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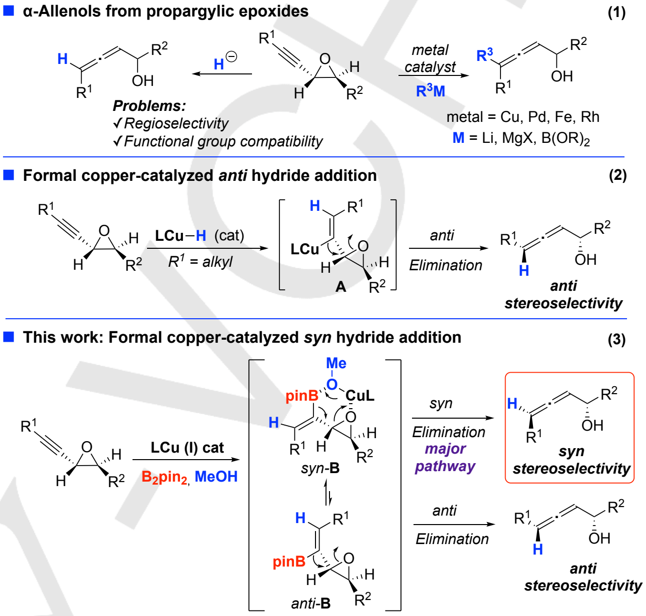
Stereoselective Traceless Borylation-Allenation of Propargylic Epoxides: Dual Role of the Copper-Catalyst.

Carlos Jarava-Barrera, Alejandro Parra, Laura Amenós, Ana Arroyo and Mariola Tortosa*

Abstract: Chiral α-allenols are prepared with high diastereocontrol through an unprecedented and spontaneous β-oxygen elimination of an α-epoxy vinyl boronate. Stochiometric experiments and DFT calculations support a dual role of the copper catalyst, which orchestrates the hydroboration and the *syn*-elimination step.

Allenes have become an important class of building blocks with a unique reactivity along their axially chiral backbone.[1] Among chiral allenes, α-hydroxyallenes are particularly interesting because they can be readily transformed into 2,5-dihydrofurans,[2] furanones[3] and different hetero-substituted allenes.[4] Although a number of methods have been recently developed,[5] the S_N2' substitution of propargylic epoxides with organometallic reagents is still the most general approach for the stereoselective preparation of α-allenols (Scheme 1, eq 1).[6] Despite significant efforts made in this field, the addition of a hydride anion, the smallest possible nucleophile, has proven a particular challenge in this space. The use of highly reactive metal hydrides presents problems regarding regiochemistry and functional group compatibility.[7] In 2007, Krause developed an elegant solution using catalytically generated copper hydride (Scheme 1, eq 2).[8] The reaction proceeded through the formation of vinyl copper species **A** that underwent an *anti* β-oxygen elimination to produce *anti*-allenols from *trans* epoxides, with high levels of diastereocontrol.

Inspired by this mechanism, we wondered if an α-epoxy vinyl boronate such as **B**, would participate in a β-oxygen elimination to generate allenes (Scheme 1, eq 3). While the β-oxygen elimination of vinyl metal species to produce allenes is a known pathway,[9] the use of a metalloid such as boron, has not been previously reported. Indeed, α-epoxy vinyl boronates **B** are elusive structures that had not been described in the literature. We planned to access these challenging intermediates from propargylic epoxides using copper-catalysis, by careful reaction optimization. We reasoned that the boron atom might provide an opportunity to -



Scheme 1. α-Allenols from propargylic epoxides

Challenges to this approach included potential regioselectivity issues in the borylation step, competition between the *syn-* and *anti*-elimination pathways and further undesired borylation of the products. However, if suitable conditions could be identified, this strategy would offer a route to prepare disubstituted α-allenols with relative stereochemistry and substitution patterns that complement those obtainable by existing methods. Importantly, this synthetic challenge would be tackled while exploring a novel mechanistic pathway. Herein, we report our efforts towards this goal.

