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Asymmetric Catalysis

Cu-Catalyzed Enantioselective Borylative Desymmetrization of 1-Vinyl Cyclobutanols and Axial-to-Point Chirality Transfer in a Diastereoconvergent/Stereoretentive Allylation Scenery

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Abstract: Cu-catalyzed asymmetric allylic borylation of 3,3'-disubstituted 1-vinylcyclobutan-1-ols renders axially chiral allylborane systems, with high asymmetric induction for both enantiomers, by precise selection of the *cis* or *trans* substrate. The enantioenriched alkylidenecyclobutanes served as chiral platform to prove the conceptually challenging transference of the axial-to-point chirality through two new stereocenters and one pseudoasymmetric carbon generated via diastereoconvergent allylation of aldehydes, without enantioselective erosion.

Introduction

The stereoselective generation of chiral molecular entities remains at the central core of research in organic synthesis due to the crucial role played by chirality in molecules that interfere in biological processes or drug discovery platforms.[1] The three-dimensional shape affects the macroscopic properties of chiral compounds, to the extent that each enantiomer of a chiral drug can exhibit reduced or even deleterious effects based on their relative stereochemistry. In this sense, the archetypal mode of chirality in organic molecules is the stereogenic carbon (point chirality). Nevertheless, as the molecular complexity increases, other types of chirality emerge, such as planar or axial chirality, being atropoisomeric biaryls and allenes the most representative examples of the latter (Figure 1). Specifically, the preparation of axially chiral compounds entails a challenging task by itself due to the very specific geometric elements that have to be assembled when generating such type of chiral molecular entities.

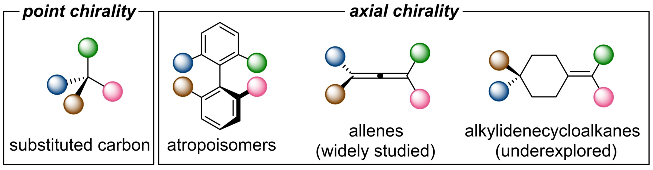

Figure 1. Point vs. axial chirality and examples of axially chiral molecules.

In this sense, the desymmetrization approach,[2] in which the inherent symmetry of a symmetrical precursor is disrupted via chemical transformation, shows up as an unconventional and powerful methodology for the enantioselective synthesis of axially chiral molecules. However, desymmetrization protocols have been principally applied to the generation of chiral species where the chiral axis involves restricted rotation around C–C or C-heteroatom σ-bonds, thus being circumscribed to the control of atroposelectivity. In addition, while the stereocontrolled synthesis of axially chiral allenes has also been widely covered in the literature, the enantioselective access to axially chiral alkylidenecycloalkanes remains underexplored with scarce examples based on kinetic resolution,[3] photochemical deracemization[4] and enantioselective olefination reactions.[5–10] More recently, enantioenriched alkylidenecycloalkanes have efficiently been obtained through catalytic enantioselective (2+2) cycloaddition,[11] Cu-catalyzed hydrosilylation of allenes,[12] and via enantioselective coupling chemistry[13] or allylic substitution under transition metal catalysis.[14–17] In particular, Zheng, Shi and co-workers have designed an elegant method to synthesize axially chiral alkylidenecycloalkanes via palladium-catalyzed asymmetric allylic alkylation.[14] This conceptual breakthrough is a robust method with a wide substrate scope, but the presence of all carbon stereocenters in the cyclic molecule was scarcely studied (Scheme 1a). In that report the relative diastereomeric nature of the substrate resulted critical, since the enantioselectivity observed was high starting from the *trans*-isomer, whereas the *cis*-isomer generated the product with the opposite configuration, as expected, but with notable low e.r. (Scheme 1a). Inspired by this desymmetrization process, we speculated that Cu-catalyzed asymmetric

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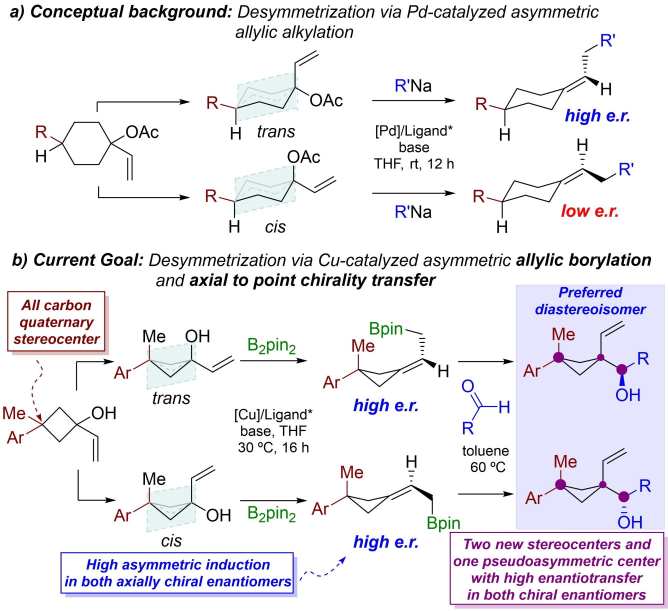
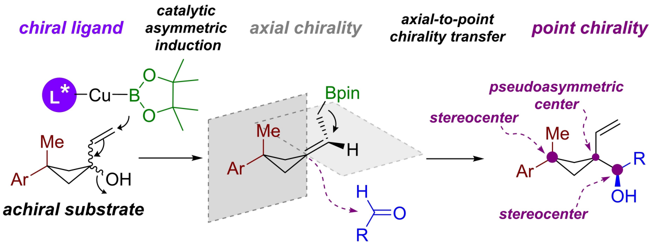


Scheme 1. Desymmetrization of allylic acetate and allylic alcohol substrates.



