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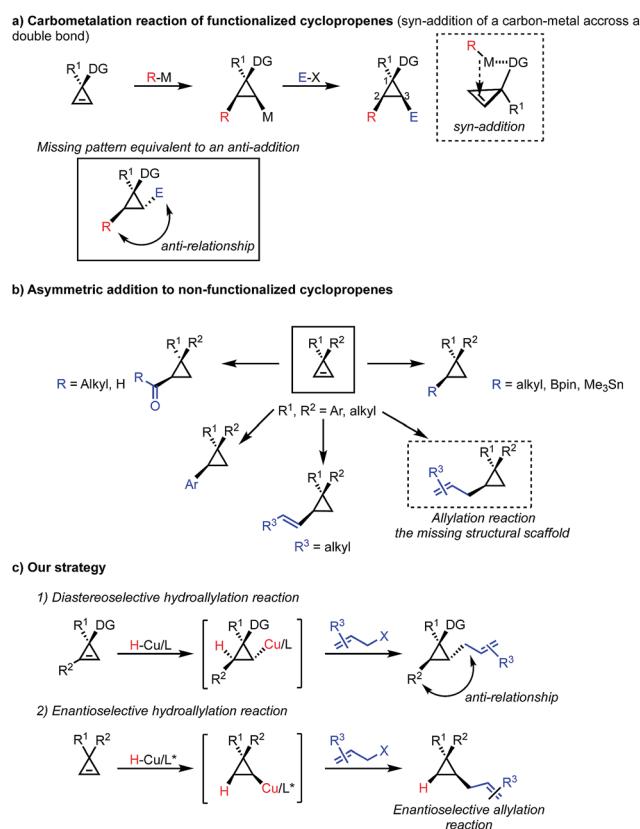
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Introduction

The synthesis of enantioenriched cyclopropane containing scaffolds constitutes an ongoing challenge in organic synthesis despite significant advancements over the past few decades.^{1–4} The dominant strategies^{5–7} construct stereoselectively cyclopropanes from olefins and the metal-catalyzed decomposition of diazoesters,^{8–11} the addition of zinc carbenoid^{12,13} or the Michael addition followed by an 1,3-elimination reaction.^{14–21} An alternative approach consists in the manipulation of an existing scaffold and in this context the carbometalation of cyclopropenes has proven to be a very efficient method leading to a large variety of polysubstituted cyclopropane derivatives from a single precursor.^{22,23} Our group^{24–33} and others^{34–40} have contributed to the last approach by reporting several transition-metal catalyzed protocols for the addition of carbon nucleophiles to cyclopropenes with high diastereo- and enantioselectivities (Scheme 1a). However, as the incoming alkyl residues (nucleophiles) and the organometallic species are always introduced in a *cis*-relationship across the unsaturation, all the above discussed strategies of carbometalation provide only access to 1,2-*syn* functionalized cyclopropanes. The formation of 1,2-*anti* di-functionalized cyclopropane derivatives remained an unsolved synthetic problem (Scheme 1c). On the other hand, the asymmetric addition of nucleophiles (alkyl, vinyl, aryl, acyl, metalloids) to C₂-symmetric cyclopropenyl rings led to various functionalized cyclopropanes in high diastereo- and enantioselective ratios (Scheme 1b).^{41,42} Yet, the catalytic asymmetric allylation of non-functionalized cyclopropenes represent one of the missing structural scaffolds (Scheme 1c). This class of racemic structure can solely be accessed through stoichiometric addition of allylindium,^{43,44} allylgallium⁴⁵ on 1,2-disubstituted

cyclopropenes, asymmetric allylzincation of cyclopropenone ketal,⁴⁶ or cyclopropenyl metal species,⁴⁷ respectively. To address the issues stated above, we decided to pursue a different approach for the synthesis of 1,2-*anti* trisubstituted cyclopropanes.



