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Authors: Mariola Tortosa, Laura Amenós, Laura Trulli, Luis Nóvoa, and Alejandro Parra

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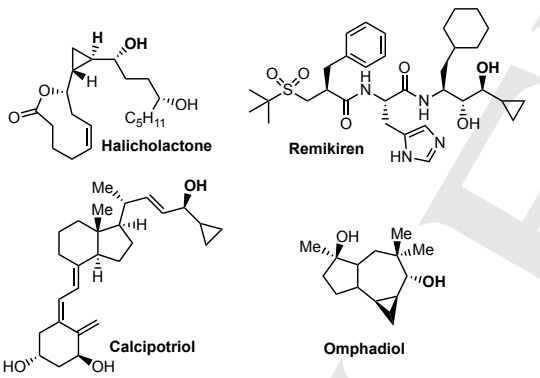
Stereospecific Synthesis of α-Hydroxy-Cyclopropylboronates from Allylic Epoxides

Laura Amenós, Laura Trulli, Luis Nóvoa, Alejandro Parra and Mariola Tortosa*[a]

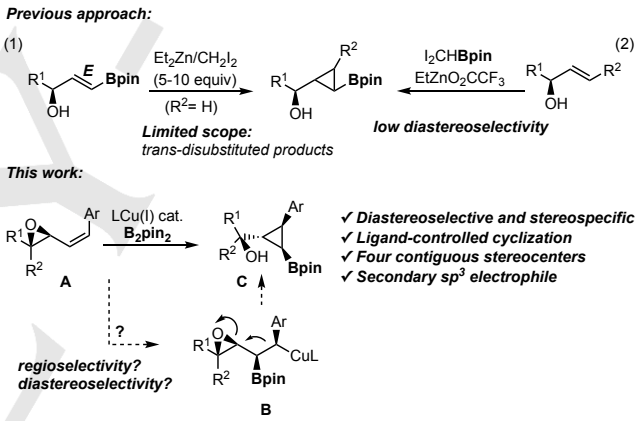
Abstract: *Herein, we report a catalytic and stereospecific method for the preparation of enantioenriched α-hydroxy cyclopropylboronates with control in four contiguous stereocenters. The reaction involves the borylation of readily available allylic epoxides using an inexpensive Cu(I) salt and a commercially available phosphine ligand. High diastereocontrol is achieved and different diastereomers can be selectively prepared. Functionalization of the carbon-boron bond provides access to different enantiomerically enriched trisubstituted cyclopropanes from a common intermediate.*

Stereodefined cyclopropanes are increasingly important scaffolds in modern drug discovery research.[1] The introduction of the cyclopropyl fragment into a lead compound can enhance the potency, increase metabolic stability, improve binding to the target and reduce the off-target effects.[2] Cyclopropanes with multiple stereocenters provide rigidity while also increasing three-dimensionality. These two properties make them ideal fragments to explore new areas of chemical space in medicinal chemistry.[3] Among biologically active cyclopropane derivatives, the α-hydroxy cyclopropyl fragment represents a prevalent core structure present in several natural products and drugs (Scheme 1).



Scheme 1. α-Hydroxy cyclopropanes in natural products and drugs.

Recently, we and others have been involved in the design of new synthetic methods to prepare stereodefined cyclopropylboronates.[4] These versatile molecules are promising synthetic intermediates for the preparation of functionalized cyclopropanes. The carbon-boron bond is configurationally stable and the boryl moiety offers a handle for further functionalization.[5] Enantiomerically enriched cyclopropylboronates have been prepared through cyclopropanation of vinyl boronates,[6] desymmetrization of cyclopropenes[7] and borylative ring closure of allylic carbonates and phosphates.[8],[9] However, one important subclass of cyclopropylboronates that is still underdeveloped is that containing a secondary α-hydroxy group, such as those shown in Scheme 1. The introduction of a boryl moiety to this fragment would provide a modular platform to incorporate α-hydroxy cyclopropanes into organic molecules. The main approach used for the preparation of α-hydroxy cyclopropylboronates is the diastereoselective cyclopropanation of vinyl boronates or allylic alcohols (eq. 1-2, Scheme 2). This strategy presents limitations in the structural scope and the stereoselectivity. Starting from hydroxy vinyl boronates (eq. 1, Scheme 2) only *trans*-disubstituted products can be formed (R^2 = H).[10] Alternatively, the use of allylic alcohols and *in situ* generated boronate-substituted zinc carbenoids (eq. 2, Scheme 2) provides low diastereselectivity.[11]



Scheme 2. Synthesis of enantioenriched α-hydroxy cyclopropylboronates.

