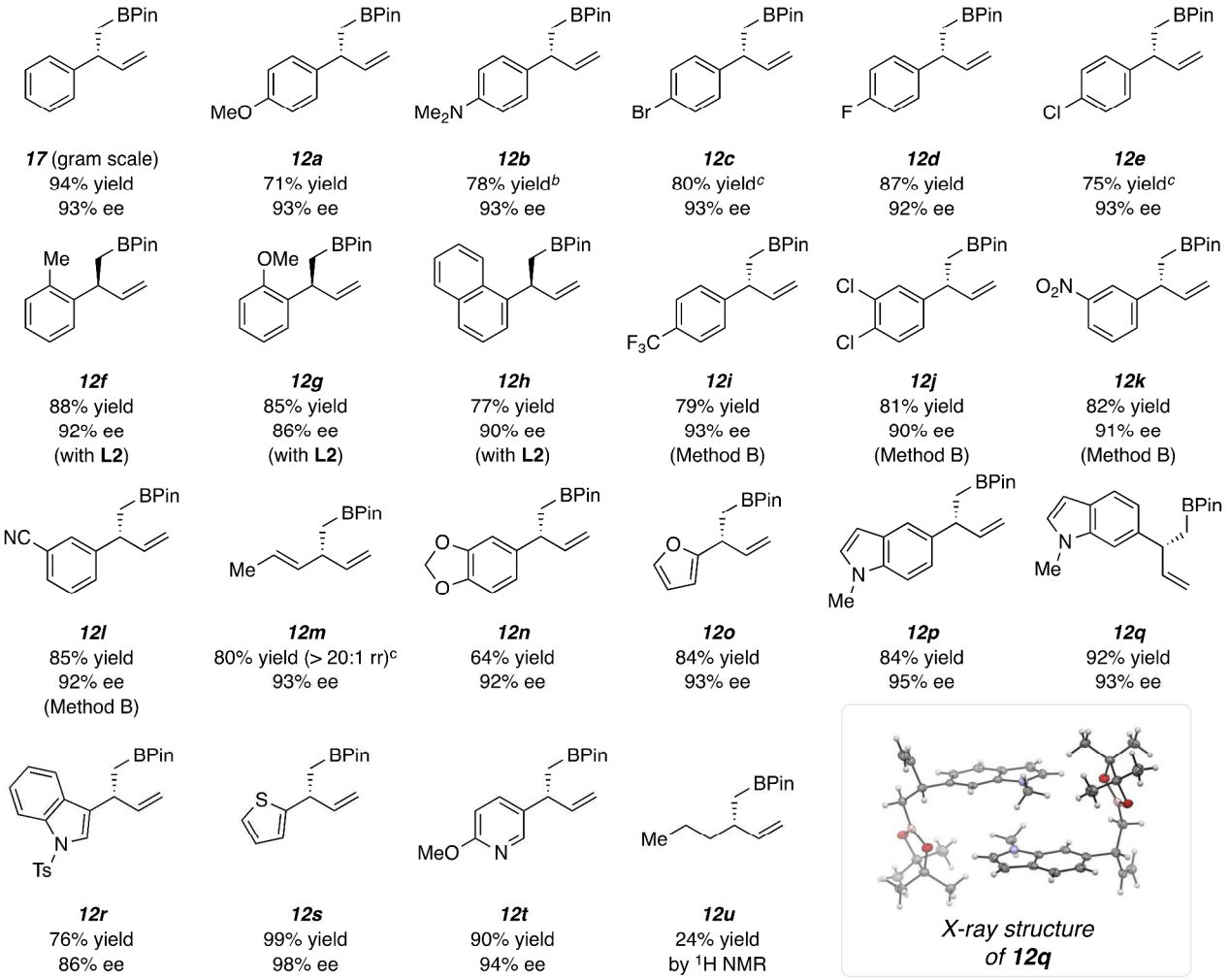
We began our study by investigating the model reaction between bisborylmethane **10** (1.5 equiv) and *tert*-butyl cinnamyl carbonate (**13**, 1.0 equiv), adopting the previously established conditions of iridium-catalyzed AAS reactions,[14] with LiO*t*Bu employed as the activator of **10** (Table 1, entry 1). Under these