To test our hypothesis, we prepared racemic propargylic epoxide **1a** and treated it under copper-catalyzed borylation conditions. We chose a phenyl substituent on the alkyne[10] hoping to overcome the inherent tendency of the copper-boryl complex generated *in situ* to form allenyl boronates from propargylic electrophiles through a formal S_N2' addition.[11] Moreover, over-borylation of the allene was a possible pathway that we needed to avoid.[12] Using B_2pin_2 (1.1 equiv.), CuCl (10 mol%), xantphos (11 mol%), NaO-*t*-Bu (20 mol%) and MeOH (2 equiv.) in THF we observed the formation of a 41:50:9 mixture of **2a**, **3a**, and homolallylic alcohol **4a**, with moderate yield (Table 1, entry 1). We reasoned that compound **4a** was probably formed through hydroboration-protodeboronation of allene **2a** under the reaction conditions. We did not observe formation of allenyl boronate **6,** and, surprisingly, no sign of vinyl boronate intermediate **5a** was observed in the ^{1}H NMR of the crude product. This experiment suggested that the hydroboration was taking place with the desired regiochemistry to give **5a**, and that the proposed elimination occurred spontaneously. This result was striking and encourage us to further optimize the reaction conditions to pursuit stereocontrol.

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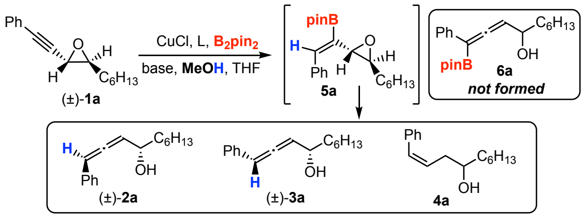
Table 1. Optimization of the reaction conditions[a]



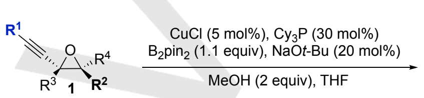
Entry	L	Base	**2a**:**3a**:**4a**[b]	Yield[c] (%)
1	xantphos	NaO-*t*-Bu	41:50:9	55
2	Ph_3P	NaO-*t*-Bu	79:9:12	70
3	Cy_3P	NaO-*t*-Bu	89:7:4	70
4	*t*-Bu_3P	NaO-*t*-Bu	87:10:3	75
5[d]	IMesCuCl	NaO-*t*-Bu	93:5:2	67
6	-	NaO-*t*-Bu	87:10:3	25
8	Cy_3P	LiO-*t*-Bu	93:7:0	38
9	Cy_3P	KO-*t*-Bu	56:36:8	72
10	Cy_3P	NaOPh	67:7:26	64
11[e]	Cy_3P	NaO-*t*-Bu	95:5:0	64
12[f]	***Cy₃P***	***NaO-t-Bu***	***97:3:0***	***65***

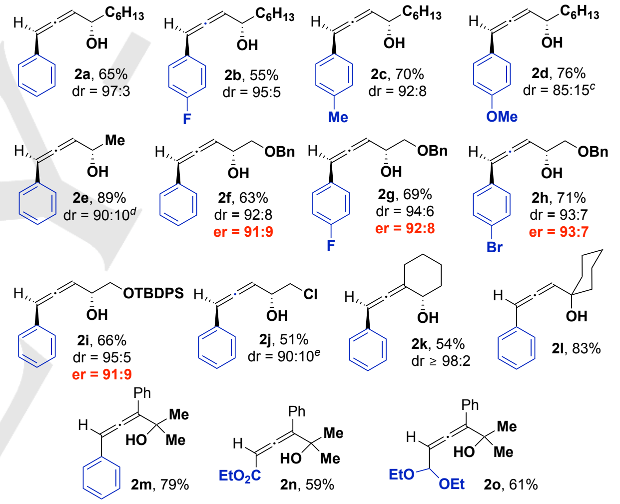
[a] Reaction conditions: **1a** (0.2 mmol), B_2pin_2 (0.22 mmol), base (20 mol%), CuCl (10 mol%), L (11 mol%), MeOH (0.4 mmol), THF (0.2 M). [b] Determined by ^1H NMR analysis. [c] Combined isolated yield. [d] IMesCuCl (10 mol%) was used instead of CuCl. [e] CuCl (5 mol%), Cy_3P (11 mol%). [f] CuCl (5 mol%), Cy_3P (30 mol%).

