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COMMUNICATION

Consecutive borylcupration/C-C coupling of γ-alkenyl aldehydes towards diastereoselective 2-(borylmethyl)cycloalkanols

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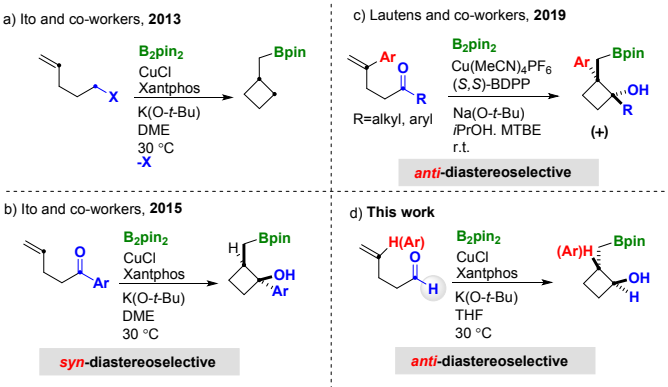
Copper (I) catalyzes the borylative cyclization of γ-alkenyl aldehydes through chemo- and regioselective addition of Cu-B to C=C and concomitant intramolecular 1,2-addition of Cu-C on the C=O. The products are formed in an exclusive diastereoselective manner and computational analysis identify the key points for the chemo- and diastereoselectivity observed.

Copper-catalyzed borylative ring closing of unactivated alkenes bearing electrophilic sites constitutes a strategic intramolecular 1,2-carboboration process.[1] Ito and co-workers developed the concept demonstrating that CuCl/Xantphos/KO^{t}Bu catalyzed the consecutive borylcupration/C–C coupling of alkenyl halides toward the synthesis of cyclobutanes with a pending methylboryl moiety (Scheme 1a).[2] However the loss of the leaving group (X= Br, I, OCO_2Me, $OP(O)(OR)_2$, OMs) reduced the atom economical properties of the transformation. The same authors extended the concept of copper(I)-catalyzed borylative *exo*-cyclization to γ-alkenyl aryl ketones and they found that under similar catalytic system and reaction conditions the regioselective borylcupration was followed by intramolecular 1,2-addition on the carbonyl group to give 2-(borylmethyl)cycloalkanols with excellent *syn*-diastereoselectivity (Scheme 1b).[3] An opposite *anti*-diastereselection has been found by Lautens and co-workers, in the borylative cyclization of γ-alkenyl aryl/alkyl ketones using $Cu(MeCN)_4PF_6$/BDPP as the catalytic system and NaO^{t}Bu as the base.[4] They found that isopropyl alcohol as additive was critical to the reaction's success together with MTBE as solvent, achieving high levels of enantioselectivity when (S,S)-BDPP was the chiral ligand employed.[4] However, this new methodology is limited to the use of 1,1-disubstituted alkenes containing an aryl substituent (Scheme 1c).

In the present work we generate new knowledge about this challenging borylative ring closing reaction demonstrating the viability of borylative cyclization of γ-alkenyl aldehydes, proving the favored chemoselective borylcupration of the double bond versus the carbonyl group, but also the resulting exclusive formation of 2-(borylmethyl)cycloalkanols with *anti*-diastereoselection (Scheme 1d). Also, based on DFT calculations, we are able to propose a new reaction mechanism identifying and evaluating the factors that control the chemo- and diastereoselectivity.



Scheme 1. Copper-catalyzed borylative ring closing reactions.

Initial experiments were conducted on the borylative cyclization of 4-allyltetrahydro-2H-pyran-4-carbaldehyde (**1**) as model substrate in the presence of CuCl/Xantphos. The substrate was quantitatively converted to the desired spirocyclic compound **2**, when bases such as Na(O-*t*-Bu) or K(O-*t*-Bu) were involved (Table 1, entry 1). To the best of our knowledge, this is the first example of a borycupration followed by intramolecular electrophilic trapping of the alkylcopper intermediate with the aldehyde, despite the fact that intermolecular versions are known.[5] Interestingly, the copper-catalyzed ring closing reaction of **1** resulted in exclusive *anti*-diastereoselectivity. This favored diastereoselection is in contrast to the *syn*-diastereoselectivity observed by Ito and co-workers in the borylative cyclization of alkenyl aryl ketones where a dialkylcopper(III) species was postulated as intermediate.[3]

