Regio- and diastereoselective reactions of chiral secondary alkylcopper reagents with propargylic phosphates: preparation of chiral allenes†

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The diastereoselective SN2- substitution of secondary alkylcopper reagents with propargylic phosphates enables the preparation of stereodefined alkylallenes. By using enantiomerically enriched alkylcopper reagents and enantioenriched propargylic phosphates as electrophiles anti-SN2-substitutions were performed leading to α-chiral allenes in good yields with excellent regioselectivity and retention of configuration. DFT-calculations were performed to rationalize the structure of these alkylcopper reagents in various solvents, emphasizing their configurational stability in THF.

Introduction

Allenes are common intermediates in organic synthesis and found in natural products.1 They are typically prepared by the substitution reaction of propargylic electrophiles with nucleophiles, such as organocopper reagents.2 Thereby, these propargylic reagents bear a good leaving group, such as acetates, ethers, epoxides, phosphates or halides.3–4 Axially chiral allenes are generally prepared from enantioenriched propargylic substrates5 or by the use of chiral ligands.4 The chirality transfer from the chiral propargylic substrate to the allene depends on the nature of the electrophile and nucleophile as well as on the solvent and temperature.4,6 However, the enantioselective preparation of axially chiral allenes bearing a stereocenter in α-position (“α-chiral allenes”) is rather difficult and only a few examples have been reported.2 Thereby, the stereochemistry of the α-position results from an asymmetric synthesis using chiral ligands.

Recently, we reported a zinc-mediated anti-SN2'-substitution reaction of alkylcopper reagents of type 1 with allylic substrates (2) leading to chiral allenes of type 3 with excellent regioselectivity and high retention of configuration (see Scheme 1(b and c)).6,7 These organocopper reagents were prepared from the corresponding alkyl iodide 4 via l/Li-exchange reaction leading to allyllithium reagent 5. Subsequent transmetallation with CuBr·P(OEt)3 afforded alkylcopper reagent 1.4 The regioselectivity (SN2' : SN2 ratio) of the substitution reactions highly depended on the choice of allylic electrophile 2 and the used organometallic species. The reaction of alkylcopper reagents 1 with allylic bromides 2a exclusively led to the SN2-product 3a (γ : α < 1 : 99; see Scheme 1(a)). The addition of zinc chloride and the use of chiral allylic phosphates 2b as electrophiles exclusively led to the SN2'-products 3b (γ : α > 99 : 1; (b)).6,8 Furthermore, we reported anti-SN2'-substituptions of secondary alkylcopper-zinc reagents with allylic phosphates 2c leading to chiral allylic alcohols of type 3c (γ : α > 95 : 5; (c)).7 This method was used in the total synthesis of the natural product (3S,6R,7S)-zingiberenol.7

Scheme 1. Stereoretentive preparation of chiral secondary alkylcopper reagents 1: (a–c): subsequent SN2- and zinc-mediated anti-SN2'-substitution reactions with allylic substrates. (d): Anti-SN2'-substitution with chiral propargylic phosphates leading to axially chiral allenes.
Herein, we wish to report the $anti$-$S_N2^\prime$-substitution of secondary alkylcopper reagents 1 with chiral propargylic phosphates 6 leading to $\alpha$-chiral allenes of type 7 with retention of the configuration (see Scheme 1(d)). Remarkably, this overall $anti$-$S_N2^\prime$-substitution reaction proceeded directly with the alkycopper reagent 1 with transfer of chirality from the propargylic substrate 6 to the allene 7.

