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

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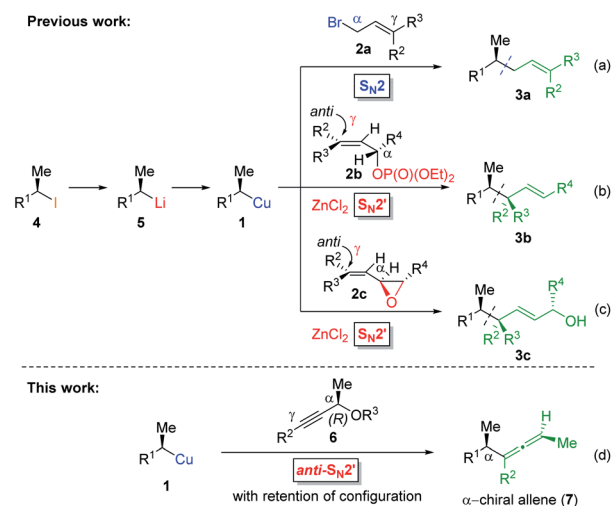
The diastereoselective  $S_N2'$ -substitution of secondary alkylcopper reagents with propargylic phosphates enables the preparation of stereodefined alkylallenes. By using enantiomerically enriched alkylcopper reagents and enantioenriched propargylic phosphates as electrophiles *anti*- $S_N2'$ -substitutions were performed leading to  $\alpha$ -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.<sup>1</sup> They are typically prepared by the substitution reaction of propargylic electrophiles with nucleophiles, such as organocopper reagents.<sup>2</sup> Thereby, these propargylic reagents bear a good leaving group, such as acetates, ethers, epoxides, phosphates or halides.<sup>2–4</sup> Axially chiral allenes are generally prepared from enantioenriched propargylic substrates<sup>3</sup> or by the use of chiral ligands.<sup>4</sup> 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.<sup>1c</sup> However, the enantioselective preparation of axially chiral allenes bearing a stereocenter in  $\alpha$ -position (“ $\alpha$ -chiral allenes”) is rather difficult and only a few examples have been reported.<sup>5</sup> Thereby, the stereochemistry of the  $\alpha$ -position results from an asymmetric synthesis using chiral ligands.

Recently, we reported a zinc-mediated *anti*- $S_N2'$ -substitution reaction of alkylcopper reagents of type **1** with allylic substrates (**2**) leading to chiral alkenes of type **3** with excellent regioselectivity and high retention of configuration (see Scheme 1(b and c)).<sup>6,7</sup> These organocopper reagents were prepared from the corresponding alkyl iodide **4** via I/Li-exchange reaction leading to alkyl lithium reagent **5**. Subsequent transmetalation with CuBr·P(OEt)<sub>3</sub> afforded alkylcopper reagent **1**.<sup>8</sup> The regio-selectivity ( $S_N2'$  :  $S_N2$  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  $S_N2$ -product **3a** ( $\gamma$  :  $\alpha$  < 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  $S_N2'$ -products **3b** ( $\gamma$  :  $\alpha$  > 99 : 1; (b)).<sup>6</sup> Furthermore, we reported *anti*- $S_N2'$ -substitutions of secondary alkylcopper-zinc reagents with allylic epoxides **2c** leading to chiral allylic alcohols of type **3c** ( $\gamma$  :  $\alpha$  > 95 : 5; (c)).<sup>7</sup> This method was used in the total synthesis of the natural product (3*S*,6*R*,7*S*)-zingiberenol.<sup>7</sup>



**Scheme 1** Stereoretentive preparation of chiral secondary alkylcopper reagents **1**: (a–c): subsequent  $S_N2$ - and zinc-mediated *anti*- $S_N2'$ -substitution reactions with allylic substrates. (d): *Anti*- $S_N2'$ -substitution with chiral propargylic phosphates leading to axially chiral allenes.