Scheme 2. Sequential, two-step-procedure involving enantioselective Cu-catalyzed allylic borylation of 3,3-disubstituted 1-vinylcyclobutan-1-ols leading to axially chiral allylboronates followed by in situ axial-to-point chirality transfer throughout allylation with aldehydes.

allylic borylation of 3,3’-disubstituted 1-vinylcyclobutan-1-ols would provide axially chiral allylboranes with high asymmetric induction in both enantiomers, including all carbon stereocenters in the cyclic scaffolds (Scheme 1b).

Our ultimate goal was to conceptually demonstrate the challenging transfer of the axial chirality obtained in the allylborane systems to point chiral molecules. Considering that chirality transfer is strictly defined as a process in which a new chiral element is created while the chirality from the original element is lost,[18] we envisaged two successive stereoselective transformations: the desymmetrization of 3,3-disubstituted 1-vinylcyclobutan-1-ols, through Cu-catalyzed asymmetric allylic borylation, followed by in situ allylation of aldehydes (Scheme 1b). The allylation of carbonyl compounds with chiral allylboronates is considered a philosopher’s stone in asymmetric synthesis,[19] but to the best of our knowledge, application of this reaction toward the synthesis of optically enriched chiral molecules involve exclusively point-to-point chirality transfer. In our working hypothesis, the axial-to-point chirality transfer, entails an additional difficulty associated to the pseudoasymmetric nature of the carbon atom generated at the cycloalkane moiety. This implies that not only facial selectivity has to be optimized during the allylation reaction between the axially chiral allylboronate with the aldehyde, but also diastereoselection has to be controlled at the pseudoasymmetric center, in order to favor a single isomer (Scheme 2).

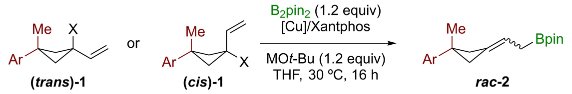
Results and Discussion

Cu-catalyzed asymmetric allylic borylation is usually reported to be efficient when activated allylic substrates, such as allylic carboxylates, carbonates, acetates, phosphates and halides are employed.[20–28] The possibility of performing this reaction directly on allylic alcohols is significantly more challenging,[29] due to the lower ability of the hydroxyl to function as leaving group. Despite this downside, the minimization of waste production associated to the preparation of the activated allylic substrates justifies their use in allylic borylation sequences and enhances the synthetic usefulness of this approach.[30–35]

According to this assumption, we first explored whether OH could be used, as an efficient leaving group, in the Cu-catalyzed allylic borylation of 3-methyl-3-(p-ClC_6H_4)-1-vinylcyclobutan-1-ol **(*trans*)-1a**. We selected $[Cu(MeCN)_4]PF_6$ as the Cu(I) salt and Xantphos as the bidentate ligand, together with KO*t*-Bu as base, to promote the catalytic borylcupration on the terminal double bond, in the presence of bis(pinacolato)diboron (B_2pin_2).[36] Working at 30 °C, with THF as solvent, the desired allylboronic ester **2a** was essentially formed and isolated in high yield (Table 1, entry 1). For comparison, we prepared the ester analogue **(*trans*)-1a’**, with OAc as leaving group, but the yield on **2a** was slightly lower (Table 1, entry 2). No major differences were observed in the allylboronic ester formation starting from the diastereomeric substrate **(*trans*)-1a** or **(*cis*)-1a** (Table 1, entries 1 and 3). The nature of the base influenced the formation of **2a** since the use of LiO*t*-Bu afforded higher yields than KO*t*-Bu (Table 1, entries 3 and 4). The source of Cu salt was also investigated and the allylic borylation of **(*trans*)-1a** with CuCl/Xantphos resulted less efficient in view of the obtained NMR yields (Table 1, entry 5). The application of the optimized reaction conditions to substrates **(*cis*)-1** varying the nature of the aryl group (**1b**: 2-napthyl, **1c**: p-$MeOC_6H_4$, **1d**: o-MeC_6H_4 and **1e**: p-MeC_6H_4) led to the formation of the corresponding allylboronic ester **2b–e** in high yields regardless the different steric or electronic properties of the aryl group (Table 1, entries 6–9).

We considered the possibility to incorporate an additional substituent at the alkene moiety to evaluate its influence along the Cu-catalyzed allylic borylation. Substrate **(*cis*)-1f**, incorporates a Ph group on the alkene, and under optimized reaction conditions for the Cu-catalyzed allylic alkylation, we isolated the allylboronic ester **2f** together with the isolation of 1-methyl-3-[(1-phenylvinyl)cyclobutyl]benzene (**2f’**) as a 72/28 mixture of diastereoisomers (Scheme 3). We justify the formation of **2f’**

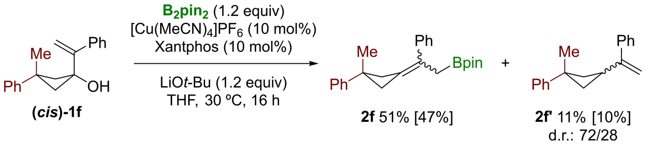
Table 1: Optimization conditions for Cu-catalyzed allylic borylation of 3,3-disubstituted 1-vinylcyclobutan-1-ols **1** (X=OH) and cyclobutyl ester **1'** (X=OAc) with B_2pin_2.[a]



a (Ar= *p*-ClC_6H_4); **b** (Ar= 2-naphthyl); **c** (Ar= *p*-$MeOC_6H_4$); **d** (Ar= *o*-MeC_6H_4); **e** (Ar= *p*-MeC_6H_4)

