Introduction

Allenes are common intermediates in organic synthesis and found in natural products. They are typically prepared by the substitution reaction of propargylic electrophiles with nucleophiles, such as organocopper reagents. Thereby, these propargylic reagents bear a good leaving group, such as acetates, ethers, epoxides, phosphates or halides. Axially chiral allenes are generally prepared from enantioenriched propargylic substrates or by the use of chiral ligands. 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. 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. Thereby, the stereochirality of the α-position results from an asymmetric synthesis using chiral ligands.

Recently, we reported a zinc-mediated anti-SN2'-substitution reaction of allylaluminum reagents of type 1 with allylic substrates leading to chiral alkenes of type 3 with excellent regioselectivity and high retention of configuration (Scheme 1a). These organocopper reagents were prepared from the corresponding allyl iodide via I/I-exchange reaction leading to allyllithium reagent. Subsequent transmetalation with CuBr-P(OEt)3 afforded organocopper reagent 1. The regio-selectivity (SN2' : SN2 ratio) of the substitution reactions highly depended on the choice of allylic electrophile 2 and the used organometallic species. The reaction of allylaluminum reagents 1 with allylic bromides exclusively led to the SN2-product 3a (γ : α < 1 : 99; see Scheme 1a). 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). Furthermore, we reported anti-SN2'-substitutions of secondary allylaluminum-zinc reagents with allylic epoxides leading to chiral allylic alcohols of type 3c (γ : α > 95 : 5; c). This method was used in the total synthesis of the natural product (35,68,7S)-zingiberenol.

Scheme 1  Stereoretentive preparation of chiral secondary allylaluminum 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'-substitution of secondary alkylcopper reagents 1 with chiral propargylic phosphates 6 leading to α-chiral allenes of type 7 with retention of the configuration (see Scheme 1(d)). Remarkably, this overall anti-S_N2'-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 SN2'-reaction. Thus, we prepared the secondary alkyl lithium reagent anti-5a via V/Li-exchange of the corresponding alkyl iodide anti-4a at −100 °C in pentane/diethyl ether-mixture (3 : 2) using t-BuLi (2.2 equiv.) followed by subsequent treatment with CuBr-P(O)(OEt)$_2$ (2.0 equiv.) leading to alkylcopper reagent anti-1a (see Table 1). This alkylcopper reagent was configurationally stable in THF up to −50 °C and thus, we performed a solvent switch at this temperature. Subsequent addition of the propargylic bromide 9 anti-iodide anti-performed a solvent switch at this temperature.

In preliminary experiments, we examined the leaving group anti-4a at −100 °C in pentane/diethyl ether-mixture (3 : 2) using t-BuLi (2.2 equiv.) followed by subsequent treatment with CuBr-P(O)(OEt)$_2$ (2.0 equiv.) leading to alkylcopper reagent anti-1a (see Table 1). This alkylcopper reagent was configurationally stable in THF up to −50 °C and thus, we performed a solvent switch at this temperature. Subsequent addition of the propargylic bromide anti-iodide anti-performed a solvent switch at this temperature. Subsequent addition of the propargylic bromide anti-iodide anti-performed a solvent switch at this temperature. Subsequent addition of the propargylic bromide anti-iodide anti-performed a solvent switch at this temperature.

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

| Entry | Electrophile | Yield of anti-7a (%) | dr of anti-7a |
|-------|--------------|----------------------|--------------|
| 1     | 6a: X = Br   | Traces               | —            |
| 2     | 6b: X = OAc  | 5                    | 90 : 10      |
| 3     | 6c: X = COC$_6$F$_5$ | 48 | 91 : 9 |
| 4     | 6d: X = P(O)(O)(OPh)$_2$ | 50 | 93 : 7 |
| 5     | 6e: X = P(O)(O)(OEt)$_2$ | 59 | 98 : 2 |

The stereoisomeric rearrangement of secondary alkylcopper reagent anti-1a and subsequent reaction with various propargylic substrates 6 leading to the allene 7a. The diastereoselectivity (dr; anti : syn ratio) was determined by $^1$H- or 13C-NMR analysis. The $S_{N2}$ to $S_{N2}$ ratio was higher than 90 : 1. The yield was determined by GC-analysis using dodecane as internal standard.

