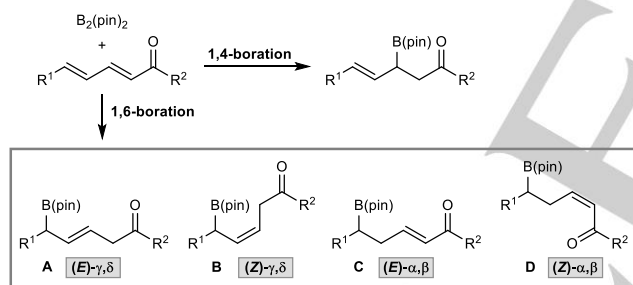# Switchable Synthesis of *Z*-Homoallylic Boronates and *E*-Allylic Boronates by Enantioselective Copper-Catalyzed 1,6-Boration

Yunfei Luo, Steven M. Wales, Stamatis E. Korkis, Iain. D. Roy, William Lewis, and Hon Wai Lam*

Abstract: The enantioselective Cu-catalyzed 1,6-boration of (*E*,*E*)-α,β,γ,δ-unsaturated ketones is described, which gives homoallylic boronates with high enantiomeric purity and unexpectedly high *Z*-selectivity. By changing the solvent, the outcome can be altered to give *E*-allylic boronates.

Enantiomerically enriched α-stereogenic alkylboron compounds have numerous applications in organic synthesis.[1–3] One important route to these compounds is the catalytic enantioselective boration of electron-deficient alkenes.[4–7] Although numerous examples of 1,4-boration are known,[4–7] only a few examples of 1,6-boration have been described.[8,9] Aside from promoting 1,6-boration over competing 1,4-boration, the 1,6-boration of electron-deficient conjugated dienes has the potential to give four products which differ in the position and/or the *E*/*Z* geometry of the remaining alkene (Scheme 1). Controlling the selectivity to obtain only one product, especially for fully acyclic substrates, presents a considerable challenge.

Kobayashi and co-workers have developed Cu(II)-catalyzed 1,6-borations of β,β-disubstituted α,β,γ,δ-unsaturated cyclic ketones that give products of type **C** [(*E*)-α,β],[8a] whereas we have described enantioselective Cu(I)-catalyzed 1,6-borations of

acyclic α,β,γ,δ-unsaturated esters and ketones that give products of type **A** [(*E*)-γ,δ].[8b] The ability to access products of type **B** and **D** would also be advantageous to open up additional avenues for post-boration manipulation. However, to our knowledge, 1,6-borations of this type are hitherto unknown, which is perhaps unsurprising as they contain thermodynamically less-stable *Z*-alkenes.[10,11] Compared with *E*-alkenes, there are fewer effective methods for the highly stereoselective synthesis of *Z*-alkenes,[12] and new reactions that address this issue are therefore valuable.

Herein, we describe enantioselective copper-catalyzed 1,6-borations of acyclic α,β,γ,δ-unsaturated ketones that give homoallylic boronates of type **D**. In addition to containing α-stereogenic alkyl pinacolboronates, the products possess *Z*-conjugated enones with high stereoselectivities. The complete *E* to *Z* isomerization of the alkene next to the ketone is highly unusual. Furthermore, the outcome of the reaction can be switched to give *E*-allylic boronates of type **A** simply by changing the reaction solvents and concentration.[13]

During our studies of enantioselective copper-catalyzed 1,6-borations that give *E*-allylic boronates of type **A**,[8b] we discovered that α,β,γ,δ-unsaturated ketones with a quaternary center adjacent to the carbonyl group unexpectedly gave significant quantities of *Z*-homoallylic boronates of type **D**. For example, reaction of α,β,γ,δ-unsaturated ketone **1a** (Table 1) with $B_2(pin)_2$ (1.2 equiv) in THF (0.1 M) in the presence of $CuF(PPh_3)_3 \cdot 2MeOH$ (0.20 mol%), Josiphos SL-J001-1 (**L1**, 0.24 mol%), and *i*PrOH (2.0 equiv) at room temperature for 15 h, a 1:1 mixture of *Z*-homoallylic boronate **2a** and *E*-allylic boronate **3a** was obtained (entry 1). Interestingly, increasing the quantity of *i*PrOH changed the outcome to favor **3a** (entry 2). Although other solvents such as EtOH and cyclohexane did not provide high selectivities in favor of either product (entries 3 and 4), a