Switching to monodentate phosphine ligands, the diastereoselectivity improved dramatically (Table 1, entries 2-4). Ph_3P afforded allene **2a** with a 91:9 diastereomeric ratio (Table 1, entry 2) along with a small amount of homoallylic alcohol **4a**. Electron-rich monodentate phosphines such as Cy_3P and *t*-Bu_3P shut down the second borylation, minimizing the formation of **4a**, while maintaining high levels of diastereocontrol. *N*-Heterocyclic carbene ligand IMes gave similar results (Table 1, entry 5). In the absence of a ligand, allene **2a** was obtained in poor yield and lower diastereocontrol (Table 1, entry 6). The initial use of NaO-*t*-Bu as base proved fortuitous in limiting the formation of **3a** and **4a** (Table 1, entries 8-10). With LiO-*t*-Bu the diastereoselectivity was high, and we did not observe formation of **4a**, but the yield dropped significantly (Table 1, entry 8). However, KO-*t*-Bu afforded **3a** as the major diastereomer, albeit with low stereocontrol (Table 1, entry 9), while NaOPh was less effective at avoiding the formation of homoallylic alcohol **4a**. When the amount of CuCl was reduced to 5 mol% while maintaining the ligand (11 mol%), the diastereoselectivity was slightly improved (dr = 95:5) and **4a** was not observed (Table 1, entry 11). Finally, the use of 5 mol% of CuCl and 30 mol% of Cy_3P proved optimal for maximizing the diastereoselectivity while eliminating byproduct **4a** (Table 1, entry 12). The relative stereochemistry of **2a** was established by single crystal X-ray crystallography.[13]

Next, we prepared a series of propargylic epoxides to test the scope of our protocol (Table 2). Propargylic epoxides with different aromatic rings on the alkyne (R^1) afforded the desired allenols with good yield and high diastereoselectivity (compounds **2b**-**2d**). Starting from enantioenriched propargylic epoxides **1f**-**1i**, benzyl ethers **2f**-**2h** and silyl ether **2i** were obtained in good yields with excellent chirality transfer. These examples show that the enantiopurity of the epoxide is transferred completely to the product. Remarkably, the C-Cl bond in **2j** remained intact through the transformation.[14] The slighty lower dr observed for **2d**, **2e** and **2j** is a reflection of the diastereomeric ratio of the starting epoxides. Starting from a cyclic epoxide, compound **2k** was prepared in moderate yield but with complete stereocontrol. We also studied the hydroboration-allenation sequence with tri- (R^3,R^4 ≠ H) and tetrasubstituted (R^2,R^3,R^4 ≠ H) epoxides to prepare compounds **2l**-**2o**. Although there is no stereoselectivity involved in these examples, they show that the allenation takes places in good yield despite increased steric hindrance around the epoxide. Importantly, compounds **2n** and **2o** prove that the regioselectivity in the hydroboration step can be controlled not only with an aromatic ring but also with an ester and an acetal group.

Table 2. Copper-catalyzed synthesis of α-allenols[a,b,c]





2a, 65%
dr = 97:3

2b, 55%
dr = 95:5

2c, 70%
dr = 92:8

2d, 76%
dr = 85:15[c]

2e, 89%
dr = 90:10[d]

2f, 63%
dr = 92:8
er = 91:9

2g, 69%
dr = 94:6
er = 92:8

2h, 71%
dr = 93:7
er = 93:7

2i, 66%
dr = 95:5
er = 91:9

2j, 51%
dr = 90:10[e]