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Scheme 1 (a) Carbometalation of cyclopropenes: *syn*-1,2-bisalkylation reaction. (b) Asymmetric hydrofunctionalization of cyclopropenes. (c) Proposed strategy for 'anti'-selective hydrofunctionalization and asymmetric allylation.

At the outset of this study, we were interested in the development of a broadly applicable protocol that would allow us to access a variety of hydrofunctionalized cyclopropane derivatives in a concise manner. Inspired by the recent developments in copper mediated hydro- and boroallylations of olefins and alkynes,^{48–54} we expected that a similar strategy might be amenable to the synthesis of allylated cyclopropanes (Scheme 1c). As the initiating step involves a hydrometalation of the cyclopropene followed by an electrophilic trapping, this strategy places the two substituents in the 2,3-position in an *anti*-relationship. The hydroallylation of cyclopropanes would therefore provide a valuable solution for the synthesis of these desirable products.⁵⁵ Based on previous observations in carbometalations of 1,2-disubstituted cyclopropanes, we expected the hydrometalation to occur similarly in a highly regio- and diastereoselective fashion. Accordingly, an *in situ* generated ligated copper hydride species would add across the cyclopropene double bond furnishing a cyclopropyl copper intermediate that would be trapped by an allyl electrophile. From earlier studies on copper mediated boro⁵⁶- and hydrometalations,⁵⁷ we anticipated that the highly reactive cyclopropyl copper intermediate might undergo a variety of undesired pathways, *e.g.* oxidation, dimerization or cycloaddition.

Results and discussion

Despite all potential pitfalls, we decided to investigate the above mentioned transformation and determine the most suitable reaction parameters, initially on the readily available 1,2-disubstituted cyclopropenyl ester **1a**.⁵⁸ Optimization of reaction conditions quickly revealed a major influence of the ligand on the diastereomeric ratio (Table 1). In the presence of a variety of bidentate phosphine ligands (**L₁** to **L₁₀**), the hydroallylation product **3a** was obtained in moderate to excellent diastereomeric ratios (Table 1, entries 1 to 10). In the presence of triphenylphosphine no conversion was observed (Table 1, entry 11) whereas in the absence of ligand (Table 1, entry 12), an equimolar mixture of the two diastereomers was formed. Stronger bases *ca.* NaOtBu or KOtBu only led to decomposition while weaker bases did not furnish any product (not shown in Table 1). A reduction of the amount of silane led to a pronounced decrease in the reaction rate but the quantity of LiOtBu could be reduced to 1.5 equivalents without considerable loss of reactivity. It should be noted that from the 4 possible diastereoisomers, only two were detected where the major isomer **3a**, as indicated in Table 1, results from a *syn*-hydroallylation reaction proceeding *anti* to the ester group. With the optimized conditions in hand for the formation of the formally 1,2-*trans*-cyclopropanes with excellent diastereoselectivity (Table 1, entry 13), we surveyed a variety of different cyclopropenyl esters **1a–f** with allyl electrophiles **2a–d** (Scheme 2).

We found that besides allyl phosphate **2a**, various substitutions at the 2-position of the allylic fragment (**2b–d**), including sterically encumbered groups, are well tolerated (Scheme 2, **3b–d**). It should be noted that substitutions at the terminal position of the allyl fragment and electron-rich arenes at the 2-position are not tolerated. On the cyclopropene moiety, longer (Scheme

Table 1 Optimization for the copper catalyzed hydroallylation of 1,3-disubstituted cyclopropanes^a

Entry	Ligand	Conv. [%]	dr
1	L₁	91	68 : 32 : 0 : 0
2	L₂	100	86 : 14 : 0 : 0
3	L₃	100	89 : 11 : 0 : 0
4	L₄	100	85 : 15 : 0 : 0
5	L₅	100	87 : 13 : 0 : 0
6	L₆	100	93 : 07 : 0 : 0
7	L₇	100	93 : 07 : 0 : 0
8	L₈	100	91 : 09 : 0 : 0
9	L₉	100	91 : 09 : 0 : 0
10	L₁₀	74	82 : 18 : 0 : 0
11	PPh ₃	No conv.	—
12	—	100	50 : 50 : 0 : 0
13	L₈	100 ^b (62% isol.)	95 : 05 : 0 : 0

