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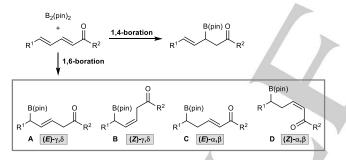
# Switchable Synthesis of *Z*-Homoallylic Boronates and *E*-Allylic Boronates by Enantioselective Copper-Catalyzed 1,6-Boration

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**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.

**E**nantiomerically enriched  $\alpha$ -stereogenic alkylboron compounds have numerous applications in organic synthesis.<sup>[1-3]</sup> One important route to these compounds is the catalytic enantioselective boration of electron-deficient alkenes.<sup>[4-7]</sup> Although numerous examples of 1,4-boration are known,<sup>[4-7]</sup> only a few examples of 1,6-boration have been described.<sup>[8,9]</sup> 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  $\beta$ , $\beta$ -disubstituted  $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -unsaturated cyclic ketones that give products of type **C** [(*E*)- $\alpha$ , $\beta$ ],<sup>[8a]</sup> 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

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acyclic  $\alpha, \beta, \gamma, \delta$ -unsaturated esters and ketones that give products of type A [(E)- $\gamma$ , $\delta$ ].<sup>[8b]</sup> 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, perhaps unsurprising which is as they contain thermodynamically less-stable Z-alkenes.[10,11] Compared with Ealkenes, there are fewer effective methods for the highly stereoselective synthesis of Z-alkenes,<sup>[12]</sup> and new reactions that address this issue are therefore valuable.

Herein, we describe enantioselective copper-catalyzed 1,6borations of acyclic  $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -unsaturated ketones that give homoallylic boronates of type **D**. In addition to containing  $\alpha$ 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.<sup>[13]</sup>

During our studies of enantioselective copper-catalyzed 1,6borations that give *E*-allylic boronates of type **A**,<sup>[8b]</sup> 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<sub>2</sub>(pin)<sub>2</sub> (1.2 equiv) in THF (0.1 M) in the presence of CuF(PPh<sub>3</sub>)<sub>3</sub>·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

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

Et ~~~	+ O Ph CuF(PPh_3)_3:2M /PrOH (2.0 eq RT,	eOH (0.20 mol%) uiv), solvent(s) 15 h ion in all cases	Ph Ph
Entry	Solvent(s)	Concentration (M)	2a:3a <sup>[b]</sup>
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

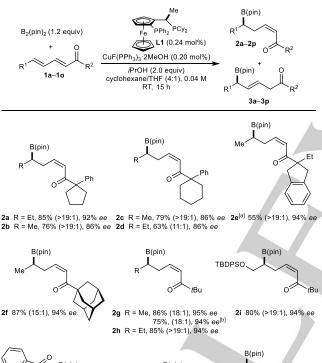
[a] Reactions were conducted using 0.20 mmol of  ${\rm 1a.}$  [b] Determined by  ${\rm ^1H}$  NMR analysis of the unpurified reaction mixtures.



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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  $\alpha, \beta, \gamma, \delta$ -unsaturated ketones with sterically hindering carbonyl substituents (Scheme 2). These reactions were generally highly selective for the formation of Zhomoallylic 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 1phenylcyclohexyl (2c and 2d), 2-ethyl-2,3-dihydro-1H-inden-2-yl (2e), adamantyl (2f), and tert-butyl (2g-2k). Groups containing silyloxy (2I-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



B(pin) B(pin) TsC OTBS Mé Ő Ме 2k 72% (>19:1), 94% ee 2i<sup>[c]</sup> 85% (12:1), 89% ee 21 93%, (>19:1), 88% ee B(pin) Me B(pin) B(pin) O.  $\sim$ OEt M

0=

20 76% (4:1), 94% ee

OEt

2p 76% (6:1), 94% ee

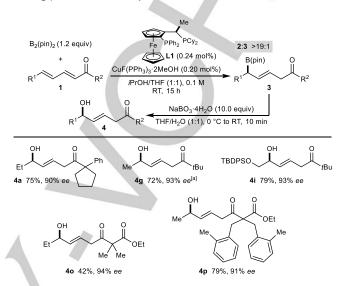
2n R = TBDPS, 58% (6:1), 93% ee Scheme 2. Preparation of Z-homoallylic boronates. Reactions were conducted with 0.30 mmol of 1. Values in parentheses refer to the ratios of 2 to 3, which were determined by <sup>1</sup>H NMR analysis of the crude mixtures. Enantiomeric excesses were determined by HPLC 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.

