Diastereo- and enantioselective copper catalyzed hydroallylation of disubstituted cyclopropenes†

Heiko Sommer and Ilan Marek *

A highly diastereo- and enantioselective protocol for the hydroallylation of 1,1- and 1,2-disubstituted cyclopropenes has been developed utilizing an in situ formed copper hydride. A variety of allyl electrophiles could be utilized yielding a diverse range of trisubstituted cyclopropanes. Finally a preliminary enantioselective variant could be established employing a recently described P-stereogenic xantphos derivative as ligand.

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 strategies5–7 construct stereoselectively cyclopropanes from olefins and the metal-catalyzed decomposition of diazoesters,8–11 the addition of zinc carbenoid12,13 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 group24–33 and others34–40 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 cyclopropanes 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 cyclopropanes, 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.
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,\textsuperscript{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 cyclopropane 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.\textsuperscript{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 cyclopropane double bond furnishing a cyclopropyl copper intermediate that would be trapped by an allyl electrophile. From earlier studies on copper mediated boro- and hydrometalations,\textsuperscript{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.\textsuperscript{56} 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 (L\textsubscript{1} to L\textsubscript{10}), 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). From earlier studies with allylated cyclopropanes, we suspected that the highly reactive cyclopropyl copper intermediate might undergo a variety of undesired pathways, e.g. oxidation, dimerization or cycloaddition.

Table 1. Optimization for the copper catalyzed hydroallylation of 1,3-disubstituted cyclopropanes\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv. [%]</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L\textsubscript{1}</td>
<td>91</td>
<td>68 : 32 : 0 : 0</td>
</tr>
<tr>
<td>2</td>
<td>L\textsubscript{2}</td>
<td>100</td>
<td>86 : 14 : 0 : 0</td>
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<td>3</td>
<td>L\textsubscript{3}</td>
<td>100</td>
<td>89 : 11 : 0 : 0</td>
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<td>4</td>
<td>L\textsubscript{4}</td>
<td>100</td>
<td>85 : 15 : 0 : 0</td>
</tr>
<tr>
<td>5</td>
<td>L\textsubscript{5}</td>
<td>100</td>
<td>87 : 13 : 0 : 0</td>
</tr>
<tr>
<td>6</td>
<td>L\textsubscript{6}</td>
<td>100</td>
<td>93 : 07 : 0 : 0</td>
</tr>
<tr>
<td>7</td>
<td>L\textsubscript{7}</td>
<td>100</td>
<td>93 : 07 : 0 : 0</td>
</tr>
<tr>
<td>8</td>
<td>L\textsubscript{8}</td>
<td>100</td>
<td>91 : 09 : 0 : 0</td>
</tr>
<tr>
<td>9</td>
<td>L\textsubscript{9}</td>
<td>100</td>
<td>91 : 09 : 0 : 0</td>
</tr>
<tr>
<td>10</td>
<td>L\textsubscript{10}</td>
<td>74</td>
<td>82 : 18 : 0 : 0</td>
</tr>
<tr>
<td>11</td>
<td>PPh\textsubscript{3}</td>
<td>No conv.</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>—</td>
<td>100</td>
<td>50 : 50 : 0 : 0</td>
</tr>
<tr>
<td>13</td>
<td>L\textsubscript{8}</td>
<td>100\textsuperscript{b} (62% isol.)</td>
<td>95 : 05 : 0 : 0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Cyclopropenyl ester 1a (0.2 mmol), allyl(OP)(OEt), 2a, (0.4 mmol), CuI (5.0 mol%), ligand (6.0 mol%), LiO Bu (200 mol%), THF (0.25 M), room temperature. \textsuperscript{b} On 0.5 mmol scale with LiO Bu (150 mol%).