## Results and discussion

In preliminary experiments, we examined the leaving group of the propargylic electrophile for achieving the desired $S_N2^\prime$-reaction. Thus, we prepared the secondary alkylcopper reagent $anti$-5a via U/Li-exchange of the corresponding alkyl iodide $anti$-4a at $-100\,^\circ C$ in pentane/diethyl ether-mixture (3 : 2) using t-BuLi (2.2 equiv.) followed by subsequent treatment with CuBr·P(OEt)$_2$ (2.0 equiv.) leading to alkycopper reagent $anti$-1a (see Table 1). This alkycopper reagent was configurationally stable in THF up to $-50\,^\circ C$ and thus, we performed a solvent switch at this temperature. Subsequent addition of the propargylic bromide 9 (6a, 3.0 equiv.) furnished only traces of the desired allene $anti$-7a (see Table 1; entry 1) after stirring for 1 h at $-50\,^\circ C$. The use of propargylic acetate 6b showed a similar result (entry 2). Switching to pentfluorobenzoate 6c or diphenylphosphate 6d as leaving groups afforded $anti$-7a in good yields, but with moderate stereoretention (48–50% yield, dr up to 93 : 7; entries 3 and 4). However, using the propargylic diethyl phosphate 6e as electrophile significantly increased the stereoretention of the secondary alkycopper center ($anti$-7a, 59% yield, dr = 98 : 2). The same reaction afforded $anti$-7a in only 40% yield and dr = 92 : 8 when no solvent switch was performed, demonstrating the necessity of THF as solvent.

With these results in hand, we performed stereoselective reactions with various diastereomerically pure alkyl iodides $syn$- or $anti$-4a–d and propargylic phosphates 6e–g leading to allenes 7a–e in 42–65% yield and with dr higher than 95 : 5 (see Table 2). In most cases, a high retention of configuration was observed. However, using the TMS-substituted propargylic phosphate 6g as electrophile led to allene $anti$-7e in 61% yield with moderate diastereoselectivity (dr = 75 : 25; entry 4). The reaction of $anti$-1a with the propargylic phosphate bearing a terminal methyl-group 6f led to the methyl-substituted allene $anti$-7b in 65% yield and dr = 97 : 3 (see Table 2; entry 3). Furthermore, the 1,2-substituted secondary alkycopper reagents $anti$- and $syn$-1b reacted with 6c to the corresponding allenes $anti$-7d (58% yield, dr = 98 : 2; entry 5) and $syn$-7d (42% yield, dr = 6 : 94; entry 6). The OTBS-substituted allenes $anti$-7e (50% yield, dr = 95 : 5; entry 7) and $syn$-7e (44% yield, dr = 4 : 96; entry 8) were prepared with high retention of configuration as well.

### Table 1: Stereoretentive preparation of secondary alkycopper reagent $anti$-1a and subsequent reaction with various propargylic substrates 6 leading to the allene $anti$-7a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Yield of $anti$-7a (%)</th>
<th>dr of $anti$-7a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a: X = Br</td>
<td>Traces</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>6b: X = OAc</td>
<td>5</td>
<td>90 : 10</td>
</tr>
<tr>
<td>3</td>
<td>6c: X = COC$_2$F$_5$</td>
<td>48</td>
<td>91 : 9</td>
</tr>
<tr>
<td>4</td>
<td>6d: X = OP(O)(OPh)$_2$</td>
<td>50</td>
<td>93 : 7</td>
</tr>
<tr>
<td>5</td>
<td>6e: X = OP(O)(OEt)$_2$</td>
<td>59</td>
<td>98 : 2</td>
</tr>
</tbody>
</table>

a The diastereosellectivity (dr; $anti$ : $syn$ ratio) was determined by GC-analysis using dodecane as internal standard.
In addition, this anti-selective substitution was extended to optically enriched alkylcopper reagents 1d–e (see Table 3). Thus, the reaction of the secondary alkylcopper reagent (R)-1d with propargylic phosphate 6e furnished (R)-7f in 41% yield and er = 93 : 7 (see Table 3; entry 1). Analogously, the corresponding (S)-enantiomer (S)-7f was prepared in 48% yield and er = 10 : 90 (entry 2). To our delight, chiral alkylcopper reagents reacted also with higher substituted chiral propargylic phosphates 6h–i leading to axially chiral allenes bearing a stereocenter in the α-position (see Table 3; entries 3–8). Thus, the reaction of the alkylcopper (R)-1d with enantiomerically pure propargylic phosphate (R)-6h, prepared from the corresponding 3-butyne-2-ol,12 led to the α-chiral disubstituted allene (R,S)-7g13 in 43% yield with high anti-S,S-2'-substitution ratio (dr = 92 : 8; er = 99 : 1, entry 3). Similarly, the allene (S,S)-7g was prepared from organo-copper (S)-1d and the chiral phosphate (R)-6h in 49% yield (dr = 12 : 88; er = 99 : 1;14 entry 4). Moreover, (R)-oct-3-yn-2-yl diethyl-phosphate (R)-6i was prepared according to literature from the corresponding optically enriched propargylic alcohol.3e,6,14 Subsequent reaction of alkylcopper (R)-1d with phosphate (R)-6i furnished the α-chiral trisubstituted allene (R,S)-7h in 59% yield (dr = 91 : 9, er = 99 : 1; entry 5). It was also possible to convert the methoxy-substituted secondary alkyl iodide (R)- and (S)-4e to the corresponding alkylcopper reagents (R)- and (S)-1e and after reaction with (R)-6h the α-chiral disubstituted allenes (R,S)-7i (52% yield, dr = 93 : 7, er = 99 : 1; entry 6) and (S,S)-7i (54% yield, dr = 12 : 88, er = 99 : 1; entry 7) were obtained. Furthermore, the reaction of (R)-1e with (R)-6i led to the