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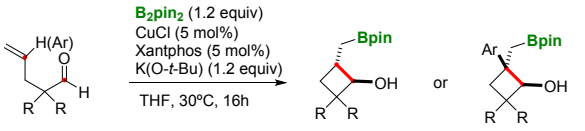
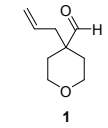
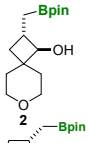
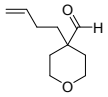
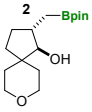
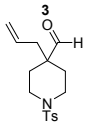
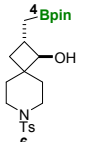
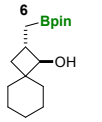
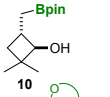
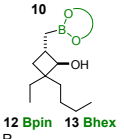
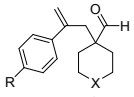
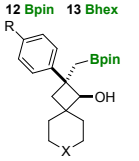
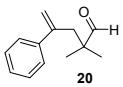
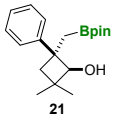
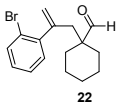
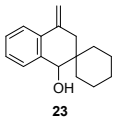
Table 1. Cu-catalyzed diastereoselective borylative ring closing of alkenyl aldehydes[a]

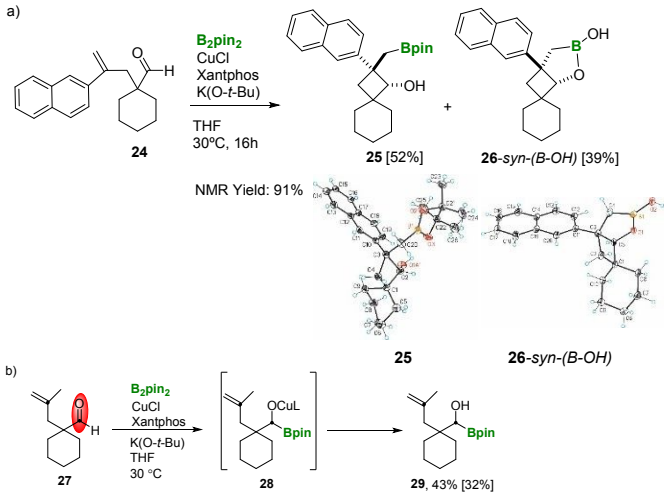


Entry	Substrate	Product	NMR Yield % Isolated Yield [%]
1	 1	 2	99% [71%] 99% [70%][b]
2	 3	 4	90% [45%]
3	 5	 6	85% [67%]
4	 7	 8	53% [50%]
5	 9	 10	64% [59%]
6	 11	 12 Bpin 13 Bhex	**12**, 72% [34%] **13**, 81% [51%]
7	 **14**, R=H, X=CH_2 **16**, R=H, X=O **18**, R=^{t}Bu, X=CH_2	 **15**, R=H, X=CH_2 **17**, R=H, X=O **19**, R=^{t}Bu, X=CH_2	**15**, 80% [76%] **17**, 73% [24%] **19**, 70% [25%]
8	 20	 21	78% [27%]
9	 22	 23	[34%]

[a]Reaction conditions: substrate (0.5 mmol), B_2pin_2 or B_2hex_2 (1.2 equiv), CuCl (5 mol%), Xantphos (5 mol%), K(O-*t*-Bu) (1.2 equiv), THF (2 mL), 30ºC, 16h. [b]Na(O-*t*-Bu) used as base.

Next, we demonstrated the efficiency of this reaction by forming the 5-membered ring spirocyclic compound **4** from δ-alkenyl aldehyde **3**, (Table 1, entry 2). This result contrasts with the unsuccessful five-membered ring formation from the analogue ketone carried out by other groups.[4]