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 allylic fragment and electron-rich arenes at the 2-position are not tolerated. On the cyclopropane moiety, longer (Scheme 2, 3e–j and 3m,n) or branched (Scheme 2, 3k,l) allyl 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 alllylation strategy\textsuperscript{54} 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.
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, a further lowering catalyst loading to 5 mol%, we could isolate the product in 80% yield as a single diastereoisomer (Table 2, entry 5). 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 cyclopropenes 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 cyclopropenes (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-dialkyldialkylcyclopropene furnished the product 5f with low diastereoselectivity (as also observed in the copper-catalyzed carboxidation and carbomagnesiation reactions).⁶¹ 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, 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 1.0 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.⁶⁴,⁶⁵ Furthermore, our groups has shown that different nucleophiles can undergo enantiomeric copper-catalyzed asymmetric additions to this class of substrates.²²

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>CuX</th>
<th>Silane</th>
<th>Conc.</th>
<th>Yield [%]</th>
<th>dr</th>
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<tbody>
<tr>
<td>1</td>
<td>CuI</td>
<td>PMHS</td>
<td>0.33 M</td>
<td>6</td>
<td>12 : 1</td>
</tr>
<tr>
<td>2</td>
<td>CuI</td>
<td>TMSOsMeSiH</td>
<td>0.33 M</td>
<td>47</td>
<td>18 : 1</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>TMSSiH</td>
<td>0.33 M</td>
<td>7</td>
<td>7 : 1</td>
</tr>
<tr>
<td>4</td>
<td>CuI</td>
<td>Me3PhSiH</td>
<td>0.33 M</td>
<td>26</td>
<td>20 : 1</td>
</tr>
<tr>
<td>5</td>
<td>CuI</td>
<td>PhSiH3</td>
<td>0.33 M</td>
<td>59</td>
<td>10 : 1</td>
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<tr>
<td>6</td>
<td>CuI</td>
<td>(MeO)2MeSiH</td>
<td>0.33 M</td>
<td>62</td>
<td>17 : 1</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>(EtO)2MeSiH</td>
<td>0.33 M</td>
<td>63</td>
<td>14 : 1</td>
</tr>
<tr>
<td>8</td>
<td>CuBr</td>
<td>(MeO)2MeSiH</td>
<td>0.25 M</td>
<td>84</td>
<td>21 : 1</td>
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<tr>
<td>9</td>
<td>CuI</td>
<td>(MeO)2MeSiH</td>
<td>0.25 M</td>
<td>87</td>
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<td>10</td>
<td>CuI</td>
<td>(MeO)2MeSiH</td>
<td>0.25 M</td>
<td>41</td>
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<tr>
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<td>CuI</td>
<td>Me3SiH</td>
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<td>74</td>
<td>12 : 1</td>
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<td>58</td>
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<tr>
<td>13</td>
<td>CuI</td>
<td>(MeO)2MeSiH</td>
<td>0.25 M</td>
<td>83</td>
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<tr>
<td>14</td>
<td>CuI</td>
<td>(MeO)2MeSiH</td>
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<tr>
<td>15</td>
<td>CuI</td>
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<td>68</td>
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<tr>
<td>16</td>
<td>CuI</td>
<td>(MeO)2MeSiH</td>
<td>0.25 M</td>
<td>80 (isol.)</td>
<td>&gt;50 : 1</td>
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</table>

⁴a 0.2 mmol, allylOP(O)(OEt)₂, 2a, 0.4 mmol, CuX (10 mol%), xanthos (12 mol%), LiOrBu (200 mol%), (MeO)₂MeSiH (400 mol%), THF, room temperature. ⁵ CuI (5.0 mol%), xanthos (6.0 mol%), (MeO)₂MeSiH (200 mol%). On 5.0 mmol scale. ⁶ GC yield using tetradecane as internal standard.

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**Scheme 2** Copper-catalyzed hydroallylation of 1,3-disubstituted cyclopropenes 1a–f. Reaction conditions: 1a–f (0.5 mmol), H₂C≡C(R)₂CH₂OP(O)(OEt)₂, 2a–d (1.0 mmol), CuI (5.0 mol%), L₈ (6.0 mol%), LiOrBu (150 mol%), (MeO)₂MeSiH (400 mol%), THF (0.25 M), room temperature. Diastereomeric ratios determined by GC.
outcompete potential side-reactions. After screening a variety of different allylating reagents in the presence of (S)-DTBM-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. 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.

### Conclusions

In summary we described a broadly applicable copper catalyzed hydroallylation of 3,3- and 1,3-disubstituted cyclopropanes. The present method features an in situ formed copper hydride species that undergoes stereoselective hydrometalation of cyclopropanes 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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Notes and references