Based on our previous experience on copper-catalyzed borylation reactions,[7b],[12] we designed a novel strategy to prepare this class of compounds. We envisioned that allylic epoxides **A** could provide trisubstituted α-hydroxy cyclopropanes **C** through a regio- and diastereoselective borylation/cyclization sequence. Enantiomerically enriched allylic epoxides can be easily prepared by direct epoxidation of dienes or from α-epoxy alcohols through an oxidation-olefination sequence.[13] We planned to take advantage of the myriad of enantioselective methods to epoxidize alkenes[14] to develop a catalytic and stereospecific process in which the chirality of the epoxide would be transferred to the cyclopropane. Ideally, switching the geometry of the epoxide and/or the alkene would selectively provide different diastereoisomers with control in four contiguous stereocenters.

We began our investigation by examining the reactivity of enantiomerically enriched vinyl epoxide **1a** with B_2pin_2 (1.2 equiv.) in the presence of a catalytic amount of a Cu(I) salt and a variety of phosphine ligands (Table 1). The use of CuCl (10 mol%), PCy_3 (11 mol%) and NaO*t*Bu (1 equiv) in THF, failed to deliver detectable amounts of cyclopropylboronate **2a**. We did not observe formation of the 1,4-addition product either,[12a] with only diene **3a** being obtained (Table 1, entry 1). We reasoned

[a] Laura Amenós, Dr. Laura Trulli, Luis Nóvoa, Dr. Alejandro Parra and Dr. Mariola Tortosa
Organic Chemistry Department
Institute for Advance Research in Chemical Sciences (IAdChem)
Universidad Autónoma de Madrid, 28949 Madrid, Spain
E-mail: mariola.tortosa@uam.es

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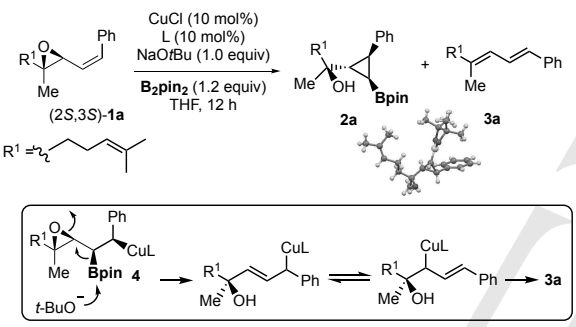
that diene **3a** could be formed from intermediate **4** (Table 1) via elimination of the boryl moiety and subsequent ring opening followed by isomerization of the resulting allyl copper intermediate and β-oxygen elimination.[15] The use of a bidentate phosphine with a small bite angle, dppBz (β_n = 83°), still favored the formation of **3a**, but we could identify a small amount of cyclopropane **2a** (Table 1, entry 2). Increasing the bite angle of the ligand had a dramatic effect on the formation of **2a**. Using DPEPhos (β_n = 102°) cyclopropane **2a** and diene **3a** were obtained in almost a 1:1 mixture (Table 1, entry 3). Switching to xantphos (β_n = 111°) the formation of diene **3a** was significantly diminished and cyclopropane **2a** was formed in high yield (Table 1, entry 4). Therefore, the ligand played a key role in the control of the cyclization over the diene formation. We then studied the effect of the base in the transformation. Changing the counterion from sodium to lithium resulted in lower yield of cyclopropane **2a** (Table 1, entry 5). On the contrary, KO*t*-Bu allowed us to completely suppress the formation of diene **3a** (Table 1, entry 6). When we reduced the amount of base (Table 1, entry 7) the yield for **2a** dropped down significantly.