The proof of concept was also applied in the transformation of 4-allyl-1-(phenylsulfonyl)piperidine-4-carbaldehyde (**5**) and 1-allylcyclohexane-1-carbaldehyde (**7**) towards the corresponding spirocyclic compounds **6** and **8** in 65% and 50% yield, respectively (Table 1, entries 3 and 4). The reaction was also explored for 2,2-dimethylpent-4-enal (**9**) providing a direct access to 2,2-dimethyl-4-(pinacolborylmethyl)cyclobutan-1-ol (**10**) in moderate isolated yield (Table 1, entry 5). Alternative diboron reagents, such as B_2hex_2, works similarly to B_2pin_2 (Table 1, entry 6). The borylative ring closing reaction was also extended to γ-Ar-substituted alkenyl aldehydes with the aim to synthesize diastereoselective polysubstituted cyclobutanols. The inclusion of a Ph group at the internal position of the C=C in substrates **14**, **16**, **18** and **20** did not change the reaction outcome, producing the desired spiro compounds in high conversion and yield (Table 1, entries 7 and 8). The reaction proceeded with exclusive diastereoselectivity keeping the borylmethyl unit in *anti* diposition with respect to the alcohol functional group. When the copper (I) catalyzed the borylative ring closing of 1-(2-(2-bromophenyl)allyl)cyclohexane-1-carbaldehyde (**22**) the expected spiro[3.5]nonan-1-ol was not observed. The unique product generated was 4'-methylene-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-naphthalen]-1'-ol (**23**) (Table 1, entry 9). Since **23** was not formed in a blank experiment in the absence of B_2pin_2, we hypothesized that the Cu-B species might be involved in the C-Br activation with a concomitant intramolecular attack to the aldehyde, generating the spirocyclic product of six-membered ring with the exocyclic double bond in opposite position to the alcohol functionality. The use of 2-naphthyl group as internal substituent of the alkene group in **24** was also tolerated in this ring closing reaction obtaining the polysubstituted spirocyclic compound **25** with the expected *anti*-diastereoselectivity in 52% isolated yields (Scheme 2a). However, the reaction also produced the boracycle **26**-*syn-(B-OH)* due to the resulting *syn*-diastereoselectivity and concomitant alcohol interaction with Bpin moiety (Scheme 3). The X-ray diffraction structures of products **25** and **26**-*syn-(B-OH)* are shown in Scheme 2.



Scheme 2. Influence on diastereo- and chemoselectivity. X-ray diffraction structures for **25** and **26**-*syn-(B-OH)*.

It is remarkable that the copper catalyzed ring closing takes place chemoselectively through borylcupration on the C=C versus C=O. It brings added value to the borylative ring closing method since it is known that copper-boryl complexes can

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efficiently catalyze the borylation of aldehydes, even at room temperature.[6] However γ-methyl-substituted alkenyl aldehyde substrates drive preferentially the borylcupration on the C=O bond versus the C=C bond. This is the case of substrate **27** that suffers a borylcupration on the aldehyde functional group generating the corresponding α-borylhydroxyl prouct **29** discarding the ring closing step (Scheme 2b).

The oxidation of the spirocyclic compounds with $NaBO_3·H_2O$, allowed the isolation of the corresponding dihydroxylated cyclobutane products **30**-**35** contributing to increase the demand of four- and five-membered ring spirocycles.[7] Single crystal X-ray diffraction of products **33** and **34** confirmed the *anti*-diastereoselection (Figure 1).

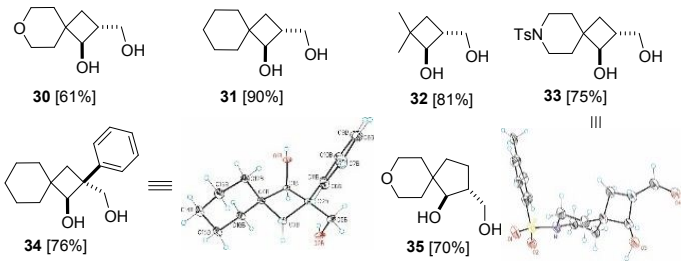

Figure 1. Dihydroxylated products **30**-**35** obtained from the oxidation of the organoboron spirocyclic compounds with $NaBO_3·H_2O$. X-Ray diffraction structures for **33** and **34.**

To propose a plausible mechanism and to understand the factors governing the chemo- and diastereoselectivity, we performed DFT calculations (ωB97X-D functional) in solution (THF).[8] Initially we characterized computationally the mechanism for the Cu(I)-catalyzed borylative ring closing reaction on substrate **1** yielding the 4-membered ring spirocyclic product **2** with *anti* diastereoselectivity. Figure 2 depicts the computed potential free-energy profile, as well as alternative pathways (dashed lines). Figure 2 and S5 show the molecular structures of the key transition states. The initial steps of the mechanism are analogous to those characterized previously for borylative ring closing of alkenyl halides by diphosphine-Cu(I) complexes.[9]

The reaction starts with the formation of Cu(O-*t*-Bu) (**I1**), resulting from mixing CuCl, K(O-*t*-Bu) and Xantphos ligand. Then, the active Cu-boryl species **I2** is generated by σ-bond metathesis between **I1** with B_2pin_2. The next step is postulated as the coordination of Cu-Bpin to the substrate **1** through alkene moiety (**I3**), and subsequent insertion of the C=C double bond into the Cu-B bond to yield the alkyl-copper(I) complex **I4**. This process occurs via transition state **TS1** with a moderate free-energy barrier of 10.7 kcal·mol^{-1} (**I2** → **TS1** in Figure 2).