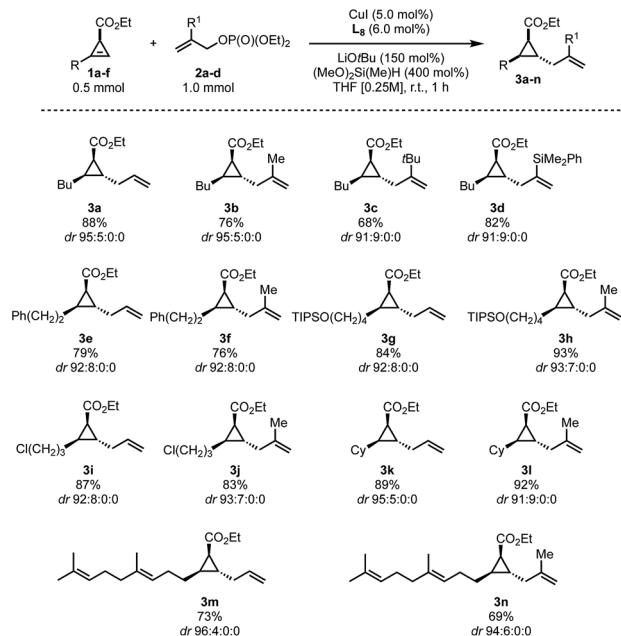
^a Cyclopropenyl ester **1a** (0.2 mmol), allylOP(O)(OEt)₂ **2a**, (0.4 mmol), CuI (5.0 mol%), ligand (6.0 mol%), LiOtBu (200 mol%), (MeO)₂MeSiH (400 mol%), THF (0.25 M), room temperature. ^b On 0.5 mmol scale with LiOtBu (150 mol%).

2, 3e–j and 3m,n or branched (Scheme 2, **3k,l**) alkyl residues are well tolerated. Furthermore, a TIPS protected alcohol (**3g,h**), a terminal chlorine (**3i,j**) or internal olefins (**3m,n**) do not impede the reaction either. Finally, the reaction could also be conducted on a 10-fold scale giving access to more than 1 gram of allylated cyclopropane in similar yields (Scheme 2, **3a** and **3k**). All transformations proceeded with a good to excellent diastereoselectivity leading to a unique *trans*-relationship between the allyl unit and all the substituents on the cyclopropyl ring. The relative configuration of **3g** has been determined by comparison with an authentic sample independently prepared by the reported allylindation strategy⁴³ and by analysis of NOE experiments on **3a** (see the ESI†). The configurations of all other products were assigned by analogy.

Having established an easy access to the general 1,2-*anti*-1,3-*syn*-trisubstituted cyclopropyl framework **3**, we sought to expand the scope to the formation of 1,1,2-trisubstituted cyclopropanes **5**.

In contrast to the disubstituted cyclopropanes **1** where we only had to develop a diastereoselective protocol, 3,3-disubstituted cyclopropanes **4** required the additional development of an enantioselective protocol. At the outset we decided first to develop a reliable diastereoselective approach which could eventually be transformed into a catalytic, asymmetric variant.





Scheme 2 Copper-catalyzed hydroallylation of 1,3-disubstituted cyclopropanes **1a–f**. Reaction conditions: **1a–f** (0.5 mmol), $\text{H}_2\text{C}=\text{C}(\text{R}^1)\text{CH}_2\text{OP}(\text{O})(\text{OEt})_2$ **2a–d**, (1.0 mmol), CuI (5.0 mol%), L_8 (6.0 mol%), LiOtBu (150 mol%), $(\text{MeO})_2\text{MeSiH}$ (400 mol%), THF (0.25 M), room temperature. Diastereomeric ratios determined by GC.