Entry	Cu(I) salt	Substrate **1**	Ar	X	M	**2** (%)[b] [%][c]
1	$[Cu]PF_6$	***(trans)*-1 a**	*p*-ClC_6H_4	OH	K	89
2	$[Cu]PF_6$	***(trans)*-1 a'**	*p*-ClC_6H_4	OAc	K	70
3	$[Cu]PF_6$	***(cis)*-1 a**	*p*-ClC_6H_4	OH	K	91
4	$[Cu]PF_6$	***(cis)*-1 a**	*p*-ClC_6H_4	OH	Li	96 [48]
5	CuCl	***(trans)*-1 a**	*p*-ClC_6H_4	OH	K	81
6	$[Cu]PF_6$	***(cis)*-1 b**	2-naphthyl	OH	Li	90 [34]
7	$[Cu]PF_6$	***(cis)*-1 c**	*p*-$MeOC_6H_4$	OH	Li	92 [42]
8	$[Cu]PF_6$	***(cis)*-1 d**	*o*-MeC_6H_4	OH	Li	93 [29]
9	$[Cu]PF_6$	***(cis)*-1 e**	*p*-MeC_6H_4	OH	Li	93 [33]

[a] General conditions: substrate (0.2 mmol), B_2pin_2 (1.2 equiv), CuCl or $[Cu]PF_6=[Cu(MeCN)_4]PF_6$ (10 mol%), Xantphos (10 mol%), MO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h. [b] NMR yields determined with naphthalene as internal standard. [c] Isolated yield after purification with flash chromatography.



Scheme 3. Cu-catalyzed allylic borylation of 3-methyl-3-phenyl-1-(1-phenylvinyl)cyclobutan-1-ol ***(cis)*-1 f**. NMR yields determined with naphthalene as internal standard and isolated yields in brackets.

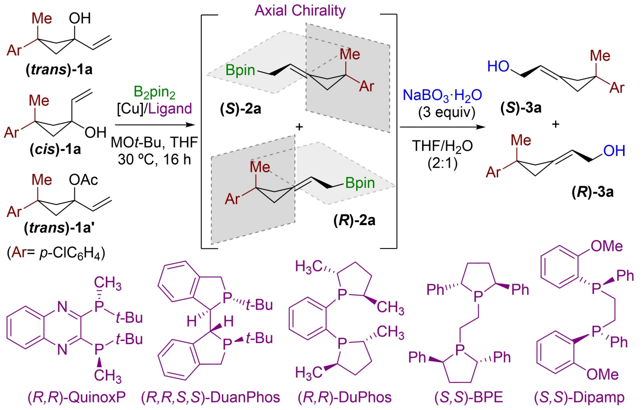
in terms of the higher reactivity of allylboronic ester **2f** towards allylic protonation.[37]

Next we planned the desymmetrization of ***(trans)*-1a**, ***(cis)*-1a** and ***(trans)*-1a'**, through the allylic borylation reaction under chiral Cu-catalysis (Table 2). To determine the enantiomeric ratio (e.r.) along the desymmetrization, we oxidized in situ the enantioenriched mixtures of the allylboronic ester **2a** with $NaBO_3$. When (*R,R*)-QuinoxP was used as chiral ligand, with CuCl as copper source, the substrate ***(trans)*-1a** was quantitatively transformed into the allylboronic ester **2a**, and after in situ oxidation the allylic alcohol **3a** was isolated in moderate yield, with 84:16 e.r. (Table 2, entry 1). Similar reaction outcome was observed starting from ***(cis)*-1a**, but obtaining the opposite enantiomer as the major product, with 16:84 e.r. (Table 2, entry 2). This confirms that each diastereomeric substrate, *trans* or *cis*, proceed through complementary stereodefined pathways to generate each corresponding enantioenriched product. Cu(I) seems to efficiently catalyze the asymmetric allylic borylation, independently of the diastereomeric substrate involved, in contrast to the palladium-catalyzed asymmetric allylic alkylation which only induce high enantioinduction starting from the *trans* diastereoisomer.[14] The nature of the leaving group also played a relevant role, since the use of OAc in ***(trans)*-1a'** contributed to decrease the enantioinduction to 77:23 e.r. (Table 2, entry 3). Replacing CuCl by $[Cu(MeCN)_4]PF_6$ had a beneficial effect on the enantioselective formation of **3a** with 93:7 e.r. (Table 2, entry 4). When the reaction temperature was 0 °C, the enantiomeric ratio was not improved, obtaining **3a** in 90:10 e.r. (Table 2, entry 5). However, the replacement of the base KO*t*-Bu by LiO*t*-Bu, resulted beneficial for the enantiocontrol, isolating **3a** in 72 % and 95.4:4.6 e.r. (Table 2, entry 6). Under these optimized reaction conditions for the asymmetric Cu-catalyzed allylic borylation of ***(trans)*-1a**, we next proceeded to screen alternative chiral ligands. When $[Cu(MeCN)_4]PF_6$ was modified with the P-stereogenic diphosphine (*S,S*)-Dipamp, the conversion into the allylboronic ester **2a** was moderate, together with a significant deleterious effect on the enantiomeric ratio isolating **3a** in 32:68 e.r. (Table 2, entry 7). The alternative bisphosphacycle chiral ligand (*R,R,S,S*)-DuanPhos, bearing also the bulky *t*-butyl group on the P-stereogenic center, contributed to convert ***(trans)*-1a** into **3a** with moderate yield and relatively high enantioinduction (Table 2, entry 8). Complementarily, the allylic borylation with bisphosphacycle chiral ligands (*S,S*)-BPE and (*R,R*)-DuPhos did not improve the enantiomeric ratio in which allylic alcohol **3a** was formed (Table 2, entries 9 and 10), pointing out the benefits of P-stereogenic chiral ligands in this reaction. Contrarily, the use of bis- and monophosphines (*R*)-Binap and (*S*)-PipPhos, with axial chirality, proved to be inefficient in the chiral induction, with 56:44 and 47:53 e.r., respectively.

