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COMMUNICATION

Copper-catalyzed Protoboration of Borylated Dendralenes: A Regio- and Stereoselective Access to Functionalized 1,3-Dienes

Andrea Chaves-Pouso, Eva Rivera-Chao and Martín Fañanás-Mastral*

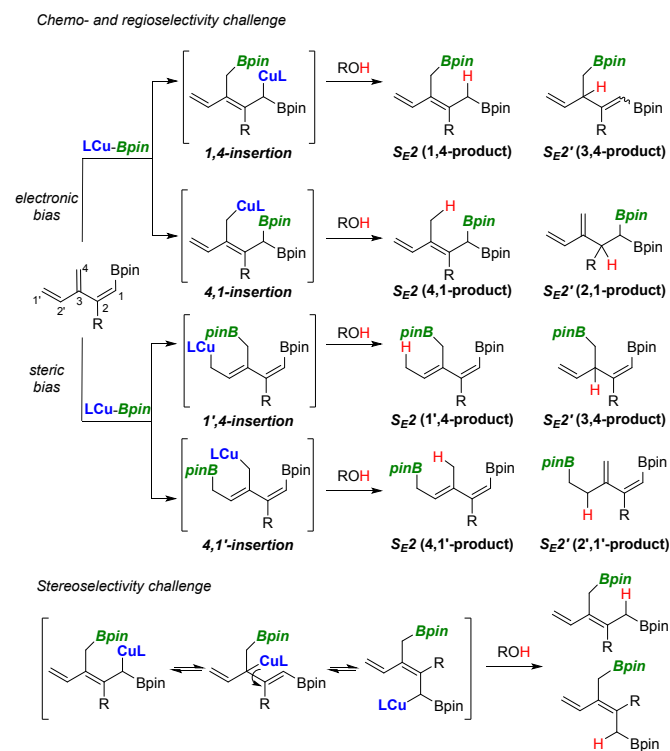
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A copper-catalyzed protoboration of borylated dendralenes is reported. The method employs an NHC-Cu catalyst and provides access to 1,4-addition products with excellent levels of chemo-, regio- and stereoselectivity. The resulting diene bis(boronates) are oxidized to the corresponding diene diols which are synthetically versatile building blocks.

Acyclic branched cross-conjugated polyenes, namely dendralenes, represent an attractive class of unsaturated hydrocarbons.¹ After being neglected in the past decades, recent discoveries on the preparation of these structures have made them available for organic synthesis.² Dendralenes have been mainly used as building-blocks to efficiently generate polycyclic structures based on their ability to engage in diene-transmissive Diels-Alder reactions.³ Moreover, dendralenes have also served as precursors for the synthesis of oligocyclopropanes⁴ and in vinylogous Nazarov reactions.⁵ Despite these advances, metal-catalyzed reactions that allow the functionalization of dendralenes are scarce and still represent a major challenge.^{2c,6} Indeed, control over the selectivity in these transformations is difficult due to the multiple potential coordination and insertion modes between these cross-conjugated hydrocarbons and a transition metal catalyst.⁷ We recently reported a catalytic methodology to synthesize borylated dendralenes and started a program on the functionalization of this new type of substrates.⁸ Among the approaches to functionalize unsaturated hydrocarbons, copper-catalyzed borylations based on LCu-Bpin insertion and electrophilic trapping of the resulting organocopper intermediate have become useful reactions to provide multifunctional structures.⁹ Within this context, we decided to develop a selective catalytic protoboration of borylated

dendralenes that would provide access to bifunctional diene structures (Scheme 1).



Scheme 1. Selectivity challenges in the copper-catalyzed protoboration of dendralenes. Possible intermediates generated from a 1,2-insertion type are omitted for clarity.¹¹

Successful implementation of this transformation requires a copper catalyst capable of performing a selective borylcupration step leading to an organocopper intermediate which undergoes selective protonation. The presence of two cross-conjugated dienes in the dendralene structure imposes a big selectivity challenge since the chemoselective recognition of one diene moiety adds to the difficulty typically associated with the control of regioselectivity in the LCu-Bpin addition across substituted 1,3-dienes.^{6,10} Moreover, the protonation of the

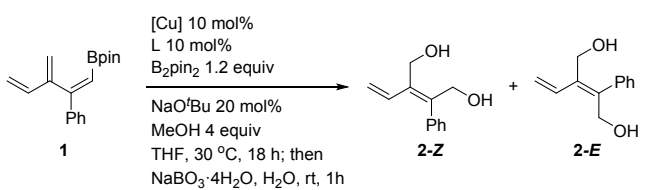
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resulting pentadienyl-copper intermediate could occur either in a formal S_E2 or a S_E2' (or even S_E2'') fashion, while 1,3-metallo shift rearrangement in the allylcopper intermediate could lead to mixtures of *Z* and *E* isomers (Scheme 1). All these mechanistic intricacies provide a challenging scenario with the potential formation of many different possible isomeric products. Herein, we report a catalytic methodology that overcomes this mechanistic puzzle and allows for the chemo-, regio- and stereoselective protoboration of borylated dendralenes. The reaction operates under mild conditions and affords 1,4-products which represent synthetically versatile bifunctional dienes.