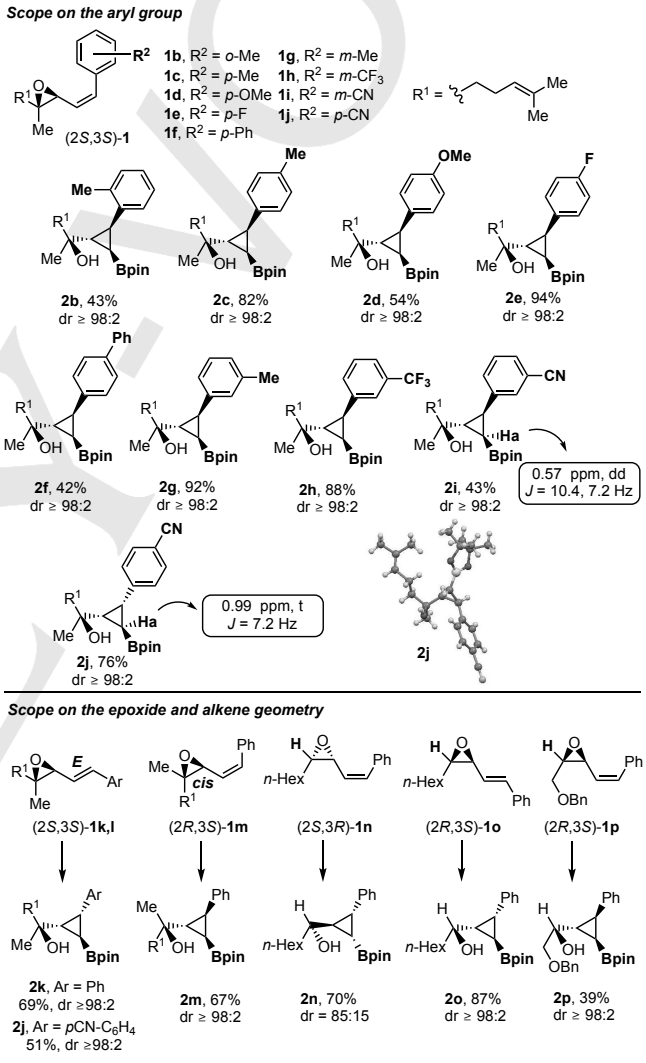
Table 1. Reaction Optimization[a]



Entry	Ligand	Change in other parameters	Yield 2a (%)[b]	Yield 3a (%)[b]
1	PCy_3	–	–	56
2	dppBz	–	4	60
3	DPEPhos	–	26	30
4	xantphos	–	77	6
5	xantphos	Using LiO*t*Bu	33	8
6	**xantphos**	**Using KO*t*Bu**	**85 (81)[c]**	**–**
7	xantphos	Using KO*t*Bu (0.5 equiv)	29	7

[a] Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.24 mmol), NaO*t*Bu (0.2 mmol), CuCl (10 mol%), **L** (11 mol%), THF (0.2 M). [b] Yield calculated by ^{1}H-NMR using 1,4-diacetylbenzene as internal standard.[c] Isolated yield.

Cyclopropane **2a** was obtained as a single diastereomer, indicating that the insertion step to form **4** and the cyclization took place with complete diastereocontrol. The relative configuration for the four contiguous sterocenters was determined from single-crystal X-ray crystallography of **2a**.[16] The exquisite control of the regio- and the diastereoselectivity in the insertion step is noteworthy and it is in contrast with our previous borylation of alkyl-substituted allylic epoxides, in which the *anti*-1,4-addition product was formed.[12a] There are several aspects of this transformation that are worth highlighting: 1) Only a few examples of cyclopropane formation from allylic epoxides are reported in the literature and they all involved the use of an excess of highly reactive organometallic species.[17] 2) This is the first example of a copper-catalyzed borylative *endo*-cyclization involving a secondary sp^3-electrophile.[8],[18] Compared to other *endo*-cyclizations, our method provides diastereoselective control and affords trisubstituted cyclopropanes with the boryl moiety and the aryl group in a *cis* relationship.[19] 3) This is an unusual example of a copper-catalyzed reaction of an allylic epoxide and a nucleophile that does not proceed *via* 1,4-addition.[13],[20]



Scheme 3. Scope of vinyl epoxides. Reaction conditions: **Table 1**, entry 6.