The absolute configuration of the major enantiomer obtained from ***(trans)*-1a** was assigned by single-crystal X-ray analysis of the *p*-methylthiobenzoate derivative of alcohol **(*S*)-3a** (Figure 2).[38] The structure leads to a (*S*) assignment of the chirality in alcohol **3a** and in allylic boronic ester **2a**. The absolute configuration of the major enantiomer obtained from ***(cis)*-1a** was assigned by comparison of the sign of the optical rotation.

Next, we proceeded to evaluate the scope of the reaction with respect to the possibility of introducing different substituents at the quaternary carbon atom of the cyclobutane scaffold (Scheme 4). Consequently, we selected the P-stereogenic diphosphine (*R,R*)-QuinoxP as the most

Table 2: Cu-catalyzed asymmetric allylic borylation of 3,3-disubstituted 1-vinylcyclobutan-1-ols **1a** and cyclobutyl ester **1a'** with B_2pin_2.[a]



Entry	Cu(I) salt	M	Ligand	**1a**	**2a** (%)[b]	**3a** [%][c]	**e.r.**[d] *S*/*R*
1	CuCl	K	(*R*,*R*)-QuinoxP	**(*trans*)-1a**	99	[56]	84:16
2	CuCl	K	(*R*,*R*)-QuinoxP	**(*cis*)-1a**	87	[38]	16:84
3	CuCl	K	(*R*,*R*)-QuinoxP	**(*trans*)-1a'**	100	[51]	77:23
4	$[Cu]PF_6$	K	(*R*,*R*)-QuinoxP	**(*trans*)-1a**	91	[58]	93:7
5[e]	$[Cu]PF_6$	K	(*R*,*R*)-QuinoxP	**(*trans*)-1a**	100	[54]	90:10
6	$[Cu]PF_6$	Li	(*R*,*R*)-QuinoxP	**(*trans*)-1a**	100	[72]	95.4:4.6
7	$[Cu]PF_6$	Li	(*S*,*S*)-Dipamp	**(*trans*)-1a**	58	[25]	32:68
8	$[Cu]PF_6$	Li	(*R*,*R*,*S*,*S*)-DuanPhos	**(*trans*)-1a**	78	[54]	89:11
9	$[Cu]PF_6$	Li	(*S*,*S*)- BPE	**(*trans*)-1a**	92	[53]	86:14
10	$[Cu]PF_6$	Li	(*R*,*R*)-DuPhos	**(*trans*)-1a**	50	[27]	72:28

[a] General conditions: substrate (0.2 mmol), B_2pin_2 (1.2 equiv), CuCl or $[Cu]PF_6=[Cu(MeCN)_4]PF_6$ (10 mol%), Ligand (10 mol%), KO*t*-Bu or LiO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h. [b] NMR yields determined with naphthalene as internal standard. [c] Isolated yields after purification with flash chromatography. [d] e.r. determined on **3a** by HPLC. [e] 0 °C.

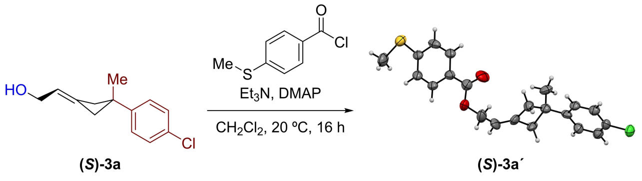
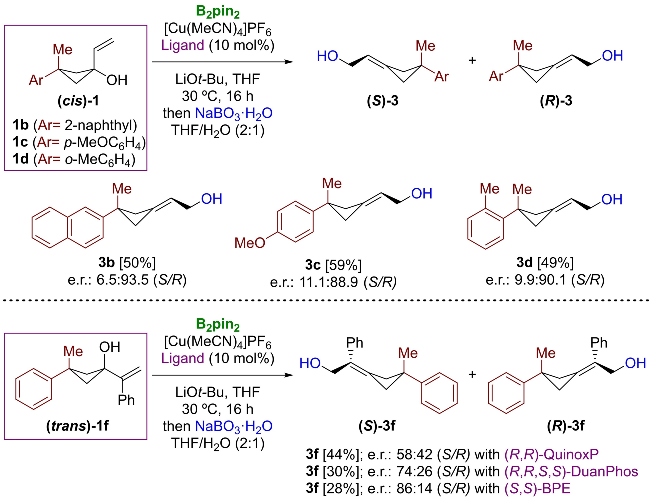


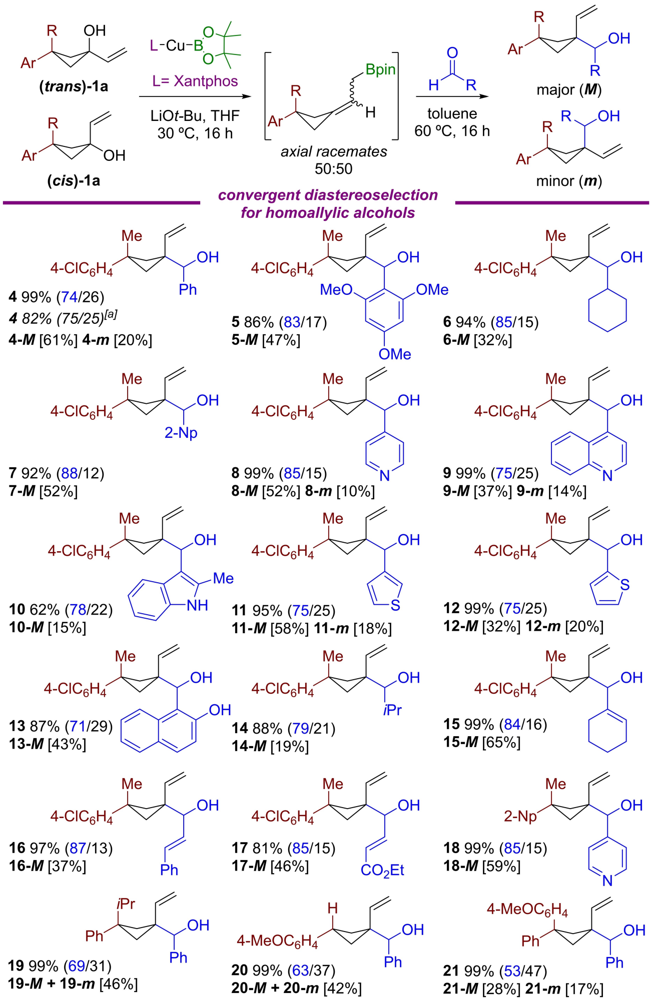
Figure 2. X-ray structure of major enantiomer of compound **(*S*)-3a'**.