conditions, the desired product **17** was delivered in a promising 32% yield and 93% ee. Also formed was a significant amount of allyl ether **16**, indicating the nucleophilic attack of LiO*t*Bu to be a competitive process.[20] Previous studies had shown that the identity of the metal counterions of the alkoxide bases exerts strong impact on the complexation processes of these bases with bisboryl alkanes (cf. **1** to **2** or **2'** in Scheme 1a): the use of NaO*t*Bu[11h] or KO*t*Bu[11g] led to a more facile formation of either α-boryl carbanion **2'** or boron ate complex **2** than the use of LiO*t*Bu.[12d] Therefore, we screened the former two bases, with the aim of raising the concentration of (the presumably more nucleophilic) **2** or **2'**, expecting to improve the yield of **17**. However, neither of these two bases gave better results than did LiO*t*Bu (entry 2 and 3). Instead, we noticed the majority of **10** was decomposed under these conditions, presumably via a protodeborylation process.[11h,g] We then proposed to modulate the reactivity of **10** as a nucleophile by addition of a copper or silver salt, since it had been reported that 1,1-bisboryl alkanes might undergo a deborylative transmetallation process to form an alkyl copper[12d,21] or alkyl silver[11g,22] species **18** in the presence of a metal alkoxide. We surmised that species **18,** if formed, might engage the allyl iridium intermediate **19** more promptly (Table 1b), thereby leading to a more rapid formation of the desired product. We were aware that the presence of other transition metals might compete with iridium metal for chiral ligands, nonetheless, we tested the use of a variety of copper and silver salts in this transformation (entry 4-9). While the use of CuBr gave mostly the undesired linear product **15** (entry 4),[11i] we were glad to find that the use of AgOTf significantly improved both the

Table 2. Substrate scope of iridium-catalyzed deborylative allylation of bisborylmethane.[a]



10 (1.5 equiv) + ***11*** (1.0 equiv) → ***12*** → ***20*** (2.1 equiv) + ***10*** (1.0 equiv)



17 (gram scale): 94% yield, 93% ee

12a: 71% yield, 93% ee

12b: 78% yield[b], 93% ee

12c: 80% yield[c], 93% ee

12d: 87% yield, 92% ee

12e: 75% yield[c], 93% ee

12f: 88% yield, 92% ee (with **L2**)

12g: 85% yield, 86% ee (with **L2**)

12h: 77% yield, 90% ee (with **L2**)

12i: 79% yield, 93% ee (Method B)

12j: 81% yield, 90% ee (Method B)

12k: 82% yield, 91% ee (Method B)

12l: 85% yield, 92% ee (Method B)

12m: 80% yield (> 20:1 rr)[c], 93% ee

12n: 64% yield, 92% ee

12o: 84% yield, 93% ee

12p: 84% yield, 95% ee

12q: 92% yield, 93% ee

12r: 76% yield, 86% ee

12s: 99% yield, 98% ee

12t: 90% yield, 94% ee

12u: 24% yield by ^{1}H NMR

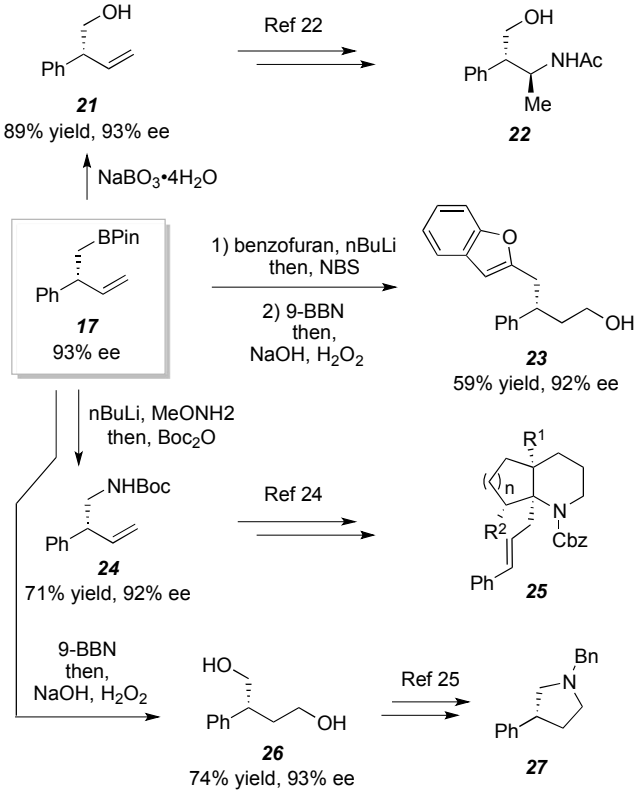
*X-ray structure of **12q***

[a]Reactions performed on 0.3 mmol scale. Method A is used unless otherwise noted. Isolated yields are reported. Ee's were determined by chiral HPLC or SFC analysis. Regioselectivity (rr) were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Reaction performed at 25 °C for 24 h. [c][Ir(COD)Cl]$_2$ (5 mol%), **L1** (10 mol%), and Ag_3PO_4 (2.8 mol%) were used. Reactions were run at 50 °C for 30 h.