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Herein, we wish to report the *anti*-S<sub>N</sub>2'-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<sub>N</sub>2'-substitution reaction proceeded directly with the alkylcopper 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<sub>N</sub>2'-reaction. Thus, we prepared the secondary alkylcopper reagent *anti*-**5a** via I/Li-exchange of the corresponding alkyl iodide *anti*-**4a** at  $-100\text{ }^{\circ}\text{C}$  in pentane/diethyl ether-mixture (3 : 2) using *t*-BuLi (2.2 equiv.) followed by subsequent treatment with CuBr·P(OEt)<sub>3</sub> (2.0 equiv.) leading to alkylcopper reagent *anti*-**1a** (see Table 1). This alkylcopper reagent was configurationally stable in THF up to  $-50\text{ }^{\circ}\text{C}$  and thus, we performed a solvent switch at this temperature.<sup>6</sup> Subsequent addition of the propargylic bromide<sup>9a</sup> (**6a**, 3.0 equiv.) furnished only traces of the desired allene *anti*-**7a** (see Table 1; entry 1) after stirring for 1 h at  $-50\text{ }^{\circ}\text{C}$ . The use of propargylic acetate (**6b**)<sup>9b</sup> showed a similar result (entry 2). Switching to pentafluorobenzoate (**6c**)<sup>9c</sup> or diphenylphosphate (**6d**)<sup>9d</sup> 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**<sup>9e</sup> as electrophile significantly increased the stereoretention of the secondary alkylcopper 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).<sup>10,11</sup> In

most cases, a high retention of configuration was observed. However, using the TMS-substituted propargylic phosphate **6g** as electrophile led to allene *anti*-**7c** 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 alkylcopper reagents *anti*- and *syn*-**1b** reacted with **6e** 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 2** Stereoselective preparation of diastereomerically pure allenes **7a–e** starting from alkyl iodides **4a–c**

Entry	Alkylcopper	Electrophile <b>6</b>	Product of type <b>7</b> <sup>a,b</sup>
1	<i>anti</i> - <b>1a</b>	<b>6e</b>	<i>anti</i> - <b>7a</b> , 55% yield, dr = 98:2
2	<i>syn</i> - <b>1a</b>	<b>6e</b>	<i>syn</i> - <b>7a</b> , 46% yield, dr = 6:94
3	<i>anti</i> - <b>1a</b>	<b>6f</b>	<i>anti</i> - <b>7b</b> , 65% yield, dr = 97:3
4	<i>anti</i> - <b>1a</b>	<b>6g</b>	<i>anti</i> - <b>7c</b> , 61% yield, <sup>c</sup> dr = 75:25
5	<i>anti</i> - <b>1b</b>	<b>6e</b>	<i>anti</i> - <b>7d</b> , 58% yield, dr = 98:2
6	<i>syn</i> - <b>1b</b>	<b>6e</b>	<i>syn</i> - <b>7d</b> , 42% yield, dr = 6:94
7	<i>anti</i> - <b>1c</b>	<b>6e</b>	<i>anti</i> - <b>7e</b> , 50% yield, dr = 95:5
8	<i>syn</i> - <b>1c</b>	<b>6e</b>	<i>syn</i> - <b>7e</b> , 44% yield, dr = 4:96

**Table 1** Stereoretentive preparation of secondary alkylcopper reagent *anti*-**1a** and subsequent reaction with various propargylic substrates **6** leading to the allene *anti*-**7a**

Entry	Electrophile	Yield of <i>anti</i> - <b>7a</b> <sup>a</sup> (%)	dr of <i>anti</i> - <b>7a</b> <sup>a</sup>
1	<b>6a</b> : X = Br	Traces	—
2	<b>6b</b> : X = OAc	5	90 : 10
3	<b>6c</b> : X = OCOC <sub>6</sub> F <sub>5</sub>	48	91 : 9
4	<b>6d</b> : X = OP(O)(OPh) <sub>2</sub>	50	93 : 7
5	<b>6e</b> : X = OP(O)(OEt) <sub>2</sub>	59	98 : 2

<sup>a</sup> The diastereoselectivity (dr; *anti* : *syn* ratio) was determined by GC-analysis using dodecane as internal standard.

