

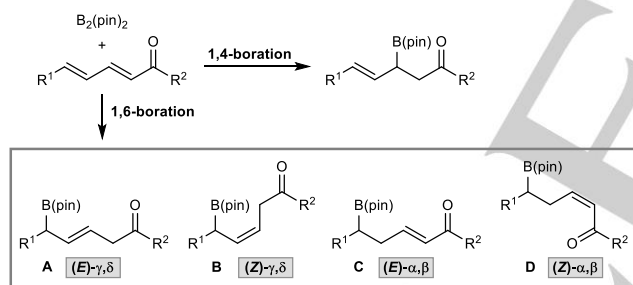
Switchable Synthesis of *Z*-Homoallylic Boronates and *E*-Allylic Boronates by Enantioselective Copper-Catalyzed 1,6-Boration

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*)- $\alpha,\beta,\gamma,\delta$ -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.

Enantioselectively 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 $\alpha,\beta,\gamma,\delta$ -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



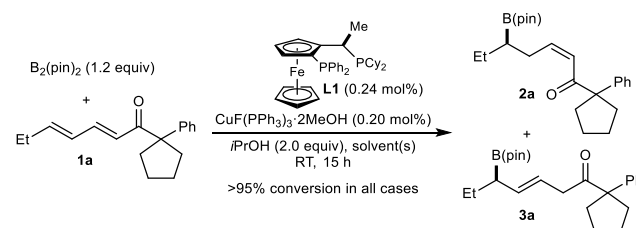
Scheme 1. Possible products from boration of an $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl

acyclic $\alpha,\beta,\gamma,\delta$ -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 $\alpha,\beta,\gamma,\delta$ -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 $\alpha,\beta,\gamma,\delta$ -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 $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **1a** (Table 1) with $B_2(\text{pin})_2$ (1.2 equiv) in THF (0.1 M) in the presence of $\text{CuF}(\text{PPh}_3)_3 \cdot 2\text{MeOH}$ (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

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>i</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 ¹H NMR analysis of the unpurified reaction mixtures.

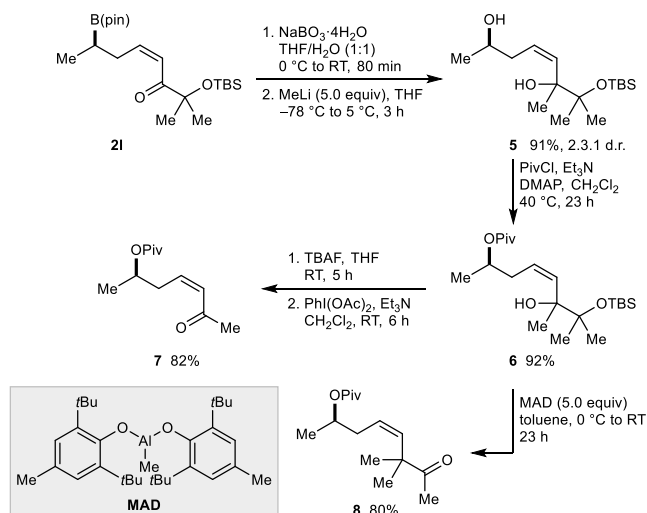
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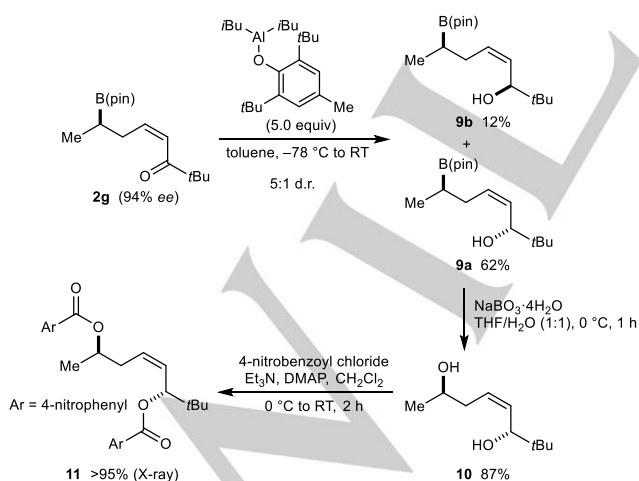
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Scheme 4. Further transformations of **2l**.

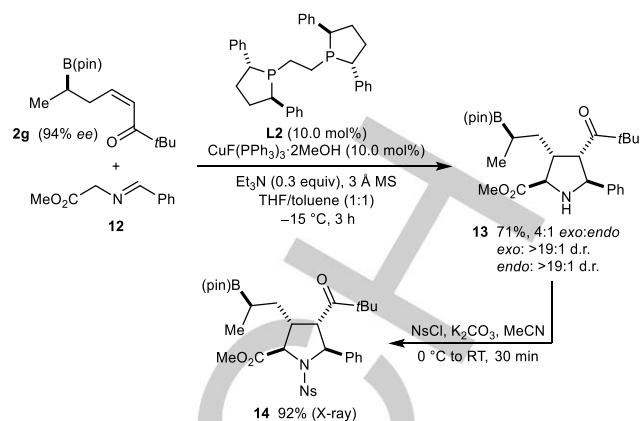
ketone **7** in 82% yield, without affecting the *Z*-alkene. Alternatively, reaction of **6** with MAD [methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)]^[16] triggered a pinacol rearrangement to give methyl ketone **8** in 80% yield, again without affecting the *Z*-alkene.

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-stereoiduction 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 NaBO₃·4H₂O^[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]



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



Scheme 6. 1,3-Dipolar cycloaddition of **2g** with **12** and conversion of pyrrolidine **13** into a crystalline derivative **14**.

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(PPh₃)₃·2MeOH (10.0 mol%), (*R,R*)-Ph-BPE (**L2**, 10.0 mol%), Et₃N (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.

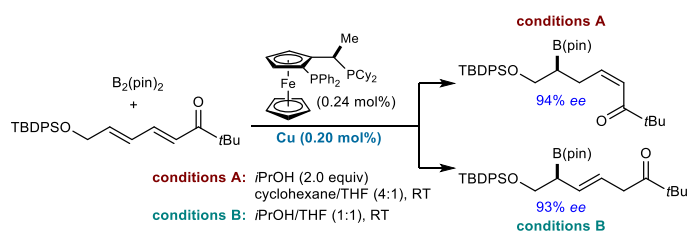
Acknowledgements

This work was supported by the European Research Council [grant number 258580] through a Starting Grant; the Engineering and Physical Sciences Research Council [grant numbers EP/I004769/1, EP/I004769/2, EP/H031588/1] through a Leadership Fellowship to H.W.L. and a PhD studentship to I.D.R.; Pfizer; GlaxoSmithKline; and the University of Nottingham.

Keywords: 1,6-addition • asymmetric catalysis • boron • copper • enantioselectivity

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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



Flip the switch: The enantioselective Cu-catalyzed 1,6-boration of (*E,E*)- $\alpha,\beta,\gamma,\delta$ -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.

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