We started our study by surveying the copper-catalyzed protoboration of dendralene **1** using bis(pinacolato)diboron (B_2pin_2) and MeOH as the protic source, and performing an additional oxidation step to allow a more facile purification of the resulting diene diol **2** (Table 1).

Table 1. Optimization studies



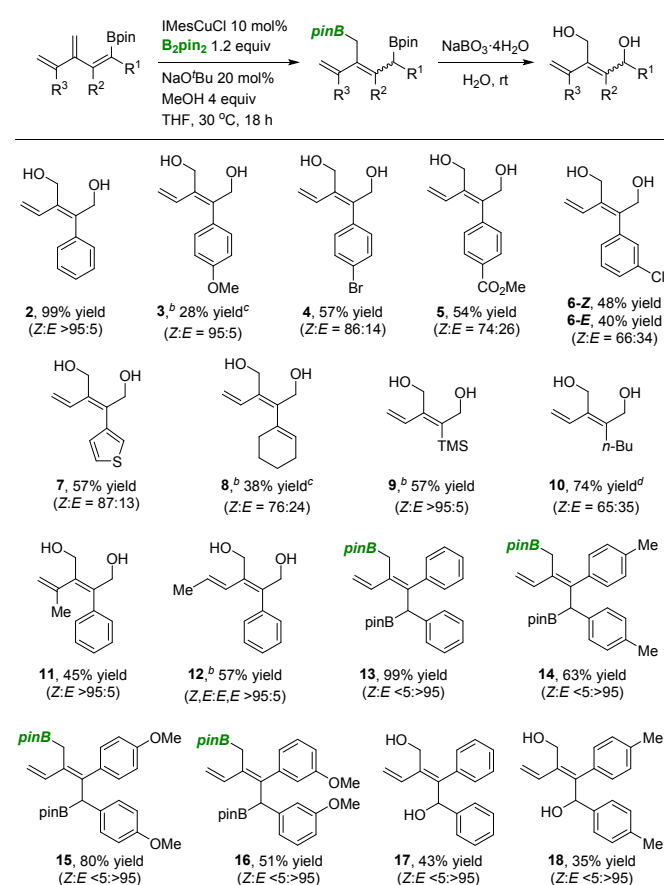
Entry ^a	[Cu]	Ligand	Z:E ^b	Yield (%)	
				2-Z ^b	2-E ^b
1	CuCl	PPh ₃	56:44	20	16
2	CuCl	PCy ₃	89:11	75	10
3		IMesCuCl	>95:5	>95	-
4		IPrCuCl	>95:5	49	-
5	CuCl	<i>rac</i> -BINAP	-	-	-
6	CuCl	dppf	-	-	-
7	CuCl	Xantphos	-	12	-

^a Reactions run on a 0.2 mmol scale. ^b Determined by ¹H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

Initial experiments showed that only the 1,4-addition product was formed, suggesting that the presence of a boronate group in the dendralenic structure may produce an electronic bias in the system thus favoring the LCu-Bpin insertion in the dienyl boronate moiety instead of the other sterically favored diene. We observed that the nature of the catalyst had a profound effect both in the efficiency and stereoselectivity of the reaction. By using CuCl/PPh₃ as catalyst diene diol **2** was obtained in low yield and as a 56:44 mixture of *Z/E* isomers (entry 1). The use of a more electron-rich phosphine PCy₃ caused a significant improvement (entry 2). This observation moved us to the exploration of NHC ligands which led to the identification of IMesCuCl as the most efficient catalyst, providing **2** as a pure *Z* isomer in almost quantitative yield (entry 3). Interestingly, the use of bidentate ligands led to negligible yields in all cases (entries 5-7).