Scheme 1. Possible products from boration of an α,β,γ,δ-unsaturated carbonyl

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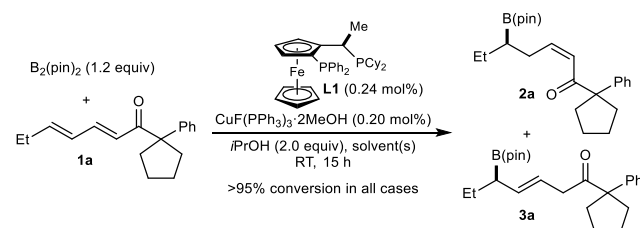
Supporting information for this article is available on the WWW under http://dx.doi.org/

Table 1: Investigation of reaction conditions for the 1,6-boration of **1a**.[a]

Entry	Solvent(s)	Concentration (M)	2a:3a[b]
1	THF	0.1	1:1
2	*i*PrOH/THF (1:1)	0.1	1:14
3	EtOH	0.1	1:1
4	cyclohexane	0.1	1:1.4
5	cyclohexane/THF (4:1)	0.1	5:1
6	toluene/THF (4:1)	0.1	4.8:1
7	isohexane/THF (4:1)	0.1	4:1
8	cyclohexane/THF (4:1)	0.04	>19:1

[a] Reactions were conducted using 0.20 mmol of **1a**. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures.

mixture of cyclohexane/THF (4:1) favored *Z*-homoallylic boronate **2a** (entry 5). Similar results were obtained using toluene or isohexane in place of cyclohexane (entries 6 and 7). However, a reaction in cyclohexane/THF (4:1) at a lower concentration of 0.04 M increased the ratio of **2a:3a** to >19:1 (entry 8).

With effective conditions in hand, the scope was investigated using various α,β,γ,δ-unsaturated ketones with sterically hindering carbonyl substituents (Scheme 2). These reactions were generally highly selective for the formation of *Z*-homoallylic boronates (ratio of **2:3** from 4:1 to >19:1), which were isolated pure in 55–87% yield with high enantioselectivities (86–95% *ee*). Substrate **1a** gave **2a** in 85% yield and 92% *ee*. The group adjacent to the ketone can be varied to 1-p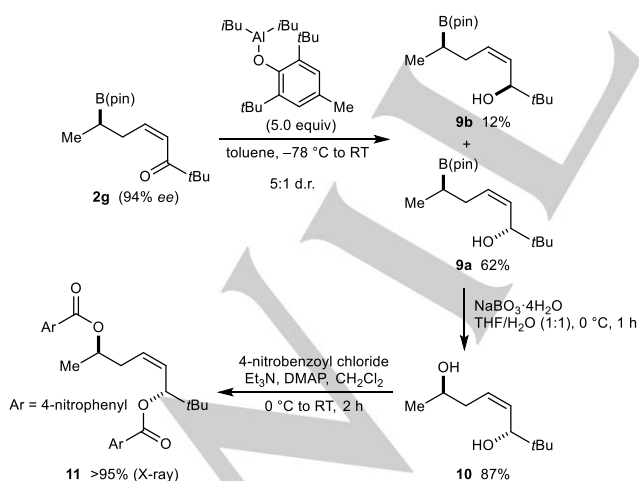henylcyclohexyl (**2c** and **2d**), 2-ethyl-2,3-dihydro-1*H*-inden-2-yl (**2e**), adamantyl (**2f**), and *tert*-butyl (**2g–2k**). Groups containing silyloxy (**2l–2n**) or ester (**2o** and **2p**) substituents are also tolerated, but the ratios of *Z*-homoallylic boronate to *E*-allylic boronate are lower in some cases (**2m** and **2n**).[14] The

formation of **2l** illustrates that an all-carbon quaternary center adjacent to the ketone is not a strict requirement for this method to be successful. Regarding the substituent at the δ-carbon, substrates containing various simple alkyl groups (**2a–2h** and **2m–2p**), oxygenated alkyl groups (**2i** and **2k**), or a (phthalimido)methyl group (**2j**) are tolerated. The 1,6-boration of **1g** using a 0.02 mol% catalyst loading also gave good results, with **2g** produced in 75% yield and 94% *ee*.