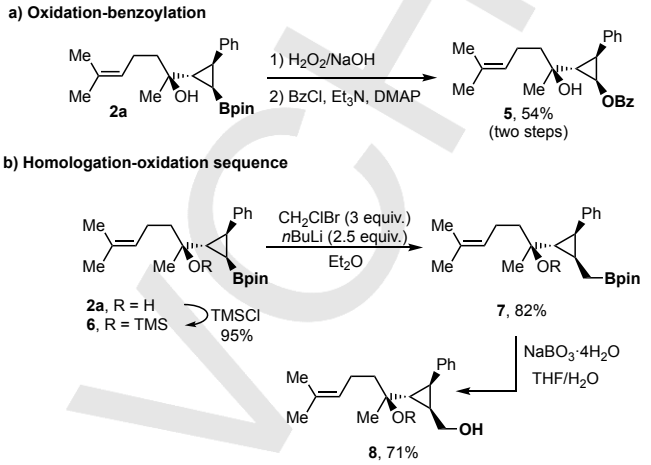
Having optimized the reaction parameters for the cyclopropane formation, we evaluated the substrate scope (Scheme 3). We first modified the stereoelectronic effects of the aryl group on the alkene. The reaction showed good tolerance to *ortho*- (**2b**), *para*- (**2c**-**2f**) and *meta*- (**2g**-**2i**) substitution. In all cases, cyclopropanes **2** were obtained as single diastereomers. Surprisingly, epoxide **1j**, with a cyano group in *para*-, cleanly afforded cyclopropylboronate **2j**, with the boronic ester and the aromatic ring in a *trans* relationship. The ^{1}H NMR of **2j** showed

significant differences (shift and multiplicity) for the proton adjacent to the boryl moiety (**Ha**) compared to the rest of the series (Scheme 3). Indeed, single-crystal X-ray crystallography analysis of **2j** revealed the formation of a different diastereomer.[21] This unexpected result could be explained by formation of an extended copper-enolate, favored by the electron-deficient aryl group.[22]

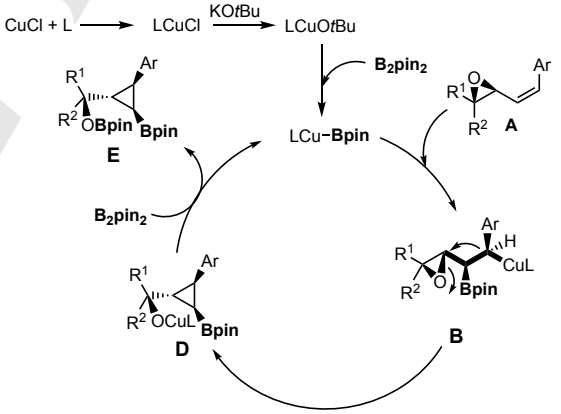
We next introduced changes in the geometry of the epoxide and the double bond. The relative configuration of the products can be controlled by careful selection of the structural features of the starting material. Allylic epoxides **1k** and **1l**, with an *E*-alkene, afforded cyclopropane **2k** and **2j** respectively, with a *trans* arrangement between the phenyl and the Bpin groups.[23] Additionally, epoxide **1m**, with a *cis* geometry in the oxirane ring, gave diastereomer **2m**, with a different relative stereochemistry between the oxygenated carbon and the three stereocenters on the cyclopropyl ring. Finally, *cis*-disubstituted epoxides **1n-p** provided cyclopropyl boronates **2n**, **2o** and **2p** in good and moderate yields. The diastereoselectivity observed for epoxide **1n** was slightly lower (dr = 85:15) but, cyclopylboronate **2n** was easily obtained as a single diastereomer after column chromatography. Cyclopropylboronate **2o** showed again that a *trans* arrangement between the phenyl and the Bpin groups is possible starting from an allylic epoxide with an *E*-alkene. The results above prove that our method is stereospecific and shows the potential to selectively access different stereoisomers. Starting from optically active epoxides, enantioenriched α-hydroxy cyclopropylboronates could be synthesized with excellent chirality transfer.[24]