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 dia-stereo selectivity (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** Stereoisomeric preparation of diastereomerically pure allenes 7a–e starting from alkyl iodides 4a–c

| Entry | Alkylcopper | Electrophile 6 | Product of type 7 | Yields and dr |
|-------|-------------|---------------|-------------------|--------------|
| 1     | anti-1a     | 6a            | anti-7a           | 56% yield, dr = 98 : 2 |
| 2     | anti-1b     | 6b            | anti-7b           | 46% yield, dr = 89 : 1 |
| 3     | anti-1b     | 6c            | anti-7c           | 55% yield, dr = 90 : 1 |
| 4     | anti-1a     | 6e            | anti-7d           | 42% yield, dr = 97 : 3 |
| 5     | anti-1b     | 6e            | anti-7e, 50% yield, dr = 75 : 22 | |
| 6     | anti-1b     | 6f            | anti-7f, 55% yield, dr = 98 : 2 | |
| 7     | anti-1c     | 6g            | anti-7g, 55% yield, dr = 98 : 2 | |
| 8     | anti-1e     | 6h            | anti-7h, 55% yield, dr = 49 : 56 | |
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 secondary alkylcopper reagent (R)-1d with propargylic phosphate 6h–i led to the α-chiral disubstituted allene (R,S)-7g in 43% yield with high anti-SN2 substitution ratio (dr = 92 : 8; er = 99 : 1, entry 3). Similarly, the allene (S,S)-7g was prepared from organocopper (S)-1d and the chiral phosphate (R)-6h in 49% yield (dr = 12 : 88; er = 99 : 1; 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.13 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-SN2 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 |
|-------|-----------------------|-------------------------|---------------------|
| 1     | (R)-1d                | 6e                      | (R)-7f, 41% yield, er = 93 : 7 |
| 2     | (R)-1d                | (R)-6h (er = 99 : 1)    | (S)-7h, 45% yield, er = 10 : 90 |
| 3     | (R)-1d                | (R)-6h (er = 99 : 1)    | (R,S)-7g, 43% yield, (dr = 92 : 8; er = 99 : 1) |
| 4     | (R)-1d                | (R)-6i (er = 99 : 1)    | (S,S)-7i, 49% yield, (dr = 12 : 88; er = 99 : 1) |
| 5     | (R)-1e                | (R)-6i (er = 99 : 1)    | (R,S)-7i, 51% yield, (dr = 93 : 7; er = 99 : 1) |
| 6     | (R)-1e                | (R)-6i (er = 99 : 1)    | (S,S)-7j, 54% yield, (dr = 12 : 88; er = 99 : 1) |
| 7     | (S)-1e                | (R)-6h (er = 99 : 1)    | (R,S)-7i, 52% yield, (dr = 93 : 7; er = 99 : 1) |
| 8     | (S)-1e                | (R)-6i (er = 99 : 1)    | (S,S)-7j, 54% yield, (dr = 12 : 88; er = 99 : 1) |

* The diastereoselectivity (dr; anti : syn ratio) was determined by 1H- or 13C-NMR analysis. The S$_\alpha$2’ to S$_\alpha$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 diastereo-selectivity \((\text{dr} = 92 : 8; \text{er} = 99 : 1; \text{entry} 8)\). Unfortunately, the preparation of tertiary propargylic phosphates was unsuccessful although the subsequent preparation of axially chiral tetrasubstituted allenes would have been 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).\textsuperscript{15} The nucleophilic organocopper reagent \(\text{rac-1d}\) can undergo a substitution either in the \(\alpha\)-position \((\text{Sn2}-\text{substitution of the phosphate})\), the \(\gamma\)-position \((\text{Sn2}-\text{attack on the propargylic site})\) or \(\gamma'\)-position \((\text{Sn2}-\text{attack on the allylic site})\). Interestingly, the reaction of \(1d\) with \(6j\) afforded the allene \(7k\), the \(\text{Sn2}-\text{product 7l}\) and the alkene \(7m\) in 58% yield\textsuperscript{16} 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 \(\text{Sn2}\)-substitution of the allylic phosphate \((\gamma'\)-position) compared to the propargylic moiety \((\gamma\)-position).