Scheme 3. Enantioselective Cu-catalyzed 1,6-boration–oxidation of electron-deficient dienes to give *E*-allylic alcohols. Reactions were conducted with 0.30 mmol of **1**. Yields are of isolated material. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] *i*PrOH/THF (2:1) was used instead of *i*PrOH/THF (1:1).

As shown in Table 1, the reaction medium has a critical influence on the product distribution, with *i*PrOH/THF (1:1) favoring the *E*-allylic boronate (entry 2). Pleasingly, this effect was general across several substrates (Scheme 3). The *E*-allylic boronates are unstable to column chromatography on silica gel, and were oxidized with NaBO$_3$·4H$_2$O[15] to give the corresponding allylic alcohols in 42–79% yield over two steps, and with high enantioselectivities (90–94% *ee*). With substrate **1g**, use of *i*PrOH/THF (1:1) gave comparable quantities of the *Z*-homoallylic boronate and *E*-allylic boronate. Fortunately, changing to *i*PrOH/THF (2:1) gave the *E*-allylic boronate exclusively, and after oxidation, **4g** was obtained in 72% yield and 93% *ee*. Although Ito and co-workers have described the temperature-controlled, switchable synthesis of allylic and homoallylic boronates from 1,3-dienes, only two examples using cyclic rather acyclic 1,3-dienes were reported.[13]

Currently, the reasons for selective formation of *Z*-homoallylic boronates as shown in Scheme 2 are not known (see the Supporting Information for discussion). Furthermore, the dependence of the product selectivity on the solvent and concentration are not understood, and insight into these phenomena awaits the results of mechanistic studies.

Next, the synthetic utility of the products was investigated. The α-silyloxyketone group of product **2l** serves as a useful handle for further transformation. For example, **2l** was converted into diol **5** in 91% yield and 2.3:1 d.r. by reaction with NaBO$_3$·4H$_2$O[15] followed by methyllithium (Scheme 4). Selective protection of the secondary alcohol of **5** as a pivaloyl ester gave **6**. Removal of the TBS group of **6** with TBAF and reaction of the resulting diol with PhI(OAc)$_2$ in the presence of Et$_3$N gave methyl

Scheme 2. Preparation of *Z*-homoallylic boronates. Reactions were conducted with 0.30 mmol of **1**. Values in parentheses refer to the ratios of **2** to **3**, which were determined by ^{1}H NMR analysis of the crude mixtures. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] Using 0.20 mmol of **1e**. [b] Results of a reaction conducted with 4.00 mmol of **1g** and a 0.02 mol% catalyst loading. [c] Substrate **1j** contained minor impurities, some of which may be alkene stereoisomers.

Scheme 4. Further transformations of **2l**.

Scheme 6. 1,3-Dipolar cycloaddition of **2g** with **12** and conversion of pyrrolidine **13** into a crystalline derivative **14**.
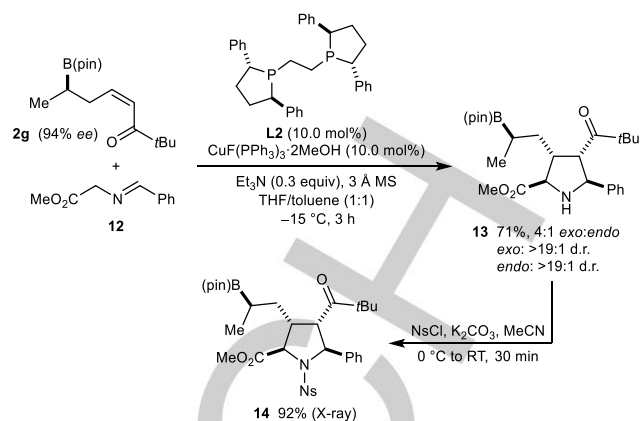
ketone **7** in 82% yield, without affecting the *Z*-alkene. Alternatively, reaction of **6** with MAD [methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)][16] triggered a pinacol rearrangement to give methyl ketone **8** in 80% yield, again without affecting the *Z*-alkene.