Having established the optimized conditions for the copper-catalyzed protoboration of borylated dendralenes (Table 1, entry 3), we set out to investigate the scope of the reaction (Scheme 2). Borylated dendralenes bearing aromatic (**2-6**),

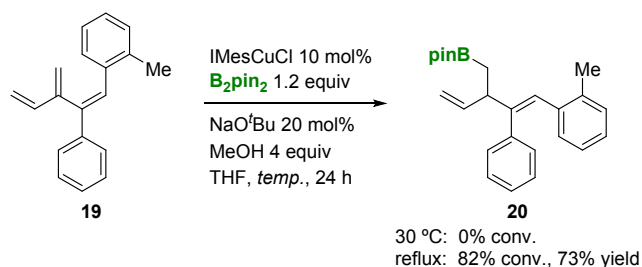
heteroaromatic (**7**), alkenyl (**8**), silyl (**9**) or aliphatic (**10**) groups in the 2-position worked well affording the corresponding 1,4-products with excellent chemo- and regioselectivity. These diene diols were generally obtained with high *Z* selectivity, although it decreased when substrates bearing electron poor aromatic groups, or an aliphatic substituent, were used. It is important to note that in most cases the *Z* isomer could be isolated pure. Dendralenes featuring substitution in both 1,3-positions could also be used, as illustrated by the synthesis of **11** and **12**. These borylated dendralenes showed slightly diminished reactivity, although they still underwent the copper-catalyzed protoboration with excellent chemo-, regio- and stereoselectivity. Dendralenes bearing an aryl group in the adjacent position to the boron atom were also efficient substrates. Surprisingly, the stereoselectivity of the reaction was totally reversed and the corresponding diene bis(boronates) **13-16** could be isolated in good yields as pure *E* isomers. Oxidation of these organoboronates produced *E*-diene diols in moderate yield with total stereoretention,¹² as illustrated with the synthesis of **17** and **18**.



Scheme 2. Scope of the reaction. ^a Reactions performed on a 0.2 mmol scale. Yields refer to isolated pure *Z* isomer unless otherwise noted. ^b Run at 50 °C. ^c Product partially decomposed under column chromatography. ^d Yield of the *Z/E* isomeric mixture.

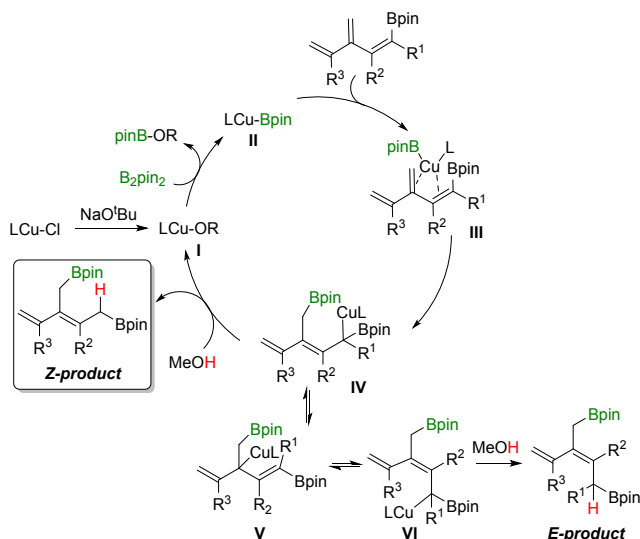
Importantly, the regioselectivity observed in the present transformation is different to the one reported by Mazet in two single examples involving the copper-catalyzed protoboration

of dendralenic 1,3-dienes.⁶ To explore the role of the boronic ester group over the reaction efficiency and selectivity we decided to investigate the protoboration of non-borylated dendralene **19** which features a similar substitution pattern than **1** (Scheme 3). Under optimized conditions, no conversion was observed. By increasing the reaction temperature, conversion was achieved observing a complete change in regioselectivity with the exclusive formation of the 3,4-product, the skipped dienylyl boronate **20**. Interestingly, NMR analysis revealed that the stereochemistry of the trisubstituted olefin was inverted in this transformation. This may be due to a LCu-Bpin 1,4-insertion followed by a S_E2'-type protonation. This result further suggests the relevance of the boronic ester in the outcome of the protoboration of borylated dendralenes.



Scheme 3. Copper-catalyzed protoboration of non-borylated dendralene **19**.

Based on these experimental observations and literature precedents, we propose the following catalytic cycle and working models for selectivity in the copper-catalyzed protoboration of borylated dendralenes (Scheme 4).