**Computational calculations**

Furthermore, DFT-calculations\textsuperscript{17} 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).\textsuperscript{18} First, we determined the structure of secondary alkylcopper reagent \(\text{anti-1a}\) in solution. Thus, we calculated the free energies of \(\text{anti-1a}\) with coordination to all possible ligands, namely triethyl phosphate \((\text{P(OEt)}_3)\); \(\text{anti-8}\), tetrahydrofuran (THF); \(\text{anti-9}\) and diethyl ether \((\text{Et}_2\text{O}; \text{anti-10})\); see Scheme 3, (1–2)).\textsuperscript{19} Comparison of the free energies of \(\text{anti-8}\) with the free energies of \(\text{anti-9}\) showed that the coordination to \(\text{P(OEt)}_3\) is thermodynamically more stable \((\Delta G = +4.6 \text{ kcal mol}^{-1}; \text{see Scheme 3, (1)})\). Similar results were obtained for the substitution of \(\text{P(OEt)}_3\) with \(\text{Et}_2\text{O}\) \((\Delta G = +6.8 \text{ kcal mol}^{-1}, (2))\) showing again the high affinity of phosphor to copper. These calculations emphasized that \(\text{anti-8}\) is the thermodynamically most stable structure. The direct comparison of \(\text{anti-9}\) and \(\text{anti-10}\) shows that the THF coordinated structure \(9\) is 3.9 kcal mol\(^{-1}\) more stable compared to the \(\text{Et}_2\text{O} \) coordinated structure \(10\). In addition, the bond energies and bond lengths of the carbon–copper bond for \(\text{anti-8}\) \((53.9 \text{ kcal mol}^{-1}, 198.5 \text{ pm})\), \(\text{anti-9}\) \((51.3 \text{ kcal mol}^{-1}, 195.9 \text{ pm})\) and \(\text{anti-10}\) \((50.6 \text{ kcal mol}^{-1}, 195.8 \text{ pm})\) were determined showing that the carbon–copper bond is most stable when the copper is coordinated to \(\text{P(OEt)}_3\). Comparison of the free energies of \(\text{anti-8}\) and \(\text{syn-8}\) showed that the \(\text{anti-isomer}\) is thermodynamically more stable \((\Delta G = +2.9 \text{ kcal mol}^{-1}; \text{see Scheme 3})\). This result is in agreement with previous reported findings.\textsuperscript{20}

Next, we investigated the epimerization of \(\text{anti-8}\) to the corresponding \(\text{syn-isomer syn-8 via cleavage of the carbon–copper bond or a planar transition state ts-8 (see Scheme 3)}\). 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 \(\text{anti-8}\) towards epimerization at \(-50 \, ^\circ\text{C}\).\textsuperscript{21} However, the slight epimerization of the secondary alkylcopper reagents \((1)\) may be due to polymolecular exchange reactions between these copper reagents.\textsuperscript{22}

**Conclusions**

In conclusion, we have reported the enantioselective preparation of axially chiral allenes bearing a stereocontrolled \(\alpha\)-chiral center via \(\text{anti-Sn2′-substitution reaction of chiral secondary alkylcopper reagents with enantioenriched propargylic phosphates with retention of configuration}\). 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

We thank the Excellence Cluster “e-conversion” and the Munich-Centre for Advanced Photonics (MAP) for financial support. We also thank Albemarle for the generous gift of chemicals. J. S. thanks the FCI Foundation for a fellowship. D. K. and J. S. acknowledge financial support by the Dr. Klaus Roemer Foundation through their PhD thesis award.

Notes and references

1 (a) Modern Allene Chemistry, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, vol. 1 and 2. For reviews see: (b) A. Hoffmann-Röder and N. Krause, Angew. Chem., Int. Ed., 2004, 43, 1196–1216; (c) S. Yu and S. Ma, Angew. Chem., Int. Ed., 2012, 51, 3074–3112; (d) R. K. Neff and D. E. Frantz, ACS Catal., 2014, 4, 519–528; (e) J. Ye and S. Ma, Org. Chem. Front., 2014, 1, 1210–1224.

2 (a) P. Rona and P. Crabbe, J. Am. Chem. Soc., 1968, 90, 4733–4734; (b) R. S. Brinkmeyer and T. L. Macdonald, J. Chem. Soc., Chem. Commun., 1978, 876–877; (c) A. C. Oechslager and E. Czyzewska, Tetrahedron Lett., 1983, 24, 5587–5590; (d) A. Alexakis, I. Marek, P. Mangeney and J. F. Normant, Tetrahedron Lett., 1989, 30, 2387–2390; (e) A. Alexakis, I. Marek, P. Mangeney and J. F. Normant, Tetrahedron, 1991, 47, 1677–1696; (f) J. A. Marshall and K. G. Pinney, J. Org. Chem., 1993, 58, 7180–7184; (g) J. P. Varghese, P. Knochel and I. Marek, Org. Lett., 2000, 2, 2849–2852.