In our previous contribution,[9] it was possible to optimize the dialkylcopper(III) intermediate proposed by Ito and co-workers[2,3] resulting from the intramolecular attack of Cu(I) to the C-X with the concomitant elimination of the halide. Nevertheless, Cu(III) species corresponded to a shallow well that could not be characterized for all the studied systems. Here, the absence of the halide leaving group makes the formation of Cu(III) complex less likely. Thus, all attempts to localize the Cu(III) intermediate where unsuccessful, including more sophisticated molecular models such as $^tBuO^-$ base coordinated to Cu, the K^+ counter cation interacting with the alkoxy moiety, and two specific THF solvent molecules. Alternatively, an intramolecular attack of the Cu-alkyl moiety to the carbonyl carbon in complex **I4** would then occur to lead the ring closing C-C coupling and the resulting alkoxy-copper(I) complex **I5**. The process needs to overcome a low energy barrier (14.4 kcal·mol^{-1}) and is exergonic by 13.0 kcal·mol^{-1}. In the corresponding transition state, **TS2**$_{anti}$, a negative charge develops at the carbonyl oxygen, which interacts with the Cu center in order to stabilize the partial negative charge. Next, intermediate **I5**$_{anti}$ can undergo another σ-bond metathesis with the diboron reagent to recover the active Cu-boryl species **I2** and yield a 4-membered ring containing the O-Bpin moiety (**I6**$_{anti}$) with *syn*-diatereoselectivity. Finally, the spirocyclic product **2** can be generated from species **I6** though the hydrolysis of O-B bond by the alcohol solvent or during the isolation of the product via column chromatography.

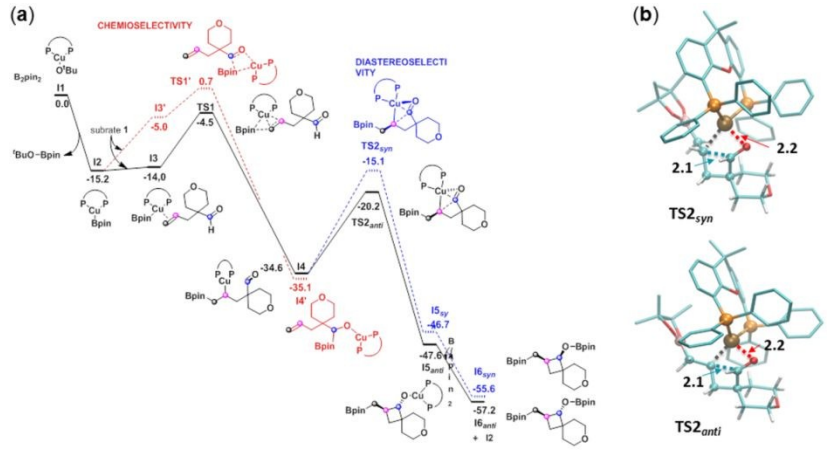

Figure 2. a) Computed free-energy profile (kcal·mol^{-1}) for the formation of **2**. Dashed lines represent alternative paths related to chemoselectivity (red lines) and diastereoselectivity (blue lines). P-P= Xantphos. b) Molecular structures and main geometric parameters (Å) of the key transition states (**TS2**$_{anti}$ and **TS2**$_{syn}$).

We also evaluated the chemoselective pathway for boryl addition to aldehyde, as illustrated for substrate **1** by red dashed lines in Figure 2. The Cu centre in **I2** can coordinate the substrate through the carbonyl moiety (**I3'**), undergoing the

1,2-addition of Cu-Bpin to the C=O via transition state **TS1'**. The overall process has a low free energy barrier (15.9 kcal·mol^{-1}) and it results in the thermodynamically stable, intermediate **I4'**. Nevertheless, the pathway for C=C borylcupration is kinetically preferred by 5.2 kcal·mol^{-1} (**TS1** versus **TS1'**in Figure 2), in agreement with the experimental results. Table 2 compares the free-energy barriers for the two competitive borylation processes in representative γ-substituted alkenyl aldehydes **1**, **7**, **14**, **24**, and **27**. Replacement of tetrahydropyran group in **1** by cyclohexane in **7** has a minor effect on the barriers. Then, incorporating aromatic substituents in the alkene moiety (substrates **14** and **24**) decreases the energy barrier for the borylation on C=C bond providing the kinetic preference for ring closing products. Since boryl-copper complexes behave as nucleophiles,[10] the electron-withdrawing aromatic substituents enhance the reactivity of the double bond. On the other hand, the methyl substituent in substrate **27** makes the alkene fragment more electron rich, increasing the borylation energy barrier and switching the chemoselectivity towards the addition on the aldehyde moiety (product **29**).