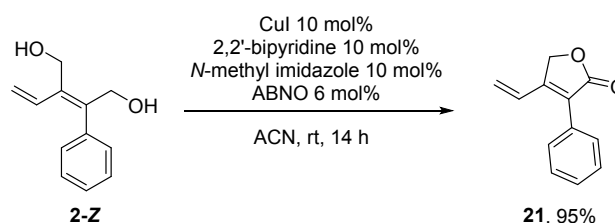


Scheme 4. Proposed mechanism

Boryl copper complex **II**, generated from B₂pin₂, IMesCuCl and NaOtBu, would coordinate the *s-cis* dienylyl boronate moiety of dendralene in a η^4 fashion giving rise to copper complex **III**. Subsequent 1,4-insertion diene would lead to *Z*-configured organocopper intermediate **IV**. Although an alternative pathway involving a 1,2-insertion followed by isomerization could also be considered, the absence of reactivity observed for copper complexes featuring bidentate ligands and the high *Z*

selectivity support a η^4 coordination and a 1,4-insertion.^{10e-f} In this regard, the conformation of the cross-conjugated triene may also play an important role favoring the *s-cis* conformation required for the η^4 coordination.^{5c,13,14} The presence of substituents in the 4 and 5 positions of the dendralene core may affect the conformation of the dienylylboronate unit and could explain the diminished reactivity of those dendralenes (synthesis of **11** and **12**).¹⁵ Moreover, formation of **IV** would be favored by electronic stabilization from the adjacent boron atom.¹⁶ A fast S_E2' protonation with MeOH would finally lead to the formation of *Z*-configured diene bis(boronate) with concomitant regeneration of copper alkoxide **I**. Erosion on the *Z* selectivity in dendralenes bearing electron poor aromatic group in the 2-position would be likely caused by stabilization of the organocopper intermediate, which could result in a competitive 1,3-metallo shift leading to the formation of an *E*-configured organocopper intermediate **VI**. The complete *E* selectivity observed for dendralenes bearing an aryl group in the position adjacent to the boron atom could be explained by an even stronger stabilization of the resulting allyl/benzyl copper intermediate, although in this case a direct 3,4-insertion leading to intermediate **V** and an alternative S_E2' protonation cannot be discarded due to a more sterically hindered situation at the 1-position.

It is important to note that this type of diene diols has been used as key building blocks in the synthesis of taxoids.¹⁷ Moreover, oxidative lactonization of *Z*-diene diol **2** under copper catalysis reported by Stahl¹⁸ afforded vinyl-substituted butenolide **21** in 95% yield and with total regioselectivity (Scheme 5).



Scheme 5. Oxidative lactonization of diene diol **2**

In conclusion, we have developed an efficient method for the protoboration of borylated dendralenes. This reaction provides bifunctional dienes with excellent levels of chemo-, regio- and stereoselectivity. Further mechanistic investigations and development of new synthetic applications of these compounds are underway.

Acknowledgements

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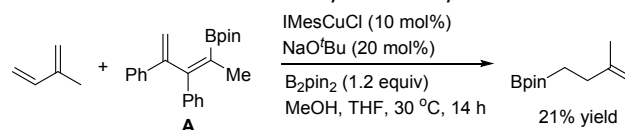
Conflicts of interest

There are no conflicts to declare.

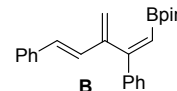
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- Formation of 1,2-addition organocopper intermediates in the borylation of 1,3-dienes is also possible but these species tend to rapidly isomerize to the 1,4 addition isomers. See reference 10a.
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- A competition experiment between isoprene and dienylboronate **A**, which resemble the substitution pattern of both 1,3-diene units of the used dendralenes, resulted in only

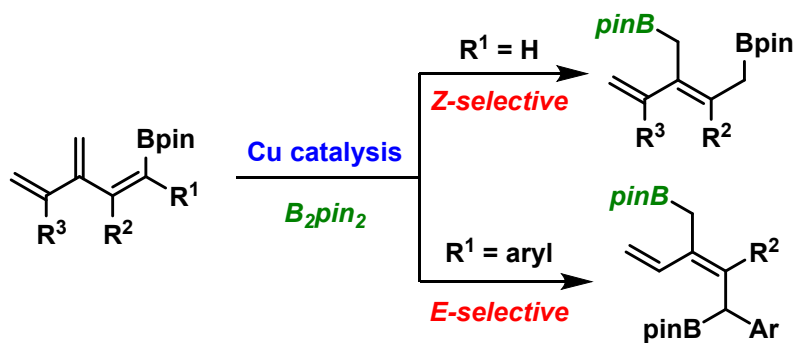
minimal protoboration of isoprene. This result supports the important role of the cross-conjugated triene structure in the conformation and thus reactivity of the borylated dendralene.



- 15 Reaction with a 5-phenyl substituted borylated dendralene **B** resulted in no conversion even at elevated temperatures.



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A copper-catalyzed protoboration of borylated dendralenes that provides stereodefined bifunctional 1,3-dienes is reported.