To demonstrate the versatility of the products we performed different transformations of the C-B bond (Scheme 4). Oxidation of compound **2a** followed by benzoylation afforded functionalized cyclopropanol derivative **5**. Matteson homologation of TMS-protected cyclopropylboronate **6** provided cyclopropane **7** in excellent yield. Boronates such as **7** are valuable synthetic intermediates that could be used as homoallylation and homocrotylation reagents.[25] Oxidation of the carbon-boron bond in **7** provided functionalized cyclopropane **8** in good yield. Finally, a Suzuki-Miyaura cross coupling reaction between boronate **6** and iodobenzene allowed us to prepare cyclopropane **9** with retention of the configuration in the newly formed stereocenter.[8a,b]

A plausible mechanism for the copper-catalyzed stereospecific cyclopropanation is shown in Scheme 5. The catalytically active copper(I)-boryl complex is first formed from copper *tert*-butoxide and a diboron compound. Next, insertion of the alkene into the copper-boryl complex takes place. In this stereo-determining step intermediate **B** is formed. The observed stereochemical outcome could be explained by a *syn* approach of the copper(I)-boryl complex to an allylic epoxide in an *s-trans* conformation (as shown in **A**). This *syn* approach could be directed by coordination of the oxygen of the epoxide to the boron atom. From **B**, intramolecular S_N2 type reaction would afford cyclopropylboronate **D**. The *cis* relationship between the boryl moiety and the aryl group may result from a W-shaped transition state (blue bonds in **B**).[26] When starting from an *E* allylic epoxide such as **1k** this relationship would be *trans* (compound **2k**) via a similar transition state. Finally, reaction between copper alkoxide **D** and B_2pin_2 would form cyclopropylboronate **E** with regeneration of the copper-boryl complex.[27]



Scheme 4. C-B bond functionalization.



Scheme 5. Proposed mechanism.

In summary, starting from readily available allylic epoxides, we have developed a catalytic and stereospecific method for the preparation of enantioenriched α-hydroxy cyclopropylboronates with control of four contiguous stereocenters. Good yields and excellent diastereoselectivities are observed using an inexpensive Cu(I) salt and a commercially available phosphine ligand. The use of xantphos as ligand is critical to control undesired reaction pathways. Structural changes in the allylic epoxide allows for the selective synthesis of different diastereomers, without modifying the reaction conditions. Functionalization of the carbon-boron bond in the products provides a variety of enantiomerically enriched α-hydroxy trisubstituted cyclopropanes.

Acknowledgements

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Keywords: cyclopropane • boron • copper • allylic epoxide • cyclopropylboronate

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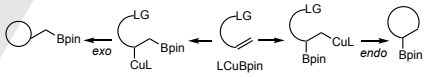
[18] We refer to borylative *endo*-cyclization to the one in which the boryl moiety is directly attached to the ring formed. On the other hand, borylative *exo*-cyclization is that in which the boryl moiety is not directly attached to the ring formed.



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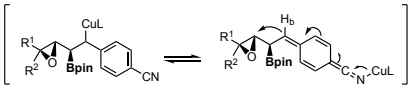
[21] CCDC 1873303 contains the supplementary crystallographic data for **2j**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

[22] The electron deficient aryl unit probably favors the formation of an extended copper-enolate that could cyclize to give **2j**, leaving H_b *cis* to the boryl moiety to minimize steric effects. Although a rapid isomerizacion of the double bond of the allylic epoxide cannot be ruled out, we did not detect any *E*-allylic epoxide when we monitored the reaction by ^{1}H NMR.



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[27] Compound **E** provides cyclopropylboronate **2** after hydrolysis of the O-B bond during work-up.

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✓ *Diastereoselective and stereospecific*
✓ *Four contiguous stereocenters*

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Copper-Catalyzed Stereoespecific Synthesis of α-Hydroxy-Cyclopropylboronates

Rigid sp^3 scaffolds: A catalytic and stereospecific method for the preparation of enantioenriched α-hydroxy cyclopropylboronates with control in four contiguous stereocenters is described. The reaction involves the borylation of readily available allylic epoxides using an inexpensive Cu(I) salt and a commercially available phosphine ligand. High diastereocontrol is achieved and different diastereomers can be selectively prepared.