selectivity profile of the reaction and the yield of the desired product **17** (entry 5). Encouraged by these results, we screened a series of other silver salts and found that all of them had beneficiary effects on the reaction outcomes (entry 5-9), of which Ag_3PO_4 gave the highest (91%) yield of **17** with an ee of 93% (entry 9). Raising the reaction temperature to 50 °C led to full conversion of cinnamyl carbonate **13** and slightly higher yield of **17**, with negligible effect on the stereoselectivity (entry 10). A ^{1}H NMR spectrum of the crude product mixture of entry 10 experiment is depicted in Table 1c, showing the overall cleanliness of this transformation, which in turn facilitated the isolation of these products. Control experiment showed that iridium is essential for the reaction to proceed (entry 11).[23]

With the conditions using **L1** optimized, we proceeded to investigate the use of **L2** and **L3** in this reaction, since the latter two ligands often show complementary substrate scope[24] to **L1** in iridium-catalyzed AAS reactions (see below). In the presence of Ag_3PO_4, we found **L2** performed well in the model reaction, giving the opposite enantiomer of **17** in decent yield and enantioselectivity (entry 12). The use of P-olefin bidentate ligand **L3** developed in the Carreira group called for the branched allylic carbonate **14** as electrophile (entry 14-16). Interestingly, nearly racemic mixture of products was formed when a *1.5*:1 ratio of **10** to **14** was used (entry 14). We speculated that under these conditions, each isomer of **14** underwent a stereoretentive allylation process,[16] leading to the formation of **17** as a racemate. With this rationale, we performed the reactions using excess (2.1 equiv) of **14**, to find the desired product **17** was obtained in excellent yield and enantioselectivity this time[25] (entry 15 and 16). The ee of the unreacted **14** in entry 15 experiment was determined to be 87%, suggestive of a kinetic resolution process.[26] Intriguingly, when either ligand was used, a silver salt proved to be essential for the efficiency and selectivity of the reaction (entry 12 vs. 13 and entry 16 vs. 17).

With the above reaction conditions established, we explored the scope and limitations of this transformation, as summarized in Table 2. First, we found the reaction efficiency is not reduced when performed at gram scale, and more than 1 gram of compound **17** was prepared in one batch with 93% ee. Besides, we noticed a variety of cinnamyl carbonate derivatives could be converted to the corresponding chiral homoallyl boronates in good to excellent isolated yields and with high enantioselectivity (**12a-t**). For example, cinnamyl carbonates containing electron-donating methoxy (**12a**) or dimethylamino group (**12b**) were effective reaction partners. Those with halogenated aromatic rings (**12c-e**) were tolerated as well. When substrates bearing *ortho*-substituents (**12f-h**) were used, ligand **L2** was required for good enantioselectivity.[24a] Cinnamyl carbonates with strongly electron-withdrawing substituents were found to be much less reactive in this reaction.[18] Nonetheless, products with electron-deficient aromatic rings (**12i-l**) could be obtained from the corresponding branched allyl carbonates (2.1 equiv) with **L3** used as the chiral ligand. Additionally, dienyl carbonates also participated in this reaction, and generated the branched product **12m** in 80% yield, with >20:1 regioselectivity and 93% ee. Unfortunately, aliphatic allylic carbonates reacted sluggishly under a variety of conditions we examined, giving only low yield of the desired product (**12u**). We were also interested in incorporating pharmaceutically relevant heterocycles into our products, and found allyl carbonates bearing dioxolane (**12n**), furan (**12o**), indole (**12p-n**), thiophene (**12s**), and pyridine (**12t**) rings underwent this reaction smoothly, delivering the branched products in good yields and selectivities. X-ray crystallographic analysis of **12q** confirmed its absolute configuration, which is the same as those



Scheme 2. Elaboration of homoallyl boronates.

of the products generated from other typical nucleophiles (e.g., amines) in Ir-catalyzed AAS reaction.