Scheme 4. Cu-catalyzed asymmetric allylic borylation/oxidation of **1b**–**1f**. Substrate (0.2 mmol), B_2pin_2 (1.2 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol%), Ligand (10 mol%), LiO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h. Isolated yields in brackets and e.r. determined by HPLC.

convenient chiral ligand for the Cu-catalyzed allylic borylation step. The presence of a 2-naphthyl substituent on substrate **(*cis*)-1b**, led to the formation of **3b**, also in a high enantiomeric ratio (6.5:93.5 e.r.) (Scheme 4, top). The electron donating *p*-OMe and *o*-Me groups present on the Ar group in substrates **(*cis*)-1c** and **(*cis*)-1d**, performed similarly towards the production of **3c** and **3d** with e.r. about 10:90 (Scheme 4). However, when 3-methyl-3-phenyl-1-(1-phenylvinyl)cyclobutan-1-ol **(*trans*)-1f** reacted with B_2pin_2 in the presence of $[Cu(MeCN)_4]PF_6$/(*R*,*R*)-QuinoxP, the yield on the allylic alcohol **3f** was moderate and enantioinduction resulted almost null (Scheme 4, bottom). In this case, changing to the alternative bisphosphacycle chiral ligand (*R*,*R*,*S*,*S*)-DuanPhos and (*S*,*S*)-BPE allowed higher enantiomeric ratios (86:14 e.r.) although in spite of the formation of **3f** in low isolated yields (Scheme 4).

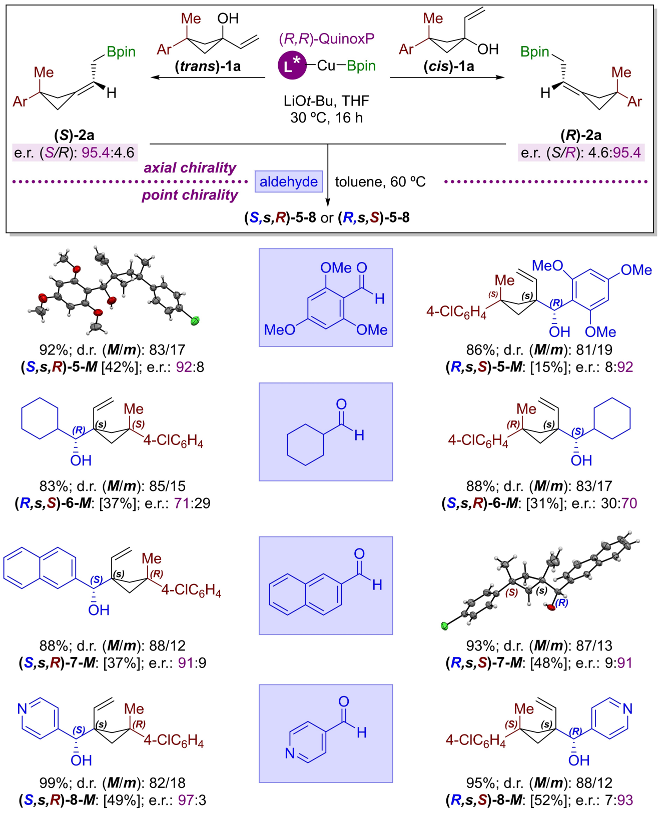
Our next challenge was to demonstrate that the axial chirality obtained in the allylic boronic esters could be transferred to point chiral homoallylic alcohols, via allylation with aldehydes. This goal entails an additional difficulty related to the pseudoasymmetric nature of the stereogenic carbon atom formed at the cyclobutane moiety after the allylation. In fact, the relative arrangement between allylboronate and aldehyde turns into the formation of mixtures of enantiomers, thus achieving high diastereoselection is an intrinsic goal for the chiral transference process. In order to gain insight about this issue, we conducted the two-step sequence consisting on borylation of **(*trans*)-1a** with B_2pin_2, in the presence of $[Cu(MeCN)_4]PF_6$/Xantphos and LiO*t*-Bu, in THF at 30 °C, followed by addition of benzaldehyde (toluene/60 °C). The formation of the homoallylic alcohol **4** was quantitative, as a 74/26 mixture of diastereoisomers with the major diastereoisomer **4-*M*** as the product with the Me group facing the vinyl moiety, which was unambiguously proved by 1D NMR NOE experiments, (Scheme 5). Similar results were achieved when KO*t*-Bu was used as base, indicating that the nature of the base did not affect the diastereoselection, in contrast to its important influence observed along the Cu-catalyzed enantioselective borylation step (Table 2, entries 4, 6). Lower temperature in the allylation pathway decreased the diastereomeric ratio, whereas higher temperature had not influence: d.r. **4-*M***/**4-*m*** = 64/36 (30 °C), 72/28 (45 °C), 74/26 (90 °C). Replacing toluene by dichloromethane or THF provided the same diastereomeric ratio. Interestingly, when substrate **(*cis*)-1a** reacted, under the same reaction conditions, we achieved the same diastereomeric ratio in favor of the **4-*M*** diastereoisomer. The borylation/allylation procedure, even using a mixture of *trans/cis* isomers of substrate **1a**, enabled a diastereoconvergent process proving the same **4-*M***/**4-*m*** diastereomeric ratio. We extended the diastereoconvergence of this transformation with a variety of aldehydes confirming the preferred major diastereoisomer formed in all cases.