In another example of further manipulation, **2g** was reduced with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (Scheme 5).[17] This reaction gave a 5:1 mixture of diastereomeric alcohols **9a** and **9b**, which were isolated in 62% and 12% yield, respectively. The diastereoselectivity is noteworthy, given the remote 1,5-stereoinduction involved. Since previous applications of this reagent required a coordinating group near the ketone for high diastereoselectivity,[17] this result suggests that aluminum may coordinate to one of the oxygen atoms of the pinacolboronate.[18] Oxidation of **9a** with NaBO$_3$·4H$_2$O[15] gave diol **10**, which was converted into diester **11** by acylation with 4-nitrobenzoyl chloride. X-ray crystallography of **11** allowed determination of the relative and absolute configuration.[19]

access chiral, highly substituted pyrrolidines, which are structures of widespread chemical and biological significance.[20] Although various dipolarophiles have been employed in these reactions,[20] *Z*-acyclic α,β-unsaturated ketones have been virtually unexplored.[21] This omission is perhaps unsurprising given that these substrates are more difficult to prepare in high stereoselectivity compared with their *E*-configured counterparts, and addressing this deficiency would give access to a wider range of functionalized pyrrolidines. Our initial attempts to react *Z*-homoallylic boronate **2g** with methyl (*E*)-2-(benzylideneamino)acetate (**12**) under various conditions employed in previously reported examples of 1,3-dipolar cycloadditions[20] were unsuccessful. However, the reaction of **2g** with **12** in the presence of CuF(PPh$_3$)$_3$·2MeOH (10.0 mol%), (*R*,*R*)-Ph-BPE (**L2**, 10.0 mol%), Et$_3$N (0.3 equiv) and 3 Å molecular sieves in toluene at room temperature gave pyrrolidine **13** in 4:1 *exo:endo* selectivity and high diastereoselectivity.[22,23] After purification, **13** was obtained in 71% yield. Reaction of **13** with *para*-nitrophenylsulfonyl chloride gave **14**, the stereochemistry of which was determined by X-ray crystallography.[19]

In summary, we have developed switchable, highly enantioselective copper-catalyzed 1,6-borations to give two different classes of products. This method can provide homoallylic boronates containing a (*Z*)-α,β-unsaturated ketone with high *Z*-selectivities (>95:5 *Z*:*E*). 1,6-Borations to access this product class have not been described previously. By changing the solvent and concentration, and increasing the equivalents of the protic additive *i*PrOH, *E*-allylic boronates are obtained (>95:5 *E*/*Z*). The utility of the *Z*-homoallylic boronates was demonstrated by a range of further transformations.
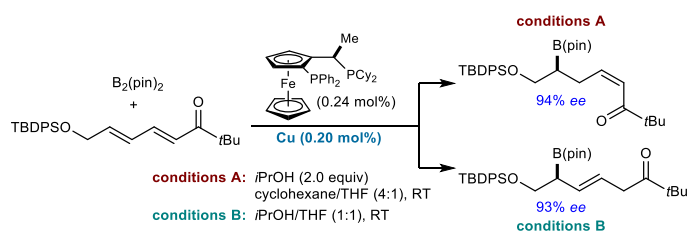
Acknowledgements

Scheme 5. Reduction of **2g** and conversion of **9a** into a crystalline derivative.

Finally, 1,3-dipolar cycloadditions of the *Z*-homoallylic boronates with azomethine ylides were investigated (Scheme 6). Enantioselective cycloadditions of azomethine ylides with electron-deficient alkenes are powerful transformations to

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[23] The minor diastereomers of the *exo*- and *endo*-cycloaddition products are those where the four stereocenters of the pyrrolidine ring are of the opposite absolute configuration.

COMMUNICATION

Y. Luo, S. M. Wales, S. E. Korkis, I. D. Roy, W. Lewis, H. W. Lam*

Switchable Synthesis of *Z*-Homoallylic Boronates and *E*-Allylic Boronates by Enantioselective Copper-Catalyzed 1,6-Boration

Flip the switch: The enantioselective Cu-catalyzed 1,6-boration of (*E*,*E*)-α,β,γ,δ-unsaturated ketones is described, which gives homoallylic boronates with high enantiomeric purity and unexpectedly high *Z*-selectivity. By changing the solvent, the outcome can be altered to give *E*-allylic boronates.