2k, 54%
dr ≥ 98:2

2l, 83%

2m, 79%

2n, 59%

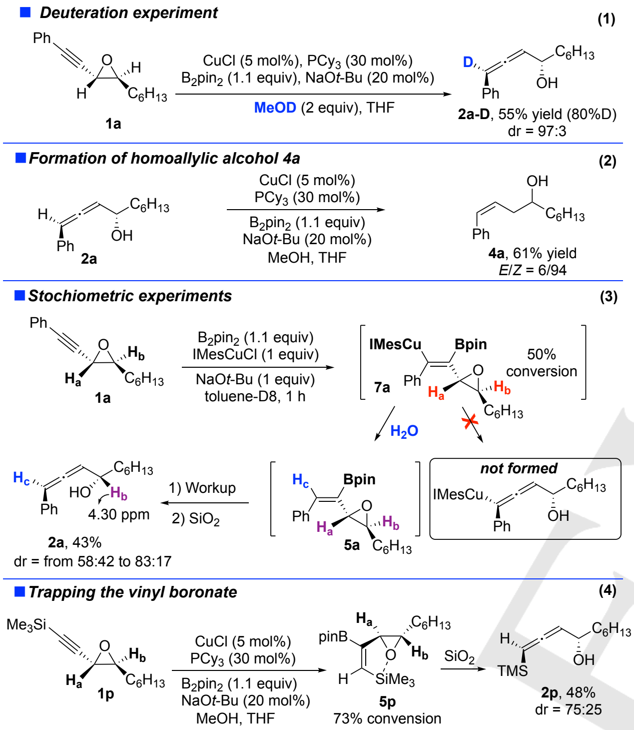
2o, 61%

[a] Reaction conditions: Table 1, entry 12. [b] dr determined by ^1H NMR analysis. [c] Starting epoxide **1d** was prepared as a 94:6-*E*:*Z* mixture. [d] Starting epoxide **1e** was prepared as a 95:5-*E*:*Z* mixture. [e] Starting epoxide **1j** was prepared as a 94:6-*E*:*Z* mixture.

From the outset, our mechanistic hypothesis involved an initial copper-catalyzed hydroboration of the alkyne to form α-epoxy vinyl boronates such as **5a**. However, generating clear evidence for the formation of **5a** was a major challenge. Indeed, we could not initially rule out the formation an allenyl boronate (**6**) followed by stereoselective protodeboronation to produce allene **2**.

We carried out a number of experiments to gain some insight into the mechanism of the reaction (Scheme 2). Using deuterated methanol, we observed the formation of allene **2a-D** (80%-D, Scheme 2, eq. 1), confirming the location of the copper atom during the hydroboration step. We also proved that homoallylic alcohol **4a**, observed during the optimization of the reaction conditions (Table 1), was formed through borylation of allene **2a** (Scheme 2, eq. 2).[15] To gain further evidence on the formation of α-epoxy vinyl boronates **5**, we run an experiment using a stoichiometric amount of catalyst in toluene-d8 (Scheme 2, eq 3). Gratifyingly, we observed the formation of vinyl copper intermediate **7a** with 50% conversion (**H_a** 3.14 ppm, **H_b** 3.26 ppm).

This intermediate was transformed into **5a** after addition of water to the NMR tube (**H**$_a$ 3.36 ppm, **H**$_b$ 3.28 ppm). Importantly, at this point we did not observe any significant peak at 4.30 ppm that would indicate allene formation.[16] This observation shows that protonation of the vinyl copper intermediate occurs prior to the elimination, precluding the formation of an allenyl copper species. Epoxide **5a** was not stable enough to be isolated and afforded allene **2a** after workup and SiO_2 purification. The diasteromeric ratio was significantly lower than that observed for **2a** in Table 1 and varied from 58:42 to 83:17 after four different trials. This observation revealed that the copper catalyst was playing a key role controlling the diastereoselectivity in the elimination step.