Me Me

2m R = TBS, 69% (10:1), 94% ee

formation of 21 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  $\delta$ -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.

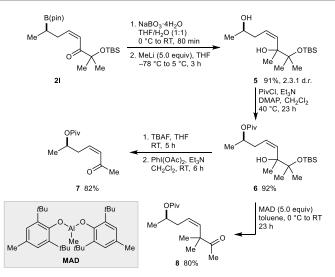


Scheme 3. Enantioselective Cu-catalyzed 1,6-boration-oxidation of electrondeficient dienes to give E-allylic alcohols. Reactions were conducted with 0.30 mmol of 1. Yields are of isolated material. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] iPrOH/THF (2:1) was used instead of iPrOH/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 NaBO3·4H2O<sup>[15]</sup> 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 Zhomoallylic boronate and E-allylic boronate. Fortunately, changing to iPrOH/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.<sup>[13]</sup>

Currently, the reasons for selective formation of Zhomoallylic 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.

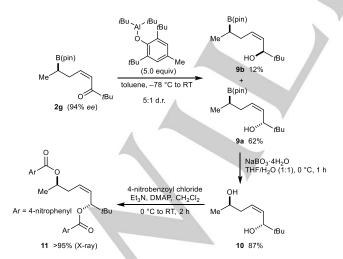
Next, the synthetic utility of the products was investigated. The a-silyloxyketone group of product 2I serves as a useful handle for further transformation. For example, 2I was converted into diol 5 in 91% yield and 2.3:1 d.r. by reaction with NaBO<sub>3</sub>·4H<sub>2</sub>O<sup>[15]</sup> followed 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)<sub>2</sub> in the presence of Et<sub>3</sub>N gave methyl



Scheme 4. Further transformations of 21.

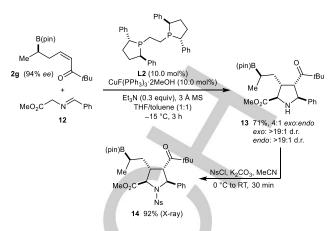
ketone **7** in 82% yield, without affecting the *Z*-alkene. Alternatively, reaction of **6** with MAD [methylaluminum bis(2,6-di*tert*-butyl-4-methylphenoxide)]<sup>[16]</sup> triggered a pinacol rearrangement to give methyl ketone **8** in 80% yield, again without affecting the *Z*-alkene.

In another example of further manipulation, 2g was reduced diisobutylaluminum 2,6-di-tert-butyl-4-methylphenoxide with (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 ketone for high the diastereoselectivity,[17] this result suggests that aluminum may coordinate to one of the oxygen atoms of the pinacolboronate.<sup>[18]</sup> Oxidation of 9a with NaBO<sub>3</sub>·4H<sub>2</sub>O<sup>[15]</sup> 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.<sup>[19]</sup>



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.<sup>[20]</sup> Although various dipolarophiles have been employed in these reactions,<sup>[20]</sup> Z-acyclic  $\alpha$ , $\beta$ -unsaturated ketones have been virtually unexplored.<sup>[21]</sup> 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 with Z-homoallylic boronate 2g methyl (E)-2-(benzylideneamino)acetate (12) under various conditions employed in previously reported examples of 1,3-dipolar cycloadditions<sup>[20]</sup> were unsuccessful. However, the reaction of 2g with 12 in the presence of CuF(PPh<sub>3</sub>)<sub>3</sub>·2MeOH (10.0 mol%), (R,R)-Ph-BPE (L2, 10.0 mol%), Et<sub>3</sub>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.<sup>[22,23]</sup> 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)- $\alpha$ , $\beta$ -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

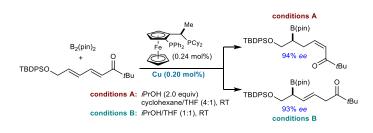
This work was supported by the European Research Council [grant number 258580] through a Starting Grant; the Engineering and Physical Sciences Research Council [grant numbers EP/I004769/1, EP/I004769/2, EP/H031588/1] through a Leadership Fellowship to H.W.L. and a PhD studentship to I.D.R.; Pfizer; GlaxoSmithKline;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

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

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- [22] This reaction using (*R*,*R*)-BPE (L2) is the stereochemically matched case. When (*S*,*S*)-Ph-BPE (*ent*-L2) or achiral bisphosphines were used, complex mixtures of diastereomeric products were obtained.
- [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.

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**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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