<sup>a</sup> The diastereoselectivity (dr; *anti* : *syn* ratio) was determined by <sup>1</sup>H- or <sup>13</sup>C-NMR analysis. <sup>b</sup> The S<sub>N</sub>2' to S<sub>N</sub>2 ratio was higher than 99 : 1. <sup>c</sup> The yield 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  $\alpha$ -position (see Table 3; entries 3–8). Thus, the reaction of the alkylcopper (*R*)-**1d** with enantioenriched propargylic phosphate (*R*)-**6h**, prepared from the corresponding 3-butyn-2-ol,<sup>12</sup> led to the  $\alpha$ -chiral disubstituted allene (*R,S*)-**7g**<sup>13</sup> in 43% yield with high *anti*-*S<sub>N</sub>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;<sup>14</sup> 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.<sup>3e,6,14</sup> Subsequent reaction of alkylcopper (*R*)-**1d** with phosphate (*R*)-**6i** furnished the  $\alpha$ -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  $\alpha$ -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<sub>N</sub>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 7 <sup>a,b,c</sup>
1			
2		<b>6e</b>	
3			
4		<b>(R)-6h</b> ( <i>er</i> = 99 : 1)	
5			
6			
7		<b>(R)-6h</b> ( <i>er</i> = 99 : 1)	
8		<b>(R)-6i</b> ( <i>er</i> = 99 : 1)	

<sup>a</sup> The diastereoselectivity (*dr*; *anti* : *syn* ratio) was determined by <sup>1</sup>H- or <sup>13</sup>C-NMR analysis. <sup>b</sup> The *S<sub>N</sub>2'* to *S<sub>N</sub>2* ratio was higher than 99 : 1. <sup>c</sup> The enantiomeric ratio (*er*) was determined by chiral GC-analysis.

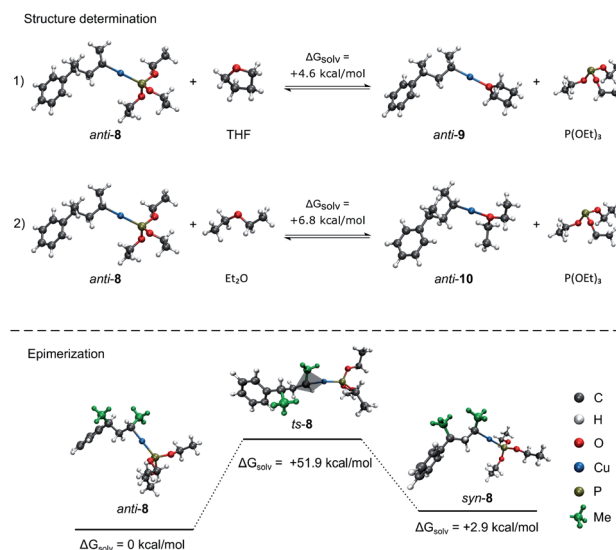


trisubstituted allene (*R,S*)-**7j** in 51% yield and good diastereoselectivity (dr = 92 : 8, er = 99 : 1; entry 8). Unfortunately, the preparation of tertiary propargylic phosphates was unsuccessful although the subsequent preparation of axially chiral tetra-substituted allenes would be of high interest 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).<sup>15</sup> The nucleophilic organocopper reagent *rac*-**1d** can undergo a substitution either in the  $\alpha$ -position ( $S_N2$ -substitution of the phosphate), the  $\gamma$ -position ( $S_N2'$ -attack on the propargylic site) or  $\gamma'$ -position ( $S_N2'$ -attack on the allylic site). Interestingly, the reaction of **1d** with **6j** afforded the allene **7k**, the  $S_N2$ -product **7l** and the alkene **7m** in 58% yield<sup>16</sup> with a ratio of 2.6 : 1.0 : 6.4 =  $\gamma$  :  $\alpha$  :  $\gamma'$ . This selectivity could be explained by steric hindrance of the  $\alpha$ -position and favoured direct  $S_N2'$ -substitution of the allylic phosphate ( $\gamma'$ -position) compared to the propargylic moiety ( $\gamma$ -position).