As a model substrate, we investigated the readily accessible cyclopropane **4a** which have been extensively studied in stereoselective carbometalations.^{59,60} Employing xantphos as ligand, we quickly learned that this substrate class posed considerably harder challenges as the choice of copper salt, ligand and silane exhibited a more pronounced influence on the reaction outcome (Table 2). Dimethoxymethylsilane proved again to be the silane of choice (Table 2, entries 1–7). Additionally, lowering the concentration had a positive effect on both yield and diastereoselectivity. Copper iodide provided optimal results among all copper salts screened and, after further lowering catalyst loading to 5 mol%, we could isolate the product in 80% yield as a single diastereoisomer (Table 2, entry 16). The relative configuration of **5a** was determined by NOE experiment and confirmed that the allyl substituent is introduced in *syn* to the Me group. With the optimized reaction conditions in hand, we have subsequently evaluated the scope of cyclopropanes **4** and allyl electrophiles **2** that could be used in this transformation. Simple modifications on the arene moiety were well tolerated as well as spiro- or naphthalene substituted cyclopropanes (Scheme 3, **5a–e**). Surprisingly, electron-rich arenes or longer alkyl chains than methyl resulted in no detectable product formation. Furthermore, as expected 1,1-dialkyl cyclopropene furnished the product **5f** with low diastereoselectivity (as also observed in the copper-catalyzed carbozincation and carbomagnesiation reactions).³² Various substitutions at the 2-position of the allyl phosphate **2** were again well tolerated. Simple methyl and more complex linear and branched alkyl chains as well as an arene and a silane cleanly underwent this transformation (Scheme 3, **5g–n**). Again,

Table 2 Optimization copper catalyzed hydroallylation of 3,3-disubstituted cyclopropanes **4a**

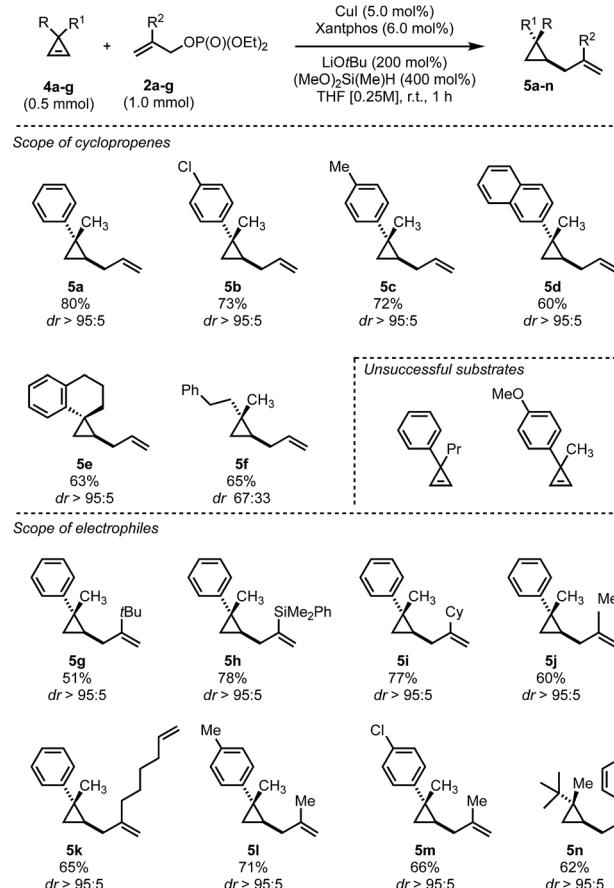
Entry	CuX	Silane	Conc.	Yield ^e [%]	dr
1	CuI	PMHS	0.33 M	6	12 : 1
2	CuI	$(\text{TMSO})_2\text{MeSiH}$	0.33 M	47	18 : 1
3	CuI	TMS_3SiH	0.33 M	7	7 : 1
4	CuI	Me_2PhSiH	0.33 M	26	20 : 1
5	CuI	PhSiH_3	0.33 M	59	10 : 1
6	CuI	$(\text{MeO})_2\text{MeSiH}$	0.33 M	62	17 : 1
7	CuI	$(\text{EtO})_2\text{MeSiH}$	0.33 M	63	14 : 1
8	CuBr	$(\text{MeO})_2\text{MeSiH}$	0.25 M	84	21 : 1
9	CuI	$(\text{MeO})_2\text{MeSiH}$	0.25 M	87	24 : 1
10	$\text{Cu}(\text{OAc})_2$	$(\text{MeO})_2\text{MeSiH}$	0.25 M	41	10 : 1
11	CuOAc	$(\text{MeO})_2\text{MeSiH}$	0.25 M	74	12 : 1
12	CuTC	$(\text{MeO})_2\text{MeSiH}$	0.25 M	58	13 : 1
13	CuI^b	$(\text{MeO})_2\text{MeSiH}$	0.25 M	83	>50 : 1
14	CuI	$(\text{MeO})_2\text{MeSiH}^c$	0.25 M	74	>50 : 1
15	CuI^b	$(\text{MeO})_2\text{MeSiH}^c$	0.25 M	68	21 : 1
16	CuI^d	$(\text{MeO})_2\text{MeSiH}$	0.25 M	80 (isol.)	>50 : 1