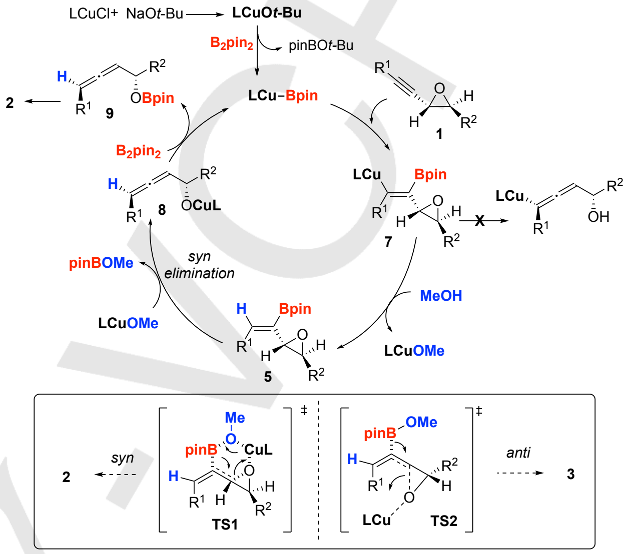


Scheme 2. Mechanistic studies

Finally, we designed an experiment that would allow us to slow down the elimination step by preventing the epoxide and the boron atom from adopting the required conformation for the *syn*-elimination. We chose propargylic epoxide **1p** with a trimethyl silyl group on the alkyne (Scheme 2, eq 4). We reasoned that the silicon atom could still direct the regiochemistry of the hydroboration and at the same time prevent the *syn*-elimination by coordination of the silicon and the oxygen of the epoxide. Indeed, using the optimized conditions, we observed formation of vinyl boronate **5p** with 73% conversion. Epoxide **5p** was stable through the workup procedure and afforded allene **2p** after column chromatography with moderate diastereoselectivity, which reinforces the role of the copper in the diastereocontrol.

With these results, we propose a mechanistic scenario consisting of an initial regioselective insertion of the alkyne into the Cu-B bond to produce vinyl copper intermediate **7**. Protonation with MeOH would afford epoxy boronate **5** and copper methoxide, which could facilitate the *syn*-elimination step through a 6-membered transition state **TS1**. DFT calculations support the preference for **TS1** (*syn*-elimination) over **TS2** (*anti*-elimination).[17] Further reaction of copper alkoxide **8** with B_2pin_2 generates α-allenol **9** and a copper-boryl complex that would re-initiate the catalytic cycle. α-Allenol **2** would be obtained after the workup and purification procedure.

Scheme 4. Proposed mechanism



In summary, chiral α-allenols are prepared with high diastereocontrol through an unprecedented and spontaneous β-oxygen elimination of an α-epoxy vinyl boronate. This transformation seems to be operating via a dual role of the copper catalyst. Further applications of this novel rearrangement to other unsaturated systems are underway.

Acknowledgements

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Keywords: allenes• stereoselective synthesis • boron • copper • epoxides

[1] For recent reviews, see: a) J. Ye, S. Ma, *Org. Chem. Front.* **2014**, *1*, 1210. b) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519. c) A. D. Allen, T. T. Tidwell, *Chem. Rev.* **2013**, *113*, 7287. d) P. Rivera-Fuentes, F. Diederich, *Angew. Chem., Int. Ed.* **2012**, *51*, 2818. e) S. Yu, S. Ma, *Chem. Commun.* **2011**, *47*, 5384. f) S. Ma, *Chem. Rev.* **2005**, *105*, 2829. g) A. Hoffmann-Roder, N. Krause, *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.
[2] N. Krause, C. Winter, *Chem Rev.* **2011**, *111*, 1994.
[3] S. Li, B. Miao, W. Yuan, S. Ma, *Org. Lett.* **2013**, *15*, 977.
[4] a) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121. b) N. Morita, N. Krause, *Angew. Chem., Int. Ed.* **2006**, *45*, 1897.
[5] a) Y. Jiang, A. B. Diagne, R. J. Thomson, S: E. Schaus, *J. Am. Chem. Soc.* **2017**, *139*, 1998. b) A. Tap, A. Blond, V. N. Wakchaure, B. J. List, *Angew. Chem., Int. Ed.* **2016**, *55*, 8962. c) J. Ye, S. Li, B. Chen, W. Fan, J. Kuang, J.