The roles played by silver salts in this transformation are not yet clear. Hartwig and coworkers showed in a recent study that the use of silver phosphate [e.g., $AgOP(O)(OPh)_2$] dramatically enhanced the diastereoselectivitity of the Ir-catalyzed allylation reaction of azlactones.[18] Through careful mechanistic study, they found the presence of phosphate counterion rather than the silver metal was key for the augmented selectivity. However, the following two observations led us to believe that silver ion might be responsible for the enhanced efficiency and selectivity in our reaction. First, various silver salts containing different types of counterions (entry 5-9 in Table 1 and Figure S1 in Supporting Information) worked efficiently in this deborylative allylation reaction, suggesting the effect of counterion not to be critical. Second, the use of AgCl, Ag_2O or AgBr gave much superior results than the use of CuCl, Cu_2O, or CuBr (see Figure S1 in Supporting Information for details). The fact that AgCl or AgBr also significantly promoted the reaction performance ruled out the possibility that silver salts exerted their effects through abstracting chloride ions from the iridium complex. Nonetheless, more detailed mechanistic studies are required to delineate the specific roles of silver additives in this reaction.

To further demonstrate the synthetic utility of this transformation, we converted the obtained homoallylic boronic esters products into other important classes of compounds using established chemistry (Scheme 2). For example, compound **17**

could be readily oxidized by $NaBO_3$•$4H_2O$ to the homoallylic alcohol **21**, which had been engaged in a diverse array of chemical transformations to generate structurally complex products, including amino alcohol derivative **22**.[27] Moreover, the boronic ester group in **17** could be converted to aromatic rings following the protocols developed in the Aggarwal group,[28] giving, after a hydroboration-oxidation sequence, alcohol **23** in 59% overall yield. Further, compound **17** underwent an efficient C–B to C–N conversion when treated with LiNHOMe,[17] and yielded homoallylamine **24** after Boc protection in the same pot. Notably, compound **24** was a key intermediate used in the preparation of bicyclic piperidines like **25**,[29] and had been previously made in 4 steps[29] from methyl cinnamyl carbonate (vs. 2 steps from *tert*-butyl cinnamyl carbonate in our sequence). Lastly, we subjected **17** to a direct hydroboration–oxidation sequence to `give` diol **26**, which has been employed in the synthesis of chiral pyrolidines like **27**.[30]

In conclusion, we have developed an efficient iridium-catalyzed asymmetric allylation strategy to prepare chiral homoallyl boronic esters. This method utilizes readily available bis[(pinacolato)boryl]methane and allylic carbonates as reactants, demonstrates broad substrate scope, and is amenable for the preparation of various β-substituted, chiral homoallyl boronic esters, including those with *ortho*-substitutions and heterocycles. The utility of these products is highlighted by their straightforward conversion to other useful synthetic intermediates. Importantly, we have noticed in this study that the addition of silver salt is essential for the efficiency and selectivity of this reaction. The information gained from this work might prove useful in the development of other iridium-catalyzed asymmetric allylation processes, some of which are ongoing in this laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterization are provided (PDF)

AUTHOR INFORMATION

Corresponding Authors

* E-mail: niudawen@scu.edu.cn; ywchen@scu.edu.cn; liujie2011@scu.edu.cn.

Author Contributions

All authors have given approval to the final version of the manuscript. / ‡These authors performed the experiments and contributed equally. / D. N conceived the idea and wrote the manuscript with feedback from M. Z., J. L., and Y. C.

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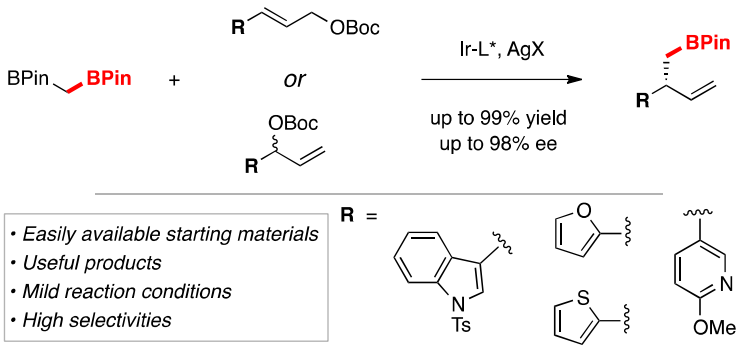
TOC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