^a **4a** (0.2 mmol), allylOP(O)(OEt)₂ **2a**, (0.4 mmol), CuX (10 mol%), xantphos (12 mol%), LiOtBu (200 mol%), $(\text{MeO})_2\text{MeSiH}$ (400 mol%), THF, room temperature. ^b CuI (5.0 mol%), xantphos (6.0 mol%). ^c $(\text{MeO})_2\text{MeSiH}$ (200 mol%). ^d On 5.0 mmol scale. ^e GC yield using tetradecane as internal standard.

substituting the 3-position of the electrophile or embedding electron rich substituents on the olefin prohibited product formation. Finally, this reaction could be scaled to give the desired cyclopropane in good yield on a 5.0 mmol scale for **5a**. Additionally, we found that the electrophile can be utilized as the limiting component provided that the diethyl phosphate is replaced by the more reactive bis(trichloroethyl) phosphate leaving group and similar yields and diastereoselectivities were obtained for three representative examples (**5a**, **5k** and **5n**).

Having established this new diastereoselective protocol, we felt confident to identify conditions that would allow us to access these substrates through asymmetric catalysis. The enantioselective, copper catalyzed hydroallylation has recently received considerable attention and a variety of catalytic systems have been established.^{48,49} Furthermore, our groups has shown that different nucleophiles can undergo enantioselective copper-catalyzed asymmetric additions to this class of substrates.³²

After extensive screening of commercially available ligands, copper salts and bases, we found that none of the combinations delivered the product in a satisfactory fashion (see *vide infra*). Although good yields were obtained at room temperature, only low levels of enantioinduction were observed. Lowering the reaction temperature led to considerable increase in stereoselectivity at the expense of dramatic loss of yield. This observation can be explained by competing undesired pathways of the intermediate cyclopropyl copper species. We surmised that the electrophile had to be rendered more reactive in order to



Scheme 3 Substrate scope of copper catalyzed hydroallylation of 3,3-disubstituted cyclopropenes **4a–g**. Reaction conditions: **4a–g** (0.5 mmol), allylOP(O)(OEt)₂ (1.0 mmol), CuI (5.0 mol%), xantphos (6.0 mol%), LiOtBu (200 mol%), (MeO)₂Si(Me)H (400 mol%), THF (0.25 M), room temperature; **5i**, **5k** and **5n** were obtained from the corresponding (bistrichloroethyl)phosphates, respectively.

outcompete potential side-reactions. After screening a variety of different allylating reagents in the presence of (*S*)-DTBMS-SEGPHOS as ligand, we eventually found that the bis(trichloroethyl) phosphate leaving group proved to be the most effective. Nevertheless, we were not able to obtain high levels of enantioinduction with concomitant high yields.