10.1002/chem.201705019

Liu, Y. Liu, B. Miao, B. Wan, Y. Wang, X. Xie, Q. Yu, W. Yuan, S. Ma, *Org. Lett.* **2012**, *14*, 1346. d) D. A. Mundal, K. E. Lutz, R. J. Thomson, *J. Am. Chem. Soc.* **2012**, *134*, 5782.

[6] a) T. Miura, M. Shimada, S.-Y. Ku, T. Tamai, M. Murakami, *Angew. Chem., Int. Ed.* **2007**, *46*, 7101; b) M. Yoshida, M. Hayashi, K. Shishido, *Org. Lett.* **2007**, *9*, 1643. c) M. Yoshida, H. Ueda, M. Ihara, *Tetrahedron Lett.* **2005**, *46*, 6705. d) A. Fürstner, M. Méndez, *Angew. Chem., Int. Ed.* **2003**, *42*, 5355. e) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677. f) A. Alexakis, I. Marek, P. Mageney, J. F. Normant *Tetrahedron Lett.* **1989**, *30*, 2387.

[7] a) T. Hamada, K. Daikai, R. Irie, T. Katsuki, *Tetrahedron: Asymmetry* **1995**, *6*, 2441. b) P. Nussbaumer, A. Stütz, *Tetrahedron Lett.* **1992**, *33*, 7507.

[8] a) C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem., Int. Ed.* **2007**, *46*, 1650. b) H. Reeker, P. Norrby, N. Krause, *Organometallics* **2012**, *31*, 8024.

[9] a) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, 112, 8042. b) X. Pu, J. M. Ready, *J. Am. Chem. Soc.* **2008**, *130*, 10874.

[10] H. R. Kim, J. Yun, *Chem. Commun.* **2011**, *47*, 2943.

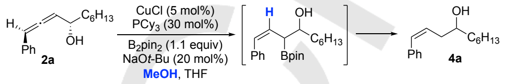
[11] a) H. Ito, Y. Sasaki, M. Sawamura, *J. Am. Chem. Soc.* **2008**, *130*, 15774. b) T. S. N. Zhao, Y. Yang, T. Lessing, K. J. Szabó, *J. Am. Chem. Soc.* **2014**, *136*, 7563. c) J. Zhao, K. J. Szabó, *Angew. Chem., Int. Ed.* **2016**, *55*, 1502.

[12] a) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Angew. Chem., Int. Ed.* **2013**, *52*, 12400. b) W. Yuan, L. Song, S. Ma. *Angew. Chem., Int. Ed.* **2016**, *55*, 3140.

[13] CCDC 1443721 contains the supplementary crystallographic data for (±)-**2a**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

[14] a) C.-T. Yang, Z. Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, L. Liu, *Angew. Chem., Int. Ed.* **2012**, *51*, 528. b) H. Ito, K. Kubota, *Org. Lett.* **2012**, *14*, 890.

[15] We believe an allylic boronate is formed first, followed by protodeboronation.



[16] See Supporting Information for details.

[17] For the complete calculated energy profile for the elimination step see Supporting Information.

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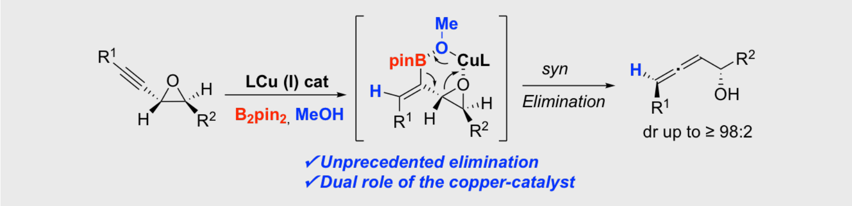

Dual Player: In this report, chiral α-allenols are prepared with high diastereocontrol through an unprecedented and spontaneous β-oxygen elimination of an α-epoxy vinyl boronate. Stochiometric experiments and DFT calculations support a dual role of the copper catalyst which orchestrates the hydroboration and the *syn*-elimination step.

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