3 (a) I. Marek, P. Mangeney, A. Alexakis and J. F. Normant, Tetrahedron Lett., 1986, 27, 5499–5502; (b) A. Alexakis, I. Marek, P. Mangeney and J. F. Normant, J. Am. Chem. Soc., 1990, 112, 8042–8047; (c) M. T. Crimmins and K. A. Emmite, J. Am. Chem. Soc., 2001, 123, 1533–1534; (d) M. Leclère and A. G. Fallis, Angew. Chem., Int. Ed., 2008, 47, 568–572; (e) H. Ohmiya, U. Yokobori, Y. Makida and M. Sawamura, Org. Lett., 2011, 13, 6312–6315.

4 (a) R. K. Dieter, N. Chen and V. K. Gore, J. Org. Chem., 2006, 71, 8755–8760; (b) H. Li, D. Müller, L. Guéene and A. Alexakis, Org. Lett., 2012, 14, 5880–5883; (c) D. Qian, L. Wu, Z. Lin and J. Sun, Nat. Commun., 2017, 8, 567.

5 Extensive studies were done by S. Ma and others: (a) M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder and M. R. Tracey, Org. Lett., 2003, 5, 2663–2666; (b) X. Jiang, C. Fu and S. Ma, Chem.–Eur. J., 2008, 14, 9656–9664; (c) Q. Li, C. Fu and S. Ma, Angew. Chem., Int. Ed., 2012, 51, 11783–11786; (d) Q. Li, C. Fu and S. Ma, Angew. Chem., Int. Ed., 2014, 53, 6511–6514; (e) J. Dai, X. Duan, J. Zhou, C. Fu and S. Ma, Chin. J. Chem., 2018, 36, 387–391; (f) B. Wang, X. Wang, X. Yin, W. Yu, Y. Liao, J. Ye, M. Wang and J. Liao, Org. Lett., 2019, 21, 3913–3917.

6 (a) The reactivity and configurational stability is considerably higher in THF. For details, see: J. Skotnitzki, L. Speissert and P. Knochel, Angew. Chem., Int. Ed., 2019, 58, 1509–1514. (b) For a recent review, see: J. Skotnitzki, A. Kremsmair and P. Knochel, Synthesis, 2020, 52, 189–196.

7 J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf and P. Knochel, Synthesis, 2020, 52, 873–881.

8 (a) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff and P. Knochel, Angew. Chem., Int. Ed., 2018, 57, 5516–5519; (b) J. Skotnitzki, V. Morozova and P. Knochel, Org. Lett., 2018, 20, 2365–2368.

9 (a) Propargyl bromide is commercially available as a solution in toluene; (b) Propargyl acetate is commercially available (Sigma-Aldrich); (c) N. N. Solodukhin, N. E. Borisova, A. V. Churakov and K. V. Zaitzev, J. Fluorine Chem., 2016, 187, 15–23; (d) J. Eisenblatter, M. Bruns, U. Fehrenbacher, L. Barner and C. Barner-Kowollik, Polym. Chem., 2013, 4, 2406–2413; (e) M. Hojo, R. Sakurai, S. Okabe and A. Hosomi, Chem. Commun., 2001, 357–358. For details, see ESL†.

10 The use of a phenyl group in α-position was unsuccessful due to dimerisation of the corresponding benzylalkylcopper reagent. Furthermore, we prepared racemic allyl 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 allyl alcohols is more challenging and under investigation in our laboratories.

11 The addition of ZnCl2 to the allylcopper reagent syn-1a as in ref. 6 and 7 led to the corresponding allylcopper-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).

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.

15 A. Czepa and T. Hofmann, J. Agric. Food Chem., 2004, 52, 4508–4514.

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†.

18 (a) S. Miertsu, E. Scrocco and J. Tomasi, Chem. Phys., 1981, 55, 117–129; (b) Continuum Solution Models in Chemical Physics, John Wiley & Sons, Ltd, 2007, DOI: 10.1002/9780470515235; (c) J. Tomasi, B. Mennucci and R. Cammi, Chem. Rev., 2005, 105, 2999–3094.

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

20 J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivier-Riedle and P. Knochel, Angew. Chem., Int. Ed., 2020, 59, 320–324.

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.