As we obtained high yields in the diastereoselective protocol in the presence of xantphos as ligand, we decided to test the possibility to employ a *P*-chiral analog of this parent ligand. Recently an optimized route towards bidentate *P*-stereogenic ligands was disclosed.⁶¹ Under the initial reaction conditions, these ligands did not provide any improvement but we found that by decreasing the reaction temperature and utilizing the allyl electrophile as the limiting reagent, high levels of enantioinduction with good yields could be achieved (Table 3).

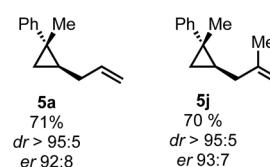
To test the applicability of this preliminary finding we applied this protocol to the synthesis on two previously described examples (Scheme 4).

Nevertheless, we could show that an enantioselective approach is feasible and can allow for the synthesis of enantioenriched 1,1,2-trisubstituted cyclopropanes.

Table 3 Optimization of an enantioselective protocol for the copper catalyzed hydroallylation of 3,3-disubstituted cyclopropane **4a**^a

Entry	CuX	Ligand	T [°C]	er	Yield ^f [%]
1 ^b	CuI	L₁₁	25	62 : 38	41
2 ^b	CuI	L₁₂	25	64 : 36	56
3 ^b	CuI	L₁₃	25	72 : 28	54
4 ^c	CuI	L₁₃	25	79 : 21	51
5 ^c	CuTC	L₁₃	25	86 : 14	33
6 ^c	Cu(OAc) ₂	L₁₃	25	86 : 14	34
7 ^{c,d}	Cu(OAc) ₂	L₁₅	25	94 : 06	30
8 ^{c,d}	Cu(OAc) ₂	L₁₃	25	82 : 18	69
9 ^{c,e}	Cu(OAc) ₂	L₁₃	0	87 : 13	72
10 ^{c,e}	CuI	L₁₄	-20	94 : 06	38
11 ^{c,e}	Cu(OAc) ₂	L₁₄	-20	96 : 04	31
12 ^{c,e}	Cu(OAc) ₂	L₁₃	-20	92 : 08	70

^a **4a** (0.2 mmol), allylOP(O)(OR)₂ **2a** (0.4 mmol), CuX (5.0 mol%), ligand (6.0 mol%), LiOtBu (200 mol%), (MeO)₂Si(Me)H (400 mol%), THF (0.25 M). ^b AllylOP(O)(OEt). ^c AllylOP(O)(OCH₂CCl₃)₂. ^d **4a** (200 mol%). ^e **4a** (300 mol%). ^f GC yield using tetradecane as internal standard.



Scheme 4 Preliminary results of the enantioselective hydroallylation of 3,3-disubstituted cyclopropane **4a**.

Conclusions

In summary we described a broadly applicable copper catalyzed hydroallylation of 3,3- and 1,3-disubstituted cyclopropenes. The present method features an *in situ* formed copper hydride species that undergoes stereoselective hydrometalation of cyclopropenes and is trapped with a variety of electrophilic allylphosphates. This protocol allows for the diastereoselective synthesis of 1,2,3- and 1,1,2-trisubstituted cyclopropanes in good to high yields with good to excellent diastereoselectivity. The robustness of this method has been showcased in the synthesis of more than 30 examples and scaled up to >1 g of product in each class of substrates. Finally, we established preliminary conditions that give rise to enantioenriched products utilizing a *P*-chiral xantphos derivative.



Conflicts of interest

There are no conflicts to declare.

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