Table 3 Stereoretentive preparation of chiral allenes 7f–j via anti-S,S-2'-substitution reaction of chiral alkylcopper reagents 1d–e with propargylic phosphates 6e, (R)-6h and (R)-6i

| Entry | Alkylcopper of type 1 | Propargylic phosphate 6 | Product of type 7f,j,Me,Cu
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-1d</td>
<td>6e</td>
<td>(R)-7f, 41% yield, er = 93.7</td>
</tr>
<tr>
<td>2</td>
<td>(S)-1d</td>
<td>(R)-6h (er = 99 : 1)</td>
<td>(S,S)-7g, 49% yield, (dr = 92.8, er = 99.1)</td>
</tr>
<tr>
<td>3</td>
<td>(R)-1d</td>
<td></td>
<td>(R,S)-7h, 59% yield, (dr = 91.9, er = 99.1)</td>
</tr>
<tr>
<td>4</td>
<td>(S)-1e</td>
<td></td>
<td>(S,S)-7i, 54% yield, (dr = 12.88, er = 99.1)</td>
</tr>
<tr>
<td>5</td>
<td>(R)-1e</td>
<td></td>
<td>(R,S)-7i, 51% yield, (dr = 92.8, er = 99.1)</td>
</tr>
</tbody>
</table>

* The diastereoselectivity (dr; anti : syn ratio) was determined by 1H- or 13C-NMR analysis. The S,S-2' : S,S-2 ratio was higher than 99 : 1. The enantiomeric ratio (er) was determined by chiral GC-analysis.
trisubstituted allene (R,S)-7j in 51% yield and good diastereoselectivity (dr = 92 : 8, er = 99 : 1; entry 8). Unfortunately, the preparation of tertiary propargylic phosphates was unsuccessful although the subsequent preparation of axially chiral tetra-substituted allenes would be of high interest for organic synthesis.

To get a better understanding of the regioselectivity, we have prepared the racemic phosphate 6j, which contains a propargylic moiety (see Scheme 2).15 The nucleophilic organocopper reagent rac-1d can undergo a substitution either in the α-position (S82-2-substitution of the phosphate), the γ-position (S82-2‘-attack on the propargylic site) or γ’-position (S82-2‘-attack on the allylic site). Interestingly, the reaction of 1d with 6j afforded the allene 7k, the S82-product 7l and the alkene 7m in 58% yield16 with a ratio of 2.6 : 1.0 : 6.4 = γ : α : γ’. This selectivity could be explained by steric hindrance of the α-position and favoured direct S82-2-substitution of the allylic phosphate (γ’-position) compared to the propargylic moiety (γ-position).