Scheme 5. Sequential, two-step: Cu-catalyzed borylation of **1**/electrophilic allylation. Substrate (0.2 mmol), B_2pin_2 (1.2 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol %), Xantphos (10 mol %), LiO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h, aldehyde (2 equiv), toluene (3 mL), 60 °C, 16 h. NMR yields and diastereomeric ratio (in parenthesis) determined with naphthalene as internal standard. Isolated yields after purification with flash chromatography, in brackets. [a] KO*t*-Bu used instead of LiO*t*-Bu.

However the diastereomeric ratio seems to correlate with the steric properties of the aldehydes employed, since for bulkier 2,4,6-trimethoxybenzaldehyde, cyclohexanecarbaldehyde and 2-naphthaldehyde, the d.r. increases from 83/17 to 88/12, (products **5**–**7**, Scheme 5). Heteroaromatic aldehydes were also compatible with the formation of homoallylic alcohols **8**–**13** in high diastereomeric ratio, allowing the isolation of both major and minor diastereoisomers for products **11** and **12** (Scheme 5). Isobutyraldehyde also reacted efficiently towards the corresponding homoallylic alcohol **14**, although yield decreased significantly (Scheme 5). Interestingly, when α,β-unsaturated aldehydes, such as cyclohex-1-ene-1-carbaldehyde and *trans*-cinnamaldehyde, participated in the allylation reaction, the C–C bond formation took place chemoselectively on the formyl group, with d.r. up to 84/16 and 87/13 for **15** and **16**, respectively (Scheme 5). Similar outcome was observed when ethyl (*trans*)-4-oxo-2-butenoate reacted with the allylic boronic ester to give chemoselectively the homoallylic alcohol **17** in high yield and 85/15 diastereomeric ratio. To evaluate the influence of the aryl group, from substrate, on the convergent diastereoselectivity, we studied the sequential Cu-catalyzed borylation of **(*cis/trans*)-1b** with isonicotinaldehyde giving access to the desired homoallylic alcohol **18**, with comparable yield and diastereomeric ratio to the analogue homoallylic alcohol **8** (Scheme 5). Alternatively, the replacement of Me group by *i*Pr, H, or 4-OMeC_6H_4 did not favor the diastereomeric ratio, in products **19**, **20** and **21**, respectively (Scheme 5).

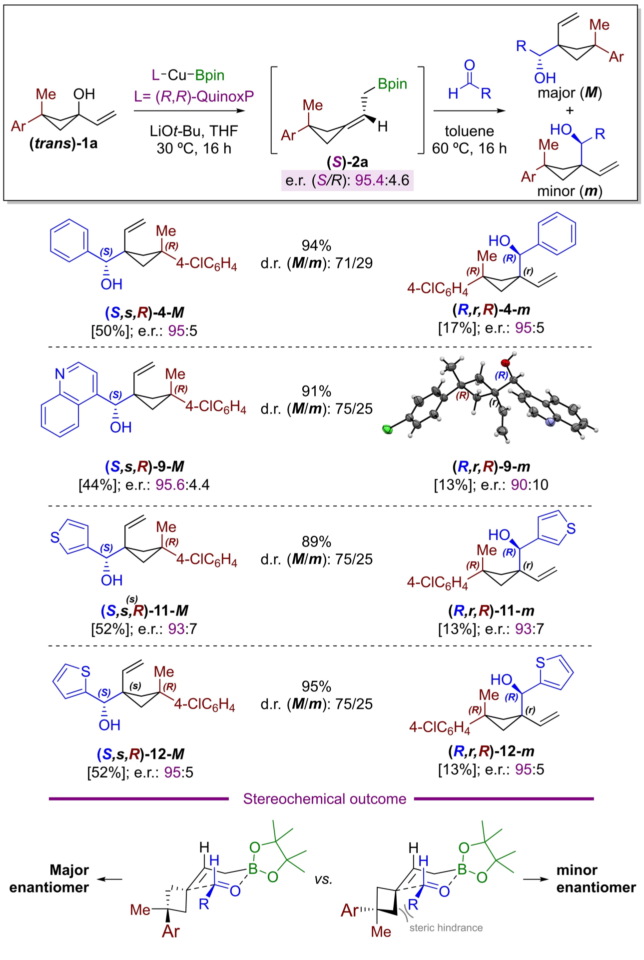
Our ultimate goal was to demonstrate that the axial chirality, achieved on the allylic boronic esters, through the [Cu]/(*R,R*)-QuinoxP catalyzed desymmetrization of **1a**, could be transferred to point chirality along the allylation of aldehydes. We faced this challenging objective, having demonstrated that convergent diastereoselection can be guaranteed along the allylation step, indistinctly of the **(*cis*)-1a** or **(*trans*)-1a** substrate used. When 2,4,6-trimethoxybenzaldehyde reacted in situ with the allylboronic ester **(*S*)-2a** (e.r.: 95.4:4.6), proceeding from **(*trans*)-1a**, the homoallylic alcohol **(*S,s,R*)-5-*M*** was quantitatively formed as the major diastereoisomer (d.r. (***M***/***m***): 83/17) as an enantioenriched mixture of 92:8 e.r. (Scheme 6). We were delighted to realize that the axial chirality was efficiently transferred from the allylic boronic ester **(*S*)-2a** to a point chiral molecule creating two news stereocenters and one pseudoasymmetric center. The X-ray diffraction of **(*S,s,R*)-**