## Computational calculations

Furthermore, DFT-calculations<sup>17</sup> 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).<sup>18</sup> 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 phosphite (P(OEt)<sub>3</sub>; *anti*-**8**), tetrahydrofuran (THF; *anti*-**9**) and diethyl ether (Et<sub>2</sub>O; *anti*-**10**; see Scheme 3, (1–2)).<sup>19</sup> Comparison of the free energies of *anti*-**8** with the free energies of *anti*-**9** showed that the coordination to P(OEt)<sub>3</sub> is thermodynamically more stable ( $\Delta G = +4.6$  kcal mol<sup>−1</sup>; see Scheme 3, (1)). Similar results were obtained for the substitution of P(OEt)<sub>3</sub> with Et<sub>2</sub>O ( $\Delta G = +6.8$  kcal mol<sup>−1</sup>, (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<sup>−1</sup> more stable compared to the



Scheme 3 Theoretical calculations for the structure determination of *anti*-**1a** and the epimerization of secondary alkylcopper reagent *anti*-**8** to *syn*-**8**.

Et<sub>2</sub>O coordinated structure **10**. In addition, the bond energies and bond lengths of the carbon–copper bond for *anti*-**8** (53.9 kcal mol<sup>−1</sup>, 198.5 pm), *anti*-**9** (51.3 kcal mol<sup>−1</sup>, 195.9 pm) and *anti*-**10** (50.6 kcal mol<sup>−1</sup>, 195.8 pm) were determined showing that the carbon–copper bond is most stable when the copper is coordinated to P(OEt)<sub>3</sub>. Comparison of the free energies of *anti*-**8** and *syn*-**8** showed that the *anti*-isomer is thermodynamically more stable ( $\Delta G = +2.9$  kcal mol<sup>−1</sup>; see Scheme 3). This result is in agreement with previous reported findings.<sup>20</sup>

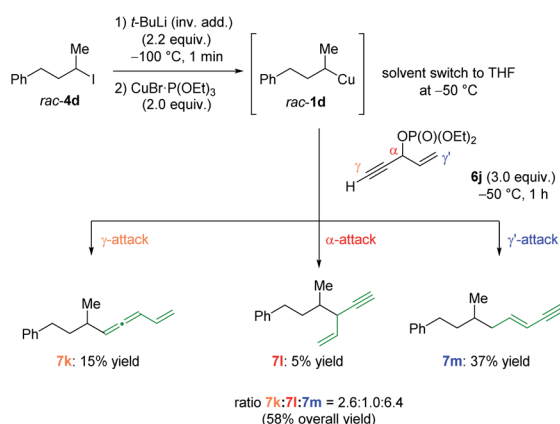
Next, we investigated the epimerization of *anti*-**8** to the corresponding *syn*-isomer *syn*-**8** via cleavage of the carbon–copper bond or a planar transition state *ts*-**8** (see Scheme 3). The high carbon–copper bond energy of 54.0 kcal mol<sup>−1</sup> as well as the transition state energy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

## Conclusions

In conclusion, we have reported the enantioselective preparation of axially chiral allenes bearing a stereocontrolled  $\alpha$ -chiral center via *anti*- $S_N2'$ -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.



Scheme 2 Regioselective addition of secondary alkylcopper reagent **1d** to allylic and propargylic moiety containing phosphate **6f**.





## Acknowledgements

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- The use of a phenyl group in  $\alpha$ -position was unsuccessful due to dimerisation of the corresponding benzyl-alkylcopper reagent. Furthermore, we prepared racemic alkyl iodides bearing a *n*-butyl and cyclohexyl substituent in  $\alpha$ -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.
- The addition of  $\text{ZnCl}_2$  to the alkylcopper reagent *syn*-**1a** as in ref. 6 and 7 led to the corresponding alkylcopper-zinc reagent. After addition of propargylic substrate **6e** comparable regioselectivity was achieved leading to *syn*-**7a**, however in lower diastereomeric ratio and yield (dr = 91 : 9 and 40% yield).
- (R)-(+)-3-Butyn-2-ol is commercially available (TCI; er >99 : 1).
- The enantiomeric ratio was determined by chiral GC analysis or chiral HPLC analysis. For details, see ESI.†
- The enantiomeric ratio was determined by chiral GC analysis. For details, see ref. 6.
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- The yield was determined by GC-analysis using dodecane as internal standard.
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- Coordination of more than one solvent molecule decreased the free energy. For details, see ESI.†
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- 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<sup>−1</sup> and 57.4 kcal mol<sup>−1</sup>). For details, see ESI.†
- All attempts to investigate the bimolecular epimerization pathway were unsuccessful due to inconclusive results from the DFT calculations.