Table 2. Calculated free-energy barriers and differences in kcal·mol^{-1} for the borylcupration of C=C *versus* C=O bond, ΔΔG‡(**TS1-TS1'**), and for the ring closing of the diastereoselective *anti versus syn* paths, ΔΔG‡(**TS2$_{anti}$-TS2$_{syn}$**).[a]

substrate	C=C:C=O (exp.)	$\Delta G^{\ddagger}_{C=C}$	$\Delta G^{\ddagger}_{C=O}$	ΔΔG‡
1	100:0	10.7	15.9	+5.2
7	100:0	12.6	16.9	+4.3
14	100:0	9.3	15.9	+6.6
24	100:0	7.2	11.7	+9.0
27	0:100	16.1	13.1	-2.9
substrate	***anti*:*syn* (exp.)**	$\Delta G^{\ddagger}_{anti}$	$\Delta G^{\ddagger}_{syn}$	ΔΔG‡
1	100:0	13.7	17.6	+5.1
3	100:0	15.5	18.7	+3.2
24	50:50	10.4	10.1	+0.3

[a] Free-energy barriers $\Delta G^{\ddagger}_{C=C}$ (**I2→TS1**), $\Delta G^{\ddagger}_{C=O}$ (**I2→TS1'**), $\Delta G^{\ddagger}_{anti}$ (**I4→TS1$_{anti}$**), and $\Delta G^{\ddagger}_{syn}$ (**I4→TS1$_{syn}$**).

The diastereoselectivity is decided at the C-C coupling step where the aldehyde functional group can adopt an *anti* or a *syn* disposition with respect to the borylmethyl unit (**TS2$_{anti}$** and **TS2$_{syn}$**). In substrate **1**, the *anti*-configuration minimizes the 1,2 repulsion between the substituents of cyclobutane, resulting in a significantly lower free energy barrier (13.7 *versus* 17.6 kcal·mol^{-} for **I4** → **TS2$_{anti}$** and **I4** → **TS2$_{syn}$**, respectively). Additional calculations were performed in model systems replacing each phenyl substituent of Xantphos ligand by hydrogen and maintained the backbone (PH_2 model) sets off ligand-substrate interactions. The results show that a free-energy difference between the two diastereoselective paths is very similar to the *real-world* ligands, ΔΔG‡ = +4.2 kcal·mol^{-1}, indicating that intramolecular interactions within the substrate (-CH_2Bpin···C=O) are responsible of the diastereoselectivity. Interestingly, introducing a 2-naphthyl group on the alkene moiety (substrate **24**) produced a mixture of *anti* and *syn* diastereoisomers. The computed free-energy difference between the two corresponding transition states, ΔΔG‡(**TS2$_{syn-24}$-TS2$_{anti-24}$**), is reduced to only 0.3 kcal·mol^{-1} (see Figure S6). In this case the bulky naphthyl substituent leads to 1,2 repulsive interactions with the carbonyl group in the *anti* path, which are similar to those between the carbonyl group and the -CH_2Bpin moiety in the *syn* isomer. Consequently, no preference for any of the two diastereoisomers is observed.

In conclusion, borycupration of alkenyl aldehydes takes place chemoselectively on the C=C followed by intramolecular electrophilic trapping of the aldehyde, with complete *anti*-diastereoselectivity. Disubstitution on the alpha-position to the aldehyde favours the cyclation but current work to extend the reactivity to non-substituted substrates is ongoing. Computational studies identify the key steps of the catalytic cycle that govern the chemo- and the diastereoselectivity.

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8 See Supporting Information for full computational details

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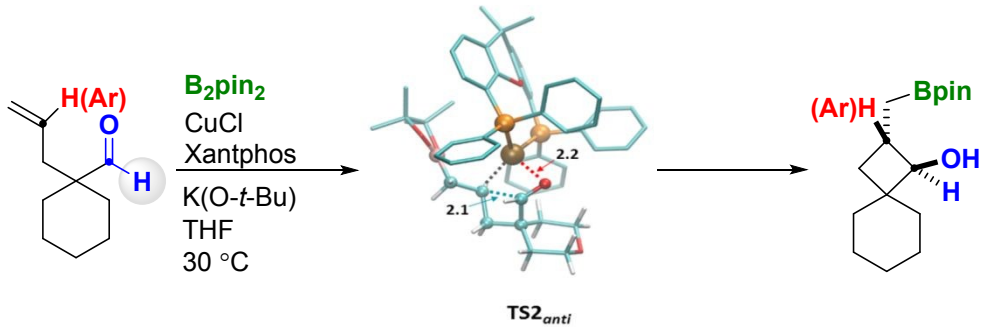

$TS2_{anti}$