Scheme 6. Sequential, two-step: Cu-catalyzed borylation of **1**/electrophilic allylation. Substrate (0.2 mmol), B_2pin_2 (1.2 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol%), (*R*,*R*)-QuinoxP (10 mol%), LiO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h, aldehyde (2 equiv), toluene (3 mL), 60 °C, 16 h. NMR yields and diastereomeric ratio determined with naphthalene as internal standard. Isolated yields in brackets and e.r. determined by HPLC.

5-*M* allowed us to determine the absolute configuration of the major enantiomer (Scheme 6).[38] When we conducted the same in situ reaction between 2,4,6-trimethoxybenzaldehyde and the allylboronic ester **(*R*)-2a** (e.r.: 4.6:95.4), proceeding from **(*cis*)-1a**, the convergent diastereoselection provided the same major isomer (d.r.: 81/19) and the opposite enantiomeric enriched homoallylic alcohol **(*R*,*s*,*S*)-5-*M*** (e.r.: 8:92) (Scheme 6). We subsequently explored other aldehydes and the in situ allylation of the allylic boronic esters **(*S*)-2a** and **(*R*)-2a** with cyclohexanecarbaldehyde also provided high conversions, convergent diastereoselection and complementarily enantioselectivity towards **(*R*,*s*,*S*)-6-*M*** (e.r.: 71:29) and **(*S*,*s*,*R*)-6-*M*** (e.r.: 30:70) showing some erosion in the enantiomeric purity (Scheme 6). We assumed that the lack of stereoretention might be related to the nature of the aliphatic aldehydes since the in situ allylation of the allylic boronic esters **(*S*)-2a** with propanal also provided high conversions, convergent diastereoselection although observing some erosion in the enantiomeric purity for **(*R*,*s*,*S*)-22-*M*** (99% [30%]; e.r.: 81:19) (*see Supporting Information*). The use of naphthaldehyde for the in situ allylation step, also resulted efficient in terms of conversion and convergent diastereoselection, with good enantioselectivity. Product **(*S*,*s*,*R*)-7-*M*** (e.r.: 91:9) was prepared from **(*S*)-2a** whereas **(*R*,*s*,*S*)-7-*M*** (e.r.: 9:91) was prepared from **(*R*)-2a** (Scheme 6). The X-Ray diffraction of **(*R*,*s*,*S*)-7-M** allowed us to determine the absolute configuration of the major enantiomer (Scheme 6).[38] Interestingly, when pyridine-4-carboxaldehyde reacted with **(*S*)-2a**, proceeding from **(*trans*)-1a**, the enantioenriched mixture of the major diastereoisomer **(*S*,*s*,*R*)-8-*M*** was e.r.: 97:3, showing a slight increase along the axial-to-point chirality transfer (Scheme 6).

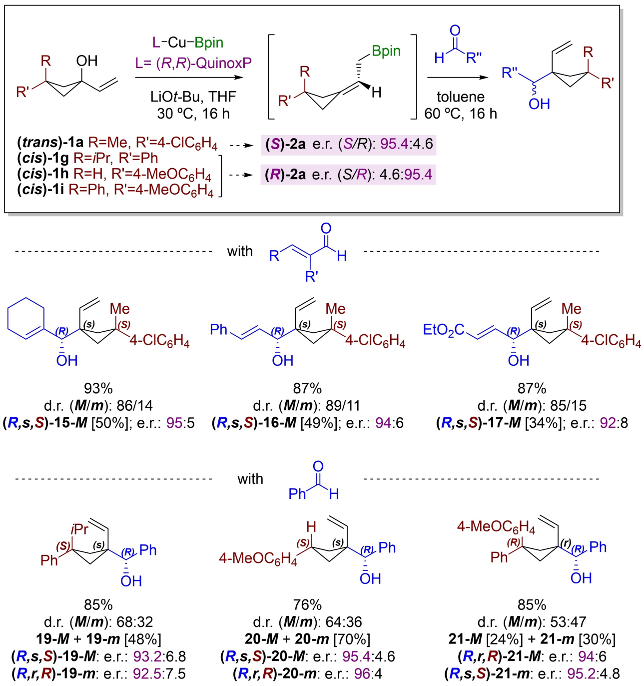
We were also concerned about the transference of axial chirality from the allylic boronic esters to point chirality on the minor diastereoisomers, along the allylation of aldehydes. To gain insights about this issue, we conducted the in situ allylation of the allylboronic ester **(*S*)-2a** (e.r.: 95.4:4.6), proceeding from **(*trans*)-1a**, with 2-benzaldehyde. The reaction resulted in 94% conversion on the homoallylic alcohol **4** with d.r. (***M*/*m***): 71/29 (Scheme 7). Both diastereoisomers were isolated separately and the enantiomeric



Scheme 7. Sequential, two-step: Cu-catalyzed borylation of **(*trans*)-1a**/electrophilic allylation. Substrate (0.2 mmol), B_2pin_2 (1.2 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol%), (*R*,*R*)-QuinoxP (10 mol%), LiO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h, aldehyde (2 equiv), toluene (3 mL), 60 °C, 16 h. NMR yields and diastereomeric ratio determined with naphthalene as internal standard. Isolated yields in brackets and e.r. determined by HPLC.