Computational calculations

Furthermore, DFT-calculations17 were performed to rationalize the high configurational stability of these chiral secondary alkylcopper reagents. Solvation effects were accounted for by the Polarizable Continuum Model (PCM).18 First, we determined the structure of secondary alkylcopper reagent anti-1a in solution. Thus, we calculated the free energies of anti-1a with coordination to all possible ligands, namely triethyl phosphate (P(OEt)3; anti-8), tetrahydrofuran (THF; anti-9) and diethyl ether (Et2O; anti-10; see Scheme 3, (1–2)).19 Comparison of the free energies of anti-8 with the free energies of anti-9 showed that the coordination to P(OEt)3 is thermodynamically more stable (ΔG = +4.6 kcal mol⁻¹; see Scheme 3, (1)). Similar results were obtained for the substitution of P(OEt)3 with Et2O (ΔG = +6.8 kcal mol⁻¹; (2)) showing again the high affinity of phosphor to copper. These calculations emphasized that anti-8 is the thermodynamically most stable structure. The direct comparison of anti-9 and anti-10 shows that the THF coordinated structure 9 is 3.9 kcal mol⁻¹ more stable compared to the Et2O coordinated structure 10. In addition, the bond energies and bond lengths of the carbon–copper bond for anti-8 (53.9 kcal mol⁻¹, 198.5 pm), anti-9 (51.3 kcal mol⁻¹, 195.9 pm) and anti-10 (50.6 kcal mol⁻¹, 195.8 pm) were determined showing that the carbon–copper bond is most stable when the copper is coordinated to P(OEt)3. Comparison of the free energies of anti-8 and syn-8 showed that the anti-isomer is thermodynamically more stable (ΔG = +2.9 kcal mol⁻¹; see Scheme 3). This result is in agreement with previous reported findings.20

Next, we investigated the epimerization of anti-8 to the corresponding syn-isomer syn-8 via cleavage of the carbon–copper bond or a planar transition state ts-8 (see Scheme 3). The high carbon–copper bond energy of 54.0 kcal mol⁻¹ as well as the transition state energy of 51.9 kcal mol⁻¹ corroborate the high stability of anti-8 towards epimerization at −50 °C.21 However, the slight epimerization of the secondary alkylcopper reagents (1) may be due to polymeric exchange reactions between these copper reagents.22

Conclusions

In conclusion, we have reported the enantioselective preparation of axially chiral allenes bearing a stereocontrolled α-chiral center via anti-S82-2‘-substitution reaction of chiral secondary alkylcopper reagents with enantioenriched propargylic phosphates with retention of configuration. DFT-calculations were performed to determine the structure of these alkylcopper reagents and rationalize the high configurational stability in THF. Further extensions are currently under investigation in our laboratories.

Conflicts of interest

There are no conflicts to declare.
Acknowledgements

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Notes and references


6 (a) The reactivity and configurational stability is considerably higher in THF. For details, see: ; (b) For a recent review, see: J. Skotnitzki, A. Kremsmair and P. Knochel, Synthesis, 2020, 52, 189–196.


10 The use of a phenyl group in α-position was unsuccessful due to dimerisation of the corresponding benzylalklylcopper reagent. Furthermore, we prepared racemic alkyl iodides bearing a n-butyl and cyclohexyl substituent in α-position, which could be used successfully for the preparation of allenes. However, the preparation of the corresponding chiral alkyl alcohols is more challenging and under investigation in our laboratories.

11 The addition of ZnCl2 to the alklylcopper reagent syn-1a as in ref. 6 and 7 led to the corresponding alklylcopper-zinc reagent. After addition of propargyl substrate 6c comparable regioselectivity was achieved leading to syn-7a, however in lower diastereomeric ratio and yield (dr = 91: 9 and 40% yield).

12 (R)+3-Butyn-2-ol is commercially available (TCI; er >99 : 1).

13 The enantiomeric ratio was determined by chiral GC analysis or chiral HPLC analysis. For details, see ESL†.

14 The enantiomeric ratio was determined by chiral GC analysis. For details, see ref. 6.


16 The yield was determined by GC-analysis using dodecane as internal standard.

17 A detailed description of the theoretical methodology, along with optimized structures and energies of all investigated compounds can be found in the ESL†.


19 Coordination of more than one solvent molecule decreased the free energy. For details, see ESL†.


21 We also performed DFT-calculations for the transition state energy with THF (ts-9) and diethyl ether (ts-10) as ligands. The energies are slightly higher (55.7 kcal mol−1 and 57.4 kcal mol−1). For details, see ESL†.

22 All attempts to investigate the bimolecular epimerization pathway were unsuccessful due to inconclusive results from the DFT calculations.