ratio determined resulting in **(*S*,*s*,*R*)-4-*M*** (e.r.: 95:5) and **(*R*,*r*,*R*)-4-*m*** (e.r.: 95:5) (Scheme 7). It can be concluded that the transference of the axial to point chirality was efficiently conducted not only for the major diastereoisomer, but also for the minor, without erosion from the axial enantioselectivity. Similarly, the allylation of 4-quinolinecarboxaldehyde with the allylboronic ester **(*S*)-2a**, generated the homoallylic alcohol **9** in 91 % conversion with d.r. (***M*/*m***): 75/25 (Scheme 7). In this case, both diastereoisomers were isolated and the transference of the chirality resulted more retentive for the major diastereoisomer **(*S*,*s*,*R*)-9-*M*** (e.r.: 95.6:4:4) than for **(*R*,*r*,*R*)-9-*m*** (e.r.: 90:10) that suffer about 5 % erosion of enantiopurity (Scheme 7). The X-ray diffraction of **(*R*,*r*,*R*)-9-*m***, allowed us to determine the absolute configuration for the preferred enantiomer of the minor diastereoisomer (Scheme 7).[38] Heteroaromatic aldehydes, such as thiophene-3-carbaldehyde and thiophene-2-carbaldehyde also proved the efficient transference of axial chirality from the allylic boronic esters to point chirality on both major and minor diastereoisomers of the homoallylic alcohols **11** and **12**, with stereoretention (Scheme 7). The spatial arrangement of CH_2 methylene on the cyclobutane moiety, with respect to the R substituent on the aldehyde, might justify the preference of the major intermediate during the allylation step (Scheme 7, bottom).

To provide a complete overall picture of the axial-to-point chirality transfer process in these diastereoconvergent allylation reactions, we explored next the compatibility with α,β-unsaturated aldehydes. When substrate **(*trans*)-1a** reacted with cyclohex-1-ene-1-carbaldehyde, the major diastereoisomer **(*R*,*s*,*S*)-15-*M*** was isolated in 44 % with e.r.: 95:5, demonstrating the efficient stereoretention along the transformation (Scheme 8). Similarly *trans*-cinnamaldehyde reacted in situ with **(*S*)-2a** to generate **(*R*,*s*,*S*)-16-*M*** in 49 % with e.r.: 94:6 (Scheme 8). The chemoselectivity demonstrated during the allylation reaction with α,β-unsaturated aldehydes, was specially convenient when **(*S*)-2a** reacted in situ with ethyl *trans*-4-oxobutenoate to synthetize the polyfunctionalized product **(*R*,*s*,*S*)-17-*M***, combining allylic and homoallylic alcohol functionalities, with e.r.: 92:8 (Scheme 8). But also we explored the influence of the substituents on 1-vinyl cyclobutanol for the stereorentetive axial-to-point chiral transfer. When Me group was replaced by *i*Pr and H groups in **(*cis*)-1g** and **(*cis*)-1h**, respectively, the Cu-QuinoxP catalyzed borylation/allylation with 2-benzaldehyde, provided products **(*R*,*s*,*S*)-19-*M*** (e.r.: 93.2:6.8) and **(*R*,*s*,*S*)-20-*M*** (e.r.: 95.4:4.6) (Scheme 8). Similar high stereoretentive process was observed for transformation of **(*cis*)-1i** (R=Ph and R'=4-$MeOC_6H_4$) into product **(*R*,*r*,*R*)-21-*M*** (e.r.: 94:6) (Scheme 8).



Scheme 8. Sequential, two-step: Cu-catalyzed borylation of **(*trans*)-1a** or **(*cis*)-1g–i** with subsequent electrophilic allylation. Substrate (0.2 mmol), B_2pin_2 (1.2 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol %), (*R*,*R*)-QuinoxP (10 mol %), LiO*t*-Bu (1.2 equiv), THF (3 mL), 30 °C, 16 h, aldehyde (2 equiv), toluene (3 mL), 60 °C, 16 h. NMR yields and diastereomeric ratio determined with naphthalene as internal standard. Isolated yields in brackets and e.r. determined by HPLC.

Conclusion

In conclusion, we have developed an efficient and general method for the desymmetrization of both (*trans*)- and (*cis*)-1-vinylcyclobutan-1-ols **1** through an asymmetric Cu-catalyzed borylation under mild conditions and robust reaction protocol. Using differently substituted cyclobutanes, containing a quaternary carbon in their structure, the reaction proceeds with high conversion to the allylic alcohol **3**, obtained after in situ oxidation of the organoboron intermediate **2**. Different type of chiral ligands have been studied in the asymmetric Cu-catalyzed borylation, however, P-stereogenic diphosphine (*R*,*R*)-QuinoxP demonstrated to be the most convenient chiral ligand, to assist the conversion of **(*trans*)-1a** into **3a** in 95.4:4.6 e.r. (*S*/*R*), whereas the diastereosiomeric substrate **(*cis*)-1a** was transformed into **3a** in 4.6:95.4 e.r. (*S*/*R*). Once the asymmetric Cu-catalyzed borylation has demonstrated the feasibility to form both enantiomers with axial chirality, we proved then that the axial-to-point chirality transfer is possible through diastereoconvergent allylation with a wide range of aldehydes, including sterically hindered aldehydes, heteroaromatic aldehydes and α,β-unsaturated aldehydes. We demonstrated that either starting from (*trans*)- or (*cis*)-1-vinylcyclobutan-1-ols **1**, the homoallylic alcohols could be synthetized favoring the same diastereoisomer, creating two new stereocenters and one pseudoasymemtric center with stereoretention for both enantiomers.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: axial-to-point chirality · diastereoconvergence · desymmetrization · copper catalysis